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

Marianne E Pavel, John D Hainsworth, Eric Baudin, Marc Peeters, Dieter Hörsch, Robert E Winkler, Judith Klimovsky, David Lebwohl, Valentine Jehl, Edward M Wolin, Kjell Öberg, Eric Van Cutsem, James C Yao, for the RADIANT-2 Study Group

Summary

Background **Everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), has shown antitumour activity in patients with advanced pancreatic neuroendocrine tumours. We aimed to assess the combination of everolimus plus octreotide long-acting repeatable (LAR) in patients with low-grade or intermediate-grade neuroendocrine tumours (carcinoid).**

Methods **We did a randomised, double-blind, placebo-controlled, phase 3 study comparing 10 mg per day oral everolimus with placebo, both in conjunction with 30 mg intramuscular octreotide LAR every 28 days. Randomisation was by interactive voice response systems. Participants were aged 18 years or older, with low-grade or intermediate-grade advanced (unresectable locally advanced or distant metastatic) neuroendocrine tumours, and disease progression established by radiological assessment within the past 12 months. Our primary endpoint was progression-free survival. Adjusted for two interim analyses, the prespecified boundary at final analysis was p≤0·0246. This study is registered at ClinicalTrials.gov, number NCT00412061.**

Findings **429 individuals were randomly assigned to study groups; 357 participants discontinued study treatment and one was lost to follow-up. Median progression-free survival by central review was 16·4 (95% CI 13·7–21·2) months in the everolimus plus octreotide LAR group and 11·3 (8·4–14·6) months in the placebo plus octreotide LAR group (hazard ratio 0·77, 95% CI 0·59–1·00; one-sided log-rank test p=0·026). Drug-related adverse events (everolimus plus octreotide LAR *vs* placebo plus octreotide LAR) were mostly grade 1 or 2, and adverse events of all grades included stomatitis (62% *vs* 14%), rash (37% *vs* 12%), fatigue (31% *vs* 23%), and diarrhoea (27% *vs* 16%).**

Interpretation **Everolimus plus octreotide LAR, compared with placebo plus octreotide LAR, improved progression-free survival in patients with advanced neuroendocrine tumours associated with carcinoid syndrome.**

Funding **Novartis Pharmaceuticals.**

Lancet 2011; 378: 2005–12

Published Online November 25, 2011 DOI:10.1016/S0140-6736(11)61742-X

See Comment page 1978

Charité-Universitätsmedizin Berlin/Campus Virchow Klinikum, Berlin, Germany (Prof M E Pavel MD); **Sarah Cannon Research Institute, Nashville, TN, USA** (Prof J D Hainsworth MD); **Oncologie Endocrinienne et Médecine Nucléaire, Institut Gustave Roussy, Villejuif, France** (E Baudin MD); **Department of Oncology, Antwerp University Hospital, Edegem, Belgium** (Prof M Peeters MD); **Klinik für Innere Medizin, Gastroenterologie und Endokrinologie, Zentrum für Neuroendokrine Tumore, Zentralklinik Bad Berka GmbH, Bad Berka, Germany** (Prof D Hörsch MD); **Ochsner Kenner Medical Center, Kenner, LA, USA (DH); Novartis Oncology, Florham Park, NJ, USA** (R E Winkler MD, J Klimovsky MD, D Lebwohl MD); **Novartis Pharma AG, Basel, Switzerland** (V Jehl MSc); **Cedars Sinai Medical Center, Los Angeles, CA, USA** (E M Wolin MD); **Department of Endocrine Oncology, University Hospital, Uppsala, Sweden** (Prof K Öberg MD); **University Hospital Gasthuisberg, Leuven, Belgium** (Prof E Van Cutsem MD); **and University of Texas MD Anderson Cancer Center, Houston, TX, USA** (J C Yao MD)

Correspondence to: Dr James C Yao, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Box 426, Houston, TX 77030, USA **jyao@mdanderson.org**

