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

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Summary

Background Effective systemic therapies for patients with advanced, progressive neuroendocrine tumours of the lung or gastrointestinal tract are scarce. We aimed to assess the efficacy and safety of everolimus compared with placebo in this patient population.

Methods In the randomised, double-blind, placebo-controlled, phase 3 RADIANT-4 trial, adult patients (aged ≥18 years) with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin were enrolled from 97 centres in 25 countries worldwide. Eligible patients were randomly assigned in a 2:1 ratio by an interactive voice response system to receive everolimus 10 mg per day orally or identical placebo, both with supportive care. Patients were stratified by tumour origin, performance status, and previous somatostatin analogue treatment. Patients, investigators, and the study sponsor were masked to treatment assignment. The primary endpoint was progression-free survival assessed by central radiology review, analysed by intention to treat. Overall survival was a key secondary endpoint. This trial is registered with ClinicalTrials.gov, number NCT01524783.

Findings Between April 3, 2012, and Aug 23, 2013, a total of 302 patients were enrolled, of whom 205 were allocated to everolimus 10 mg per day and 97 to placebo. Median progression-free survival was 11·0 months (95% CI 9·2–13·3) in the everolimus group and 3·9 months (3·6–7·4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of progression or death (hazard ratio [HR] 0·48 [95% CI 0·35–0·67], p<0·00001). Although not statistically significant, the results of the first pre-planned interim overall survival analysis indicated that everolimus might be associated with a reduction in the risk of death (HR 0·64 [95% CI 0·40–1·05], one-sided p=0·037, whereas the boundary for statistical significance was 0·0002). Grade 3 or 4 drug-related adverse events were infrequent and included stomatitis (in 18 [9%] of 202 patients in the everolimus group *vs* 0 of 98 in the placebo group), diarrhoea (15 [7%] *vs* 2 [2%]), infections (14 [7%] *vs* 0), anaemia (8 [4%] *vs* 1 [1%]), fatigue (7 [3%] *vs* 1 [1%]), and hyperglycaemia (7 [3%] *vs* 0).

Interpretation Treatment with everolimus was associated with significant improvement in progression-free survival in patients with progressive lung or gastrointestinal neuroendocrine tumours. The safety findings were consistent with the known side-effect profile of everolimus. Everolimus is the first targeted agent to show robust anti-tumour activity with acceptable tolerability across a broad range of neuroendocrine tumours, including those arising from the pancreas, lung, and gastrointestinal tract.

Funding Novartis Pharmaceuticals Corporation.

Introduction

Neuroendocrine tumours are a group of heterogeneous malignancies arising from neuroendocrine cells throughout the body.[1] Data from population-based registries indicate that 51% of neuroendocrine tumours arise from the gastrointestinal tract, 27% from the lungs, and 6% from the pancreas.[1] Clinically, neuroendocrine tumours are regarded as functional if they are associated with symptoms of hormonal hypersecretion, or non-functional if they are not associated with these symptoms. Although carcinoid syndrome is classically associated with metastatic, well-differentiated neuroendocrine tumours of the small intestine, an analysis of National Comprehensive Cancer Centre database showed that most (74%) neuroendocrine tumours are non-functional.[2] The prognosis of neuroendocrine tumours varies based on the primary site, the presence of metastatic disease, tumour grade, and stage at diagnosis.[1,3]

Advanced neuroendocrine tumours are incurable in nearly all cases. The somatostatin analogue octreotide,

Research in context

Evidence before this study

We searched MEDLINE for reports on clinical trials in advanced neuroendocrine tumours, with "mTOR" and "NET" as our primary search terms, limiting the findings to include "non-functional", "non-pancreatic", or "non-syndromic" neuroendocrine tumours. We did not limit our search by date but we searched only for articles published in English. We identified no studies of mammalian target of rapamycin (mTOR) inhibitors as monotherapy in patients with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin. We found that the phase 3 RADIANT-2 study assessed the mTOR inhibitor everolimus in combination with octreotide longacting repeatable versus placebo plus octreotide longacting repeatable in patients with advanced neuroendocrine tumours and a history of carcinoid symptoms (Pavel et al, 2011). Although the RADIANT-2 study did not meet its primary endpoint, the results provided an initial indication of the potential antitumour effect of everolimus in the patients with non-pancreatic neuroendocrine tumours. Additionally, RAMSETE (RAD001 [everolimus] in Advanced and Metastatic Silent neuroEndocrine Tumours in Europe)—a single-arm, multicentre, single-stage phase 2 trial—showed that everolimus might be effective in non-syndromic, non-pancreatic neuroendocrine tumours with diverse tumour origin sites (Pavel et al, 2012). We identified no phase 3 studies with mTOR inhibitors as monotherapy in patients with advanced, progressive, well-differentiated, non-functional neuroendocrine tumours of lung or gastrointestinal origin.

Added value of this study

Advanced neuroendocrine tumours are incurable. Targeted treatments, such as everolimus and sunitinib, are approved for advanced, progressive, pancreatic neuroendocrine tumours. Effective antineoplastic therapy options for patients with advanced, progressive, non-functional neuroendocrine tumours of the lung or gastrointestinal tract are very scarce. To our knowledge, RADIANT-4 is the first, large, randomised, placebo-controlled, phase 3 study to assess the efficacy and safety of the mTOR inhibitor everolimus as monotherapy in this patient population. Everolimus was associated with a clinically meaningful almost threefold prolongation of progression-free survival versus placebo, indicating a statistically significant 52% risk reduction in favour of everolimus. The benefit of treatment with everolimus was maintained across most of the prespecified subgroups. The adverse event findings were consistent with the known safety profile of everolimus.

Implications of all the available evidence

Taken together with results from the previous RADIANT-3 study in pancreatic neuroendocrine tumours (Yao et al, 2011), the findings from RADIANT-4 study provide robust, practice-changing evidence to support the antitumour efficacy of everolimus across a broad range of neuroendocrine tumours, including those arising from the pancreas, lung, or gastrointestinal tract.

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approved for control of hormonal syndrome, has been shown to delay disease progression in patients with previously untreated midgut neuroendocrine tumours.[4] Recently, lanreotide was shown to delay tumour growth in patients with mostly stable, advanced, enteropancreatic neuroendocrine tumours.[5] Although targeted therapies such as everolimus and sunitinib are approved for advanced pancreatic neuroendocrine tumours, for which both drugs have been associated with improved progression-free survival,[6–8] these agents are not approved for advanced lung or progressive gastrointestinal tract neuroendocrine tumours.