Introduction

Neuroendocrine tumours, also known as carcinoids, are uncommon tumours arising from various primary sites.[1] Nearly 50% of patients with neuroendocrine tumours have metastatic disease, and 65% will die within 5 years of diagnosis.[1] The 5 year survival rate for patients with advanced neuroendocrine tumours is greater for patients with well differentiated (low or intermediate grade) versus poorly differentiated tumours and locoregional versus distant disease.[1] Survival also varies by primary site; in patients with low-grade or intermediate-grade histology and distant disease, lung and colon are associated with the worst median survival (17 and 7 months, respectively), and jejunum, ileum, and caecum are associated with the best (55–65 months).[1]

Somatostatin analogues, such as octreotide and lanreotide, improve the hormone-related symptoms associated with neuroendocrine tumours. Furthermore, octreotide long-acting repeatable (LAR) has also shown antitumour activity, prolonging time to disease progression in patients with midgut neuroendocrine tumours.[2,3] No approved antitumour drugs are available for treating progressive disease in patients with gastrointestinal or lung neuroendocrine tumours.

Overactivation of the mammalian target of rapamycin (mTOR), a serine-threonine kinase that regulates cell growth, proliferation, metabolism, and angiogenesis, has been implicated in the pathogenesis of neuroendocrine tumours.[4–7] Autocrine activation of the mTOR signalling pathway, mediated through insulin-like growth factor I, has been associated with neuroendocrine tumour cell proliferation,[8] and inhibition of the mTOR pathway has shown antiproliferative effects in cell lines of neuroendocrine tumours[9,10] and primary cultures of human neuroendocrine tumours.[11] Everolimus, an oral inhibitor of mTOR, showed promising antitumour activity in advanced neuroendocrine tumours in two phase 2 studies.[12,13] Recently, everolimus showed a 6·4 month increase in progression-free survival compared with placebo in patients with advanced pancreatic

neuroendocrine tumours.[14] However, the role of everolimus in neuroendocrine tumours of other primary sites or in combination with other drugs has not been studied extensively. Combination therapy with everolimus plus octreotide LAR might enhance antitumour efficacy by simultaneously targeting upstream and downstream components of the mTOR pathway (webappendix p 1).[15,16]

See Online for webappendix

We aimed to establish whether 10 mg per day everolimus plus 30 mg octreotide LAR every 28 days compared with placebo plus 30 mg octreotide LAR every 28 days prolongs progression-free survival in patients with well differentiated or moderately differentiated advanced neuroendocrine tumours (carcinoid tumours) and a history of flushing, diarrhoea, or both.

Methods

Participants

Between Jan 10, 2007, and April 2, 2010, we did a multicentre, double-blind, phase 3 study in Australia, Belgium, Canada, Czech Republic, Finland, France, Germany, Greece, Israel, Italy, Netherlands, Slovakia, Spain, Sweden, Turkey, and the USA. We judged the participants eligible if they were aged 18 years or older, had low-grade or intermediate-grade advanced (unresectable locally advanced or distant metastatic) neuroendocrine tumours, and disease progression established by radiological assessment within the past 12 months. Our other key eligibility criteria were history of secretory symptoms (diarrhoea or flushing) attributable to carcinoid syndrome; presence of measurable disease according to Response Evaluation Criteria In Solid Tumors version 1.0 (RECIST; webappendix pp 39–40 [amended protocol pp 38–39]);[17] WHO performance status of 2 or less;[18] adequate bone marrow, renal, and hepatic function; and adequately controlled lipid concentrations. Patients were ineligible if they had poorly differentiated or high-grade neuroendocrine carcinomas.

All participants provided written informed consent. Our protocol was approved by the institutional review board or ethics committee at each participating centre. Our study was done in accordance with Good Clinical Practice and the Declaration of Helsinki. Our study was monitored by an independent data monitoring committee and overseen by the protocol steering committee.