Everolimus (Afinitor, Novartis Pharmaceuticals Corporation [East Hanover, NJ, USA]), a potent oral inhibitor of mammalian target of rapamycin (mTOR), has previously been shown to be associated with antitumour activity in advanced non-pancreatic neuroendocrine tumours.[9–11] The RADIANT-2 study[12] assessed everolimus versus placebo, both with octreotide longacting repeatable, in patients with neuroendocrine tumours and carcinoid syndrome. In the RADIANT-2 study,[12] treatment with everolimus plus octreotide longacting repeatable was associated with a 5·1-month improvement in median progression-free survival for the everolimus group versus the placebo group. However, this difference did not achieve statistical significance, possibly because of an imbalance in baseline characteristics between the treatment groups and informative censoring caused by discordance between local and central radiology review.[12] The RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) was undertaken to ascertain whether or not oral everolimus at a daily dose of 10 mg compared with placebo prolongs progression-free survival in patients with advanced, non-functional, progressive neuroendocrine tumours of lung or gastrointestinal origin.

Methods

Study design and participants

This international, multicentre, randomised, double-blind, placebo-controlled, phase 3 study was done in 97 centres in 25 countries worldwide (Austria, Belgium, Canada, China, Colombia, Czech Republic, Germany, Greece, Hungary, Italy, Japan, Lebanon, Netherlands, Poland, Russia, Saudi Arabia, Slovak Republic, South Africa, South Korea, Spain, Taiwan, Thailand, Turkey, the UK, and the USA). Adult patients (aged ≥18 years) with pathologically confirmed, advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1

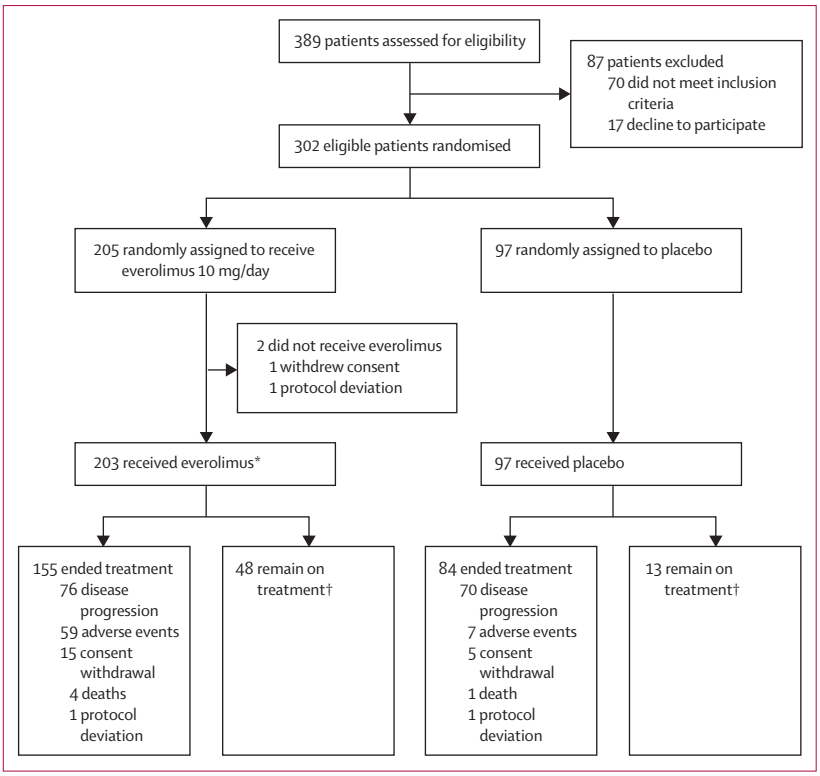


Figure 1: **Trial profile**
*The full analysis set comprised all 302 randomly assigned patients (205 patients in the everolimus group and 97 in the placebo group). Two patients randomly assigned to everolimus were not treated due to withdrawal of consent and protocol deviation and one patient randomly assigned to everolimus inadvertently received placebo treatment because of dispensation error at site; therefore, the safety set contains 202 patients in the everolimus group and 98 in the placebo group. †At data cutoff (Nov 28, 2014).

See Online for appendix

or 2 according to the 2010 WHO classification[13,14]) neuroendocrine tumours of lung or gastrointestinal origin were eligible for participation within 6 months from documented radiological disease progression. Additional key inclusion criteria included measurable disease according to modified Response Evaluation Criteria In Solid Tumors (RECIST) version 1·0 (appendix pp 2–3 and amended protocol);[15] a WHO performance status score of 0 or 1; and adequate bone marrow, liver, and kidney function. Patients previously treated with a somatostatin analogue, interferon, one line of chemotherapy, peptide receptor radionuclide therapies, or a combination of these were eligible to enrol if disease progression was documented during or after their last treatment. Antineoplastic therapy must have been discontinued for at least 4 weeks (or 6 months in the case of peptide receptor radionuclide therapies) before randomisation. Patients were ineligible if they had a history of or presented with carcinoid syndrome, poorly differentiated histology, or pancreatic neuroendocrine tumours. Patients who had previously received more than one line of chemotherapy; treatment with mTOR inhibitors (sirolimus, temsirolimus, or everolimus); hepatic intra-arterial embolisation within 6 months of randomisation; cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation; or chronic treatment with corticosteroids or other immunosuppressive agents were excluded.

The study was done in accordance with Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki, and local regulations. Independent ethics committees or institutional review boards at each participating centre reviewed and approved the study and all amendments to the protocol. All patients provided written informed consent. An independent data monitoring committee provided ongoing oversight of safety and study conduct.

Randomisation and masking

Randomisation was done by interactive voice response systems (see amended protocol in appendix). Randomisation was stratified by previous somatostatin analogue treatment (defined as continuous somatostatin analogue treatment for ≥12 weeks), tumour origin (based on prognostic level, grouped into two strata: stratum A [better prognosis]: appendix, caecum, jejunum, ileum, duodenum, or neuroendocrine tumour of unknown primary origin *vs* stratum B [worse prognosis]: lung, stomach, colon [other than caecum], or rectum), and WHO performance status (0 *vs* 1). Patients, investigators, and the study sponsor were masked to treatment assignment. The identity of experimental treatments was concealed by use of everolimus and placebo that were identical in packaging, labelling, appearance, and administration schedule. Premature unmasking (ie, before the primary analysis) was allowed only in the case of emergency.

Procedures

Eligible patients were randomly assigned in a 2:1 ratio to receive oral everolimus at a dose of 10 mg per day or identical placebo, both with best supportive care. The best supportive care included treatment deemed necessary by the physician (eg, analgesics and anti-diarrhoeals) except anti-tumour agents like somatostatin analogues, interferons, tumour ablative procedures, radiation, and concurrent chemotherapy. Radiation and surgery were allowed only for palliative intent. Concomitant somatostatin analogues during the study were allowed only for control of emergent carcinoid symptoms (eg, flushing or diarrhoea) that were not manageable by standard treatment such as loperamide.

All patients who underwent randomisation were assessed for efficacy by cross-sectional imaging with multiphasic CT or MRI every 8 weeks during the first 12 months and every 12 weeks thereafter.

Dose reductions and treatment interruption for a maximum of 28 days were allowed for patients who did not tolerate therapy or to manage adverse events that were judged to be related to study treatment. Two dose reductions were allowed: from 10 mg to 5 mg per day and,

subsequently, to 5 mg every other day. Treatment continued until documented radiological disease progression, start of new cancer therapy (any therapy with intent of oncologic treatment of cancer, potentially chemotherapy, peptide receptor radionuclide therapy, or any other targeted therapy), development of an intolerable adverse event, or withdrawal of consent. Crossover from placebo to open-label everolimus after progression was not allowed and patients and investigators remained masked to treatment assignment until the primary analysis.

Outcomes

The primary endpoint was central radiology-assessed progression-free survival, defined as the time from randomisation to death or progression as per modified RECIST version 1.0 criteria.[14] Central radiology review, masked to treatment assignment and local assessment, was done in real time (appendix p 3). Progression-free survival according to investigator assessment was a prespecified supportive analysis. Overall survival was the main secondary endpoint. Other secondary endpoints were objective response rate, disease control rate (appendix p 4), health-related quality of life, WHO performance status, pharmacokinetics, changes in chromogranin A and neuron-specific enolase levels, and safety.

All randomly assigned patients were included in the full analysis set. The primary efficacy analyses were assessed based on the data from this population on an intention-to-treat basis.

The safety population included all patients who received at least one dose of the study drug with at least one post-baseline safety assessment. Adverse events were assessed as per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Statistical analysis

Based on historical data, we assumed that median progression-free survival in the control (placebo) group would be around 5 months.[4] Sample size was estimated based on the ability to detect a clinically meaningful improvement in progression-free survival, defined as a 41% reduction in the risk of disease progression or death (hazard ratio [HR] 0·59), corresponding to a prolongation in median progression-free survival from 5 months with placebo to 8·5 months with everolimus. With 2:1 randomisation and a one-sided type 1 error rate of 2·5%, a total of 176 progression-free survival events are needed to provide 91·3% power. After adjustment for an estimated dropout rate of 15%, we calculated that roughly 285 patients were needed to be randomised in a 2:1 ratio between the everolimus and placebo groups.

Overall survival analyses were to be done if the primary endpoint was statistically significant using a group sequential design with two interim analyses and final analysis at roughly 191 events (one-sided significance level

	Everolimus (n=205)	Placebo (n=97)
Age, years	65 (22–86)	60 (24–83)
Sex		
Men	89 (43%)	53 (55%)
Women	116 (57%)	44 (45%)
WHO performance status*		
0	149 (73%)	73 (75%)
1	55 (27%)	24 (25%)
Primary tumour site		
Lung	63 (31%)	27 (28%)
Ileum	47 (23%)	24 (25%)
Rectum	25 (12%)	15 (16%)
Neuroendocrine tumour of unknown primary origin†	23 (11%)	13 (13%)
Jejunum	16 (8%)	6 (6%)
Stomach	7 (3%)	4 (4%)
Duodenum	8 (4%)	2 (2%)
Colon	5 (2%)	3 (3%)
Other‡	6 (3%)	2 (2%)
Caecum	4 (2%)	1 (1%)
Appendix	1 (1%)	0
Tumour grade§		
Grade 1	129 (63%)	65 (67%)
Grade 2	75 (37%)	32 (33%)
Time from initial diagnosis to randomisation		
≤6 months	26 (13%)	12 (12%)
>6 months to ≤18 months	51 (25%)	25 (26%)
>18 months to ≤36 months	41 (20%)	22 (23%)
>36 months	87 (42%)	38 (39%)
Previous treatments¶		
Surgery	121 (59%)	70 (72%)
Chemotherapy	54 (26%)	23 (24%)
Radiotherapy including peptide receptor radionuclide therapy	44 (22%)	19 (20%)
Locoregional and ablative therapies	23 (11%)	10 (10%)
Somatostatin analogues	109 (53%)	54 (56%)
Disease sites‖		
Liver	163 (80%)	76 (78%)
Lymph node or lymphatic system	85 (42%)	45 (46%)
Lung	45 (22%)	20 (21%)
Bone	42 (21%)	15 (16%)
Peritoneum	25 (12%)	8 (8%)
Liver tumour burden		
None	34 (17%)	14 (14%)
≤10%	119 (58%)	61 (63%)
>10% to 25%	29 (14%)	8 (8%)
>25%	21 (10%)	14 (14%)
Unknown	2 (1%)	0

Data are median (range) or n (%). *One patient in the everolimus group had a WHO performance status of 2. †Patients with well-differentiated (grade 1 or 2) neuroendocrine tumours with a primary tumour origin other than the lung or gastrointestinal tract were excluded by appropriate diagnostic procedures. ‡All patients, except for one in the everolimus group who had thymus as the primary site, had primary tumour origin from the gastrointestinal tract. §Patients with WHO grade 1 or well-differentiated neuroendocrine tumours were classified as grade 1 and those with WHO grade 2 or moderately differentiated tumours as grade 2.[13,14] Tumour grade was not available for one patient in the everolimus group. ¶A few patients (≤5%) received other previous treatments including immunotherapy, targeted therapy, and hormonal therapy other than somatostatin analogues. Included in this category are transarterial embolisation, cryoablation, and radiofrequency ablation. ‖The sites as per target and non-target lesion locations recorded at baseline by central radiology review.