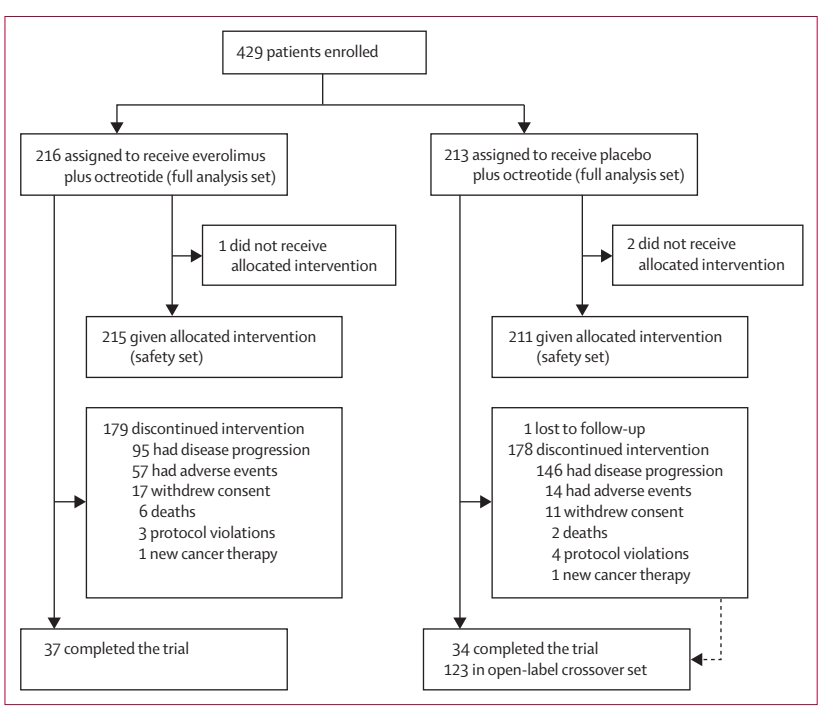


Figure 1: **Trial profile**

Randomisation and masking

Randomisation was by interactive voice response systems. Study group assignments were masked from participants and investigators, but disclosure was permitted in cases of investigator-documented disease progression according to RECIST. Participants assigned to placebo plus octreotide LAR could cross over to open-label everolimus plus octreotide LAR after disease progression was established by the investigator.

Procedures

We randomly assigned participants (1:1) to receive treatment with 10 mg oral everolimus once daily or matching placebo, both in conjunction with intramuscular 30 mg octreotide LAR every 28 days. Treatment continued until disease progression, withdrawal from treatment because of adverse events, or withdrawal of consent. Dose adjustments were permitted for safety (webappendix pp 43–44 [amended protocol pp 42–43]).

Our primary endpoint was progression-free survival according to RECIST, defined as time from random assignment to first recorded disease progression or death from any cause. Progression-free survival for our primary analysis was established by an adjudicated central review. Adjudication was done by an independent committee—from which treatment allocation was masked—assessing any discrepancies in event type or timing between local and central radiology review. Investigator-assessed progression-free survival was done as a key supportive analysis. Our secondary endpoints were objective response rate (according to RECIST), overall survival, changes from baseline in 5-hydroxyindoleacetic acid and chromogranin A concentrations, and safety.

We assessed efficacy in our full analysis set, composed of all patients randomly assigned to a study group. Tumour measurements (assessed by multiphasic CT or MRI) were done at baseline and repeated every 12 weeks.

We collected serum chromogranin A and 24 h urine samples for 5-hydroxyindoleacetic acid at baseline and, if raised (greater than the upper limit of normal) we repeated the collection on day 1 of each subsequent cycle (webappendix p 248).

In our safety population we included all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Safety assessments included monitoring of adverse events, vital signs, physical examinations every 4 weeks, chest radiograph every 12 weeks, and regular monitoring of haematological and clinical biochemistry values (laboratory assessments). We classified adverse events in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0.

Statistical analysis

We based our estimates of sample size on the ability to detect a clinically meaningful prolongation of progression-free survival, which we defined as a 33% reduction in the risk for disease progression or death (hazard ratio [HR] for progression or death 0·67), corresponding to a prolongation in median progression-free survival from 9 months with placebo plus octreotide LAR to 13·5 months with everolimus plus octreotide LAR. With a uniform accrual of 29 patients per month over 60 weeks and a minimum follow-up of 90 weeks, we needed 350 patients to obtain 287 progression-free survival events, which would yield 92·2% power with the use of an unstratified log-rank test at a one-sided significance level of 2·5%. With an estimated 10% of patients lost to follow-up, we targeted a total sample size of 390 patients. However, because of a loss of central radiology progression-free survival events (informative censoring), our study was amended to end on a date that allowed for a minimum