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

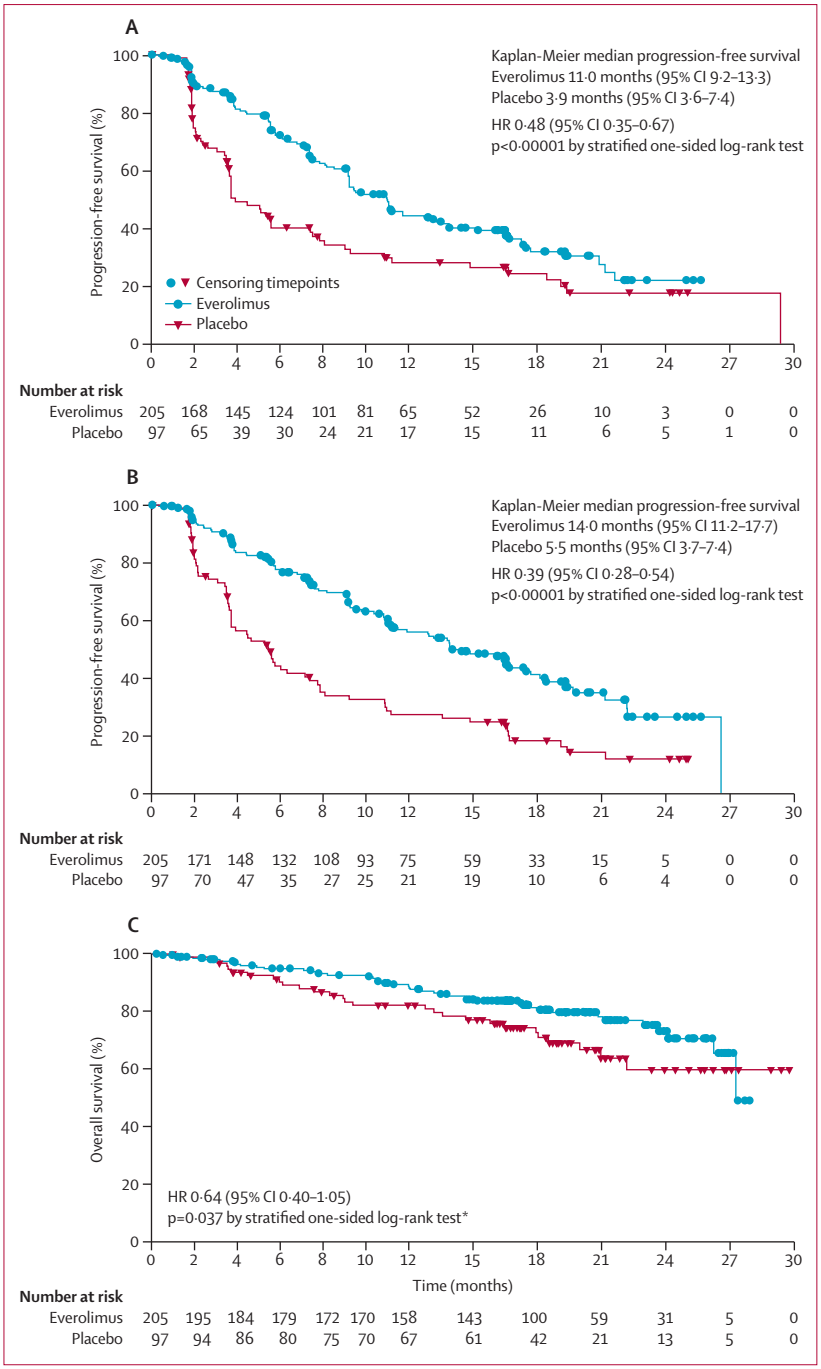


Figure 2: **Progression-free and overall survival (full analysis set)**
Kaplan–Meier curves of (A) progression-free survival as assessed by central radiology review, (B) progression-free survival as assessed by local investigators, and (C) overall survival. HR=hazard ratio. *The Lan-DeMets O'Brian-Fleming boundary for significance at first interim analysis was 0·0002.

For the **National Cancer Institute Common Terminology Criteria for Adverse Events** see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

2·5%; appendix p 4). We used the Lan-DeMets method with O'Brien-Fleming type stopping boundary to control the cumulative type I error rate.

We estimated progression-free and overall survival using the Kaplan-Meier method; we did comparisons between the treatment groups using a one-sided log-rank test, stratified according to tumour origin, WHO performance status, and previous somatostatin analogue treatment. The hazard ratio was estimated by a stratified Cox proportional hazards model. The trial protocol, including the statistical analysis plan, is available in the appendix.

This study is registered with ClinicalTrials.gov, number NCT01524783.

Role of the funding source

The study was designed by academic investigators and representatives of the funder (Novartis Pharmaceuticals Corporation). Data were collected electronically via data management systems of a contract research organisation (PPD Global Ltd, Cambridge, UK) designated by the funder and were analysed by the funder's statistical team. All authors contributed to the interpretation of data and the subsequent writing, reviewing, and amending of the report; the first draft of the report was prepared by the first author (JCY) 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.

Results

Between April 3, 2012, and Aug 23, 2013, a total of 302 eligible patients with advanced, non-functional neuroendocrine tumours of lung or gastrointestinal origin were enrolled and randomly assigned to everolimus 10 mg per day (205 patients) or placebo (97 patients; figure 1). Two patients randomly assigned to everolimus were not treated due to withdrawal of consent and protocol deviation and one patient randomly assigned to everolimus inadvertently received placebo because of dispensation error at site; therefore, the safety population comprises 202 patients in the everolimus group and 98 in the placebo group. The baseline characteristics of patients in both groups were generally well balanced (table 1).

The most common sites of tumour origin were the lung, ileum, and rectum. Median time from initial diagnosis to randomisation was 29·9 months (range 0·7–258·4) in the everolimus group and 28·9 months (1·1–303·3) in the placebo group. More than half of the patient population had a history of previous treatment with somatostatin analogue therapy (mostly for tumour control). A quarter of the patients had received chemotherapy. The two treatment groups were also similar in terms of previous radiotherapy, including peptide receptor radionuclide therapy, and locoregional therapies, including transarterial embolisation, cryo-ablation, or radiofrequency ablation.

At data analysis cutoff (Nov 28, 2014), 155 (76%) of 203 patients in the everolimus group and 84 (87%) of 97 in the placebo group had discontinued study treatment (figure 1). Common reasons for treatment discontinuation included disease progression, adverse events, and withdrawal of consent.

	Everolimus (n=205)	Placebo (n=97)	Difference	Hazard ratio* for disease progression or death with everolimus (95% CI)	p value†
Central radiology review					
Progression-free survival events‡	113 (55%)	65 (67%)	..	..	..
Number censored	92 (45%)	32 (33%)	..	..	..
Median progression-free survival, months	11·0 (9·2–13·3)	3·9 (3·6–7·4)	7·1	0·48 (0·35–0·67)	<0·00001
Local radiology review					
Progression-free survival events‡	98 (48%)	70 (72%)	..	..	..
Number censored	107 (52%)	27 (28%)	..	..	..
Median progression-free survival, months	14·0 (11·2–17·7)	5·5 (3·7–7·4)	8·5	0·39 (0·28–0·54)	<0·00001

Data are n (%) or median (95% CI) unless otherwise indicated. *Hazard ratio was obtained from the stratified Cox model. †p value was obtained from the one-sided stratified log-rank test. ‡Progression-free survival events include disease progression and death.

Table 2: **Progression-free survival (full analysis set)**

Median progression-free survival assessed by central review was 11·0 months (95% CI 9·2–13·3) in the everolimus group and 3·9 months (3·6–7·4) in the placebo group. Everolimus was associated with a 52% reduction in the estimated risk of disease progression or death (HR 0·48 [95% CI 0·35–0·67], p<0·00001; figure 2A and table 2).

The estimated progression-free survival rate at 12 months (according to central review) was 44% in the everolimus group and 28% in the placebo group (figure 2A), which suggests a durable benefit with everolimus.

Findings by investigator assessment were consistent with the central review. Median progression-free survival was 14·0 months (95% CI 11·2–17·7) with everolimus and 5·5 months (3·7–7·4) with placebo (HR 0·39 [95% CI 0·28–0·54], p<0·00001; figure 2B, table 2).

Consistent treatment benefits with everolimus were recorded irrespective of the stratification factors (figure 3A). Additional prespecified subgroup analyses of progression-free survival according to central radiological assessment showed a consistent positive treatment effect of everolimus versus placebo across major demographic and prognostic subgroups (figure 3B).

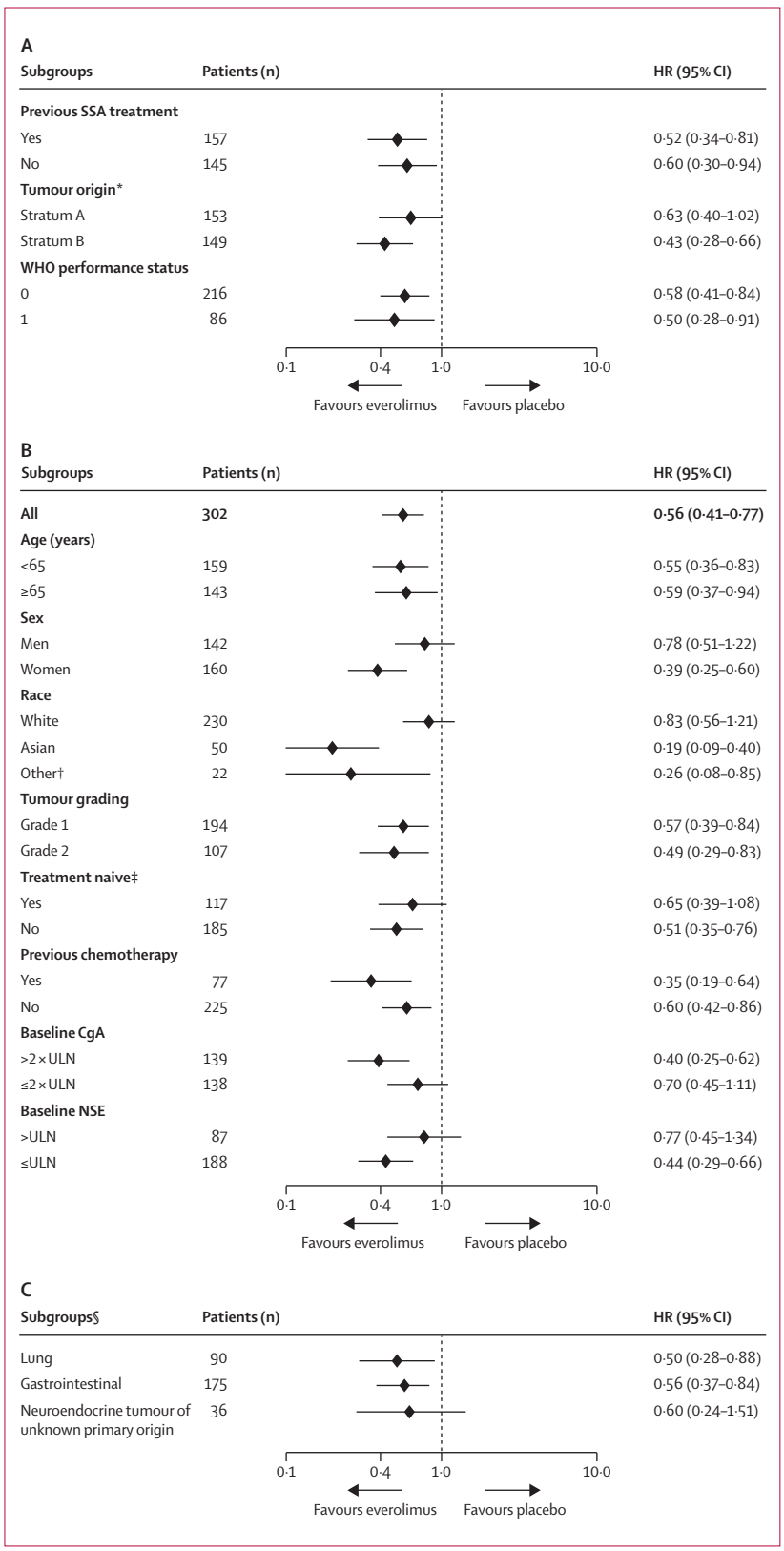
A retrospective analysis showed consistent beneficial effect across the subgroups based on primary tumour origin (lung, gastrointestinal, or neuroendocrine tumours of unknown primary origin; figure 3C). A positive treatment effect was also recorded irrespective of the extent of liver metastasis (appendix p 5).

Since the progression-free survival results were significant, a planned interim overall survival analysis was done. This first overall survival analysis was done with a total of 70 deaths and favoured everolimus with 36% reduction in the estimated risk of death relative to placebo, although statistical significance was not attained (HR 0·64 [95% CI 0·40–1·05], p=0·037 [the Lan-DeMets O'Brian Fleming boundary for significance at first interim analysis was 0·0002]; figure 2C). Data were not mature enough to provide an estimation of median overall survival. Kaplan-Meier estimates for overall survival at the 25th percentile (25% of patients having survival events) were 23·7 months (95% CI 17·6–27·3) in the everolimus group and 16·5 months (9·0–21·0) in the placebo group.

Confirmed objective responses (by central radiology review; all partial responses) were recorded in four (2%) patients receiving everolimus and in one patient (1%) receiving placebo. Disease stabilisation was the best overall response in 165 patients (81%) in the everolimus group compared with 62 patients (64%) in the placebo group. Therefore, the prolongation in progression-free survival with everolimus was probably secondary to the stabilisation of disease or minor tumour shrinkage and to fewer cases of progressive disease. Everolimus was associated with a higher disease control rate compared with placebo (appendix p 6). Of the patients that could be assessed for tumour shrinkage, 117 (64%) in the everolimus group and 22 (26%) in the placebo group had some degree of tumour shrinkage (figure 4). Results for the other secondary endpoints will be presented in future publications.

With a median follow-up period of 21 months, the median duration of treatment was nearly twice as long in the everolimus group as in the placebo group (40·4 weeks [range 0·7–120·4] in the everolimus group *vs* 19·6 weeks [4·0–130·3] in the placebo group). This difference in exposure should always be considered when comparing various rates of reported adverse events that are not adjusted for treatment duration. The median relative dose intensity (the ratio of administered doses to planned doses) was 0·9 in the everolimus group and 1·0 in the placebo group. Without adjustment for duration of treatment, dose reductions or temporary treatment interruptions occurred in 135 (67%) of 202 patients receiving everolimus and 29 (30%) of 98 receiving placebo.

Adverse events were consistent with the known safety profile of everolimus and were mostly grade 1 or 2. Rates of on-treatment deaths (those occurring during receipt of study medication or within 30 days of discontinuing therapy) were similar between the treatment groups



(seven [3·5%] in the everolimus group and three [3·1%] in the placebo group). All except three deaths (1·5%) in the everolimus group (one case each due to respiratory failure, septic shock, and cardiac failure) and two deaths (2·0%) in the placebo group (one case each due to lung infection and dyspnoea) were attributed to disease progression.

Table 3 lists the treatment-related adverse events that occurred in at least 10% of patients; the most common were stomatitis, diarrhoea, fatigue, infections, rash, and peripheral oedema. The most common grade 3 or 4 drug-related adverse events included stomatitis, diarrhoea, infections, anaemia, and fatigue. Treatment discontinuation attributed to grade 3 or 4 adverse events related to the study drug were reported in 24 patients (12%) receiving everolimus and in three (3%) receiving placebo.

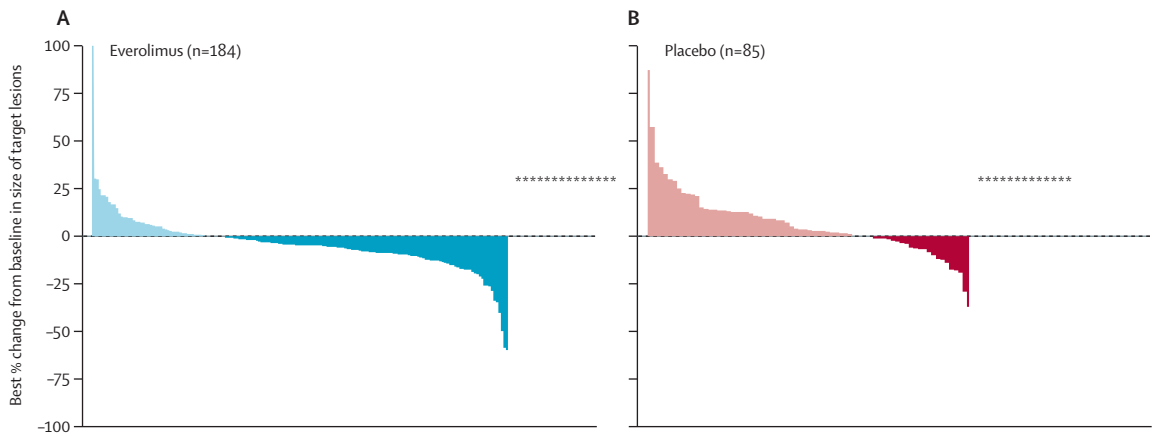
Non-infectious pneumonitis occurred in 32 patients (16%) in association with everolimus treatment. Most cases were of grade 1 or 2 severity; grade 3 pneumonitis occurred in three patients (1%) and no grade 4 cases were reported.

Discussion

In this randomised trial of patients with advanced, progressive, non-functional neuroendocrine tumours of lung or gastrointestinal origin, treatment with everolimus 10 mg per day significantly prolonged median progression-free survival by 7·1 months compared with placebo according to masked central radiology review. This almost threefold improvement in median progression-free survival corresponds with a reduction in risk of disease progression or death by 52% compared with placebo. This benefit was confirmed by the investigator-assessed progression-free survival analysis. Subgroup analyses suggested a consistent treatment benefit across major subgroups.

The availability of targeted therapies has changed the treatment paradigm for patients with advanced neuroendocrine tumours. Somatostatin analogues have now been established as a standard of care for the effective treatment of carcinoid syndrome in functional

Figure 3: **Progression-free survival in subgroups (full analysis set)**
Forest plots of the effect of study treatment on progression-free survival in predefined patient subgroups based on stratification factors (A), major demographic and prognostic subgroups (B), and a retrospective analysis in subgroups by primary tumour origin (C). Subgroup results are reported based on central review. In the retrospective post-hoc analysis, stomach, colon, rectum, appendix, caecum, ileum, duodenum, and jejunum are grouped under gastrointestinal. The HRs in all subgroups are obtained from an unstratified Cox model. HR=hazard ratio. SSA=somatostatin analogue. CgA=chromogranin A. ULN=upper limit of normal. NSE=neuron-specific enolase. *Based on prognostic level, patients were divided into two strata. Stratum A (better prognosis) consisted of patients with tumour sites originating from the appendix, caecum, jejunum, ileum, duodenum, and neuroendocrine tumours of unknown primary origin, whereas stratum B (worse prognosis) comprised patients with primary tumours of the lung, stomach, rectum, and colon (except the caecum). †Included black patients. ‡Defined as no previous chemotherapy or no somatostatin analogue therapy continuously for ≥12 weeks at any time before study. §One patient with thymus as primary tumour origin was not included.



	Everolimus, n (%)	Placebo, n (%)
Decrease in size of target lesions from baseline	117 (64%)	22 (26%)
Increase or no change in size of target lesions from baseline	53 (29%)	50 (59%)
Change in size of target lesion contradicted by overall response of progressive disease	14 (8%)	13 (15%)

Figure 4: **Percentage change from baseline in size of target lesion, central review (full analysis set)**
The plot shows the best percentage change from baseline in the size of the target lesion (ie, the best response in each patient) in the everolimus group (A) and placebo group (B). 14 patients (8%) in the everolimus group and 13 (15%) in the placebo group showed a change in the available target lesion that contradicted the overall response of progressive disease (marked by * in the graphs). Patients for whom the best percentage change in target lesion was not available (21 patients receiving everolimus and 12 receiving placebo) or was available but contradicted by overall lesion response of unknown (none) were excluded from the analysis.

	Everolimus (n=202)					Placebo (n=98)				
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis*	127 (63%)	72 (36%)	37 (18%)	18 (9%)	0	19 (19%)	17 (17%)	2 (2%)	0	0
Diarrhoea	63 (31%)	30 (15%)	18 (9%)	13 (6%)	2 (1%)	16 (16%)	10 (10%)	4 (4%)	2 (2%)	0
Fatigue	62 (31%)	35 (17%)	20 (10%)	5 (2%)	2 (1%)	24 (24%)	17 (17%)	6 (6%)	1 (1%)	0
Infections†	59 (29%)	12 (6%)	33 (16%)	10 (5%)	4 (2%)	4 (4%)	1 (1%)	3 (3%)	0	0
Rash	55 (27%)	42 (21%)	12 (6%)	1 (<1%)	0	8 (8%)	6 (6%)	2 (2%)	0	0
Peripheral oedema	52 (26%)	30 (15%)	18 (9%)	4 (2%)	0	4 (4%)	2 (2%)	1 (1%)	1 (1%)	0
Nausea	35 (17%)	26 (13%)	6 (3%)	2 (1%)	1 (<1%)	10 (10%)	7 (7%)	3 (3%)	0	0
Asthenia	33 (16%)	8 (4%)	22 (11%)	2 (1%)	1 (<1%)	5 (5%)	4 (4%)	1 (1%)	0	0
Anaemia	33 (16%)	5 (2%)	20 (10%)	8 (4%)	0	2 (2%)	0	1 (1%)	1 (1%)	0
Decreased appetite	32 (16%)	22 (11%)	9 (4%)	1 (<1%)	0	6 (6%)	2 (2%)	4 (4%)	0	0
Non-infectious pneumonitis‡	32 (16%)	5 (2%)	24 (12%)	3 (1%)	0	1 (1%)	0	1 (1%)	0	0
Dysgeusia	30 (15%)	26 (13%)	3 (1%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Pruritus	26 (13%)	19 (9%)	6 (3%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Cough	26 (13%)	18 (9%)	8 (4%)	0	0	3 (3%)	3 (3%)	0	0	0
Pyrexia	22 (11%)	14 (7%)	4 (2%)	2 (1%)	2 (1%)	5 (5%)	4 (4%)	1 (1)	0	0
Hyperglycaemia	21 (10%)	5 (2%)	9 (4%)	7 (3%)	0	2 (2%)	2 (2%)	0	0	0
Dyspnoea	21 (10%)	4 (2%)	15 (7%)	2 (1%)	0	4 (4%)	2 (2%)	1 (1)	0	1 (1)

*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †All types of infections are included. ‡Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 3: **Treatment-related adverse events reported in at least 10% of patients (safety population)**

neuroendocrine tumours. More recently, somatostatin analogues have also been shown to control tumour growth in patients with advanced neuroendocrine tumours.[4,5] Targeted therapies, such as everolimus and sunitinib, are approved in advanced, progressive, pancreatic neuroendocrine tumours.[6–8] Effective anti-neoplastic therapy options for patients with advanced, progressive, non-functional neuroendocrine tumours of the lung or gastrointestinal tract, however, are scarce.

The mTOR pathway is a central regulator of cellular proliferation, metabolism, protein synthesis, and autophagy. Although mTOR pathway mutations have been described in roughly 15% of pancreatic neuroendocrine tumours, somatic mutations in this pathway seem to be

infrequent in neuroendocrine tumours of lung or gastrointestinal origin.[16–18] The activity of mTOR inhibitors in this setting is probably due to a combination of factors including inhibition of growth factor signalling, metabolic signalling, epigenetic regulation, and perhaps undefined genomic variations, which converge to activate the mTOR pathway. Previously, using pair biopsy specimens, we showed that everolimus therapy in patients with a variety of neuroendocrine tumours leads to significantly decreased S6 phosphorylation and a consistent decrease in proliferation of the tumour indicated by decreases in Ki-67 labelling.[19,20] The findings from the RADIANT-4 study validate the role of the mTOR pathway in neuroendocrine tumours of lung or gastrointestinal origin.

In this study, we assessed everolimus as a monotherapy against placebo in non-functional neuroendocrine tumours, including those arising from the lung or gastrointestinal tract, and showed that everolimus has a durable benefit in delaying tumour growth. Prospective stratification based on known prognostic factors in our study minimised confounding. Furthermore, unlike RADIANT-2, crossover from the placebo group to the everolimus group after progression was not allowed during the masked period in our study, which would avoid potential bias in the estimation of treatment effect on survival. Indeed, an interim overall survival analysis from RADIANT-4 suggested that there might be a trend in survival benefit in favour of everolimus. Long-term overall survival results are awaited.

The safety and tolerability of everolimus in our study is consistent with the previous experience in the advanced neuroendocrine tumours setting.[6,12] The most frequent adverse events reported with everolimus were of grade 1 or 2 severity, and included stomatitis, diarrhoea, fatigue, infections, rash, and peripheral oedema; the frequencies were similar to those reported previously. Most everolimus-related adverse events were manageable through dose modification or interruption without changing the duration of treatment.

In summary, everolimus, as compared with placebo, was associated with statistically significant and clinically meaningful prolongation of progression-free survival in patients with advanced, progressive, non-functional lung or gastrointestinal neuroendocrine tumours. The first interim overall survival analysis suggested that a trend might exist towards improved survival in favour of everolimus, although this result was not statistically significant. Up to two additional overall survival analyses will be done according to the statistical plan as the survival follow-up data mature. Everolimus was well tolerated and the safety findings were consistent with previous experience. Taken together with results from the previous RADIANT-3 study in pancreatic neuroendocrine tumours,[6] everolimus has now been shown to have robust antitumour activity across a broad spectrum of neuroendocrine tumours, including those arising from the pancreas, lung, and gastrointestinal tract.

Contributors

JCY, NF, SS, CS, JS, MHK, and MEP contributed to the study concept and design. JCY, NF, SS, RB, CC, EW, JT, MR, HL, JWV, GDF, EVC, MT, YS, D-YO, JS, MHK, and MEP recruited patients. NR did the statistical analysis. JCY wrote the first draft of the report with the help of a medical writer. All authors contributed to the content of the report, provided input for data interpretation, reviewed and critically revised the content, and approved the final version for submission.

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Declaration of interests

JCY has received consulting or advisory fees from Ipsen, Lexicon, and Novartis, and research funding from Novartis. NF has received honoraria from Ipsen and Novartis; consulting or advisory fees from Ipsen, Lexicon, Novartis, and Italfarmaco; research funding from Novartis; and travel and accommodation expenses from Ipsen and Novartis. SS has received honoraria, consulting or advisory fees, travel and accommodation expenses, and research funding from Novartis. RB has received research funding from Italfarmaco, Novartis, and Otsuka, and travel and accommodation expenses from Ipsen, Italfarmaco, and Novartis. EW has received consulting or advisory fees from Celgene, Ipsen, and Novartis. JT has received honoraria, research funding, and travel and accommodation expenses from Novartis. MR has received honoraria from Celgene, Ipsen, Novartis, and Roche and consulting or advisory fees from Celgene, Ipsen, Novartis, and Roche. HL has received honoraria from Ipsen, Novartis, and Pfizer; consulting or advisory fees from Novartis and Pfizer; research funding from Novartis; and travel and accommodation expenses from Ipsen, Novartis, and Pfizer. MV, LBP, NR, and CS are employees of and own shares in Novartis. JWV has received honoraria, consulting or advisory fees, and research funding from Novartis. GDF has received consulting or advisory fees and research funding from Novartis. EVC has received research funding from Novartis. YS has received research funding from Chugai Pharma, Lilly, Novartis, and Taiho Pharmaceutical. JS has received honoraria from Novartis; consulting or advisory fees from Ipsen, Lexicon, and Novartis; research funding from Novartis and Pfizer; and is on the speaker's bureau for Bayer and Genentech. MHK has received consulting or advisory fees from Ipsen and Novartis. MEP has received honoraria from Ipsen, Lexicon, Novartis, and Pfizer; consulting or advisory fees from Ipsen, Lexicon, Novartis, and Pfizer; research funding from Novartis; and travel and accommodation expenses from Ipsen and Novartis. CC, MT, and D-YO declare no competing interests.

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References

1 Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26:** 3063–72.

2 Choti MA, Bobiak S, Strosberg JR, et al. Prevalence of functional tumors in neuroendocrine carcinoma: an analysis from the NCCN NET database. *J Clin Oncol* 2012; **30:** 4126 (abstract).

3 Yao J, Phan A. Optimising therapeutic options for patients with advanced pancreatic neuroendocrine tumours. *Eur Oncol Haematol* 2012; **8:** 217–23.

4 Rinke A, Muller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009; **27:** 4656–63.

5 Caplin ME, Pavel M, Ruszniewski P. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; **371:** 224–33.

6 Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 514–23.

7 Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 501–13.

8 Blumenthal GM, Cortazar P, Zhang JJ, et al. FDA approval summary: sunitinib for the treatment of progressive well-differentiated locally advanced or metastatic pancreatic neuroendocrine tumors. *Oncologist* 2012; **17:** 1108–13.

9 Fazio N, Granberg D, Grossman A, et al. Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study. *Chest* 2013; **143:** 955–62.

10 Pavel ME, Wiedenmann B, Capdevila J, et al. RAMSETE: a single-arm, multicenter, single-stage phase II trial of RAD001 (everolimus) in advanced and metastatic silent neuro-endocrine tumours in Europe. *J Clin Oncol* 2012; **30:** 4122 (abstr).

11 Bajetta E, Catena L, Fazio N, et al. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: an ITMO group study. *Cancer* 2014; **120:** 2457–63.

12 Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011; **378:** 2005–12.

13 Rindi G, Klimstra DS, Arnold R, et al. Nomenclature and classification of neuroendocrine neoplasm of the digestive system. In: Bosman FT, Carniero F, Hruban RH, Theise ND, eds. WHO classification of tumours of the digestive system, 4th edn. Lyon: International Agency for Research on Cancer, 2010: 13–14.

14 Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors. *Pancreas* 2010; **39:** 707–12.

15 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000; **92:** 205–16.

16 Fernandez-Cuesta L, Peifer M, Lu X, et al. Frequent mutations in chromatin-remodelling genes in pulmonary carcinoids. *Nat Commun* 2014; **5:** 3518.

17 Francis JM, Kiezun A, Ramos AH, et al. Somatic mutation of CDKN1B in small intestine neuroendocrine tumors. *Nat Genet* 2013; **45:** 1483–86.

18 Banck MS, Kanwar R, Kulkarni AA, et al. The genomic landscape of small intestine neuroendocrine tumors. *J Clin Invest* 2013; **123:** 2502–08.

19 Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. *J Clin Oncol* 2008; **26:** 4311–18.

20 Meric-Bernstam F, Akcakanat A, Chen H, et al. PIK3CA/PTEN mutations and Akt activation as markers of sensitivity to allosteric mTOR inhibitors. *Clin Cancer Res* 2012; **18:** 1777–89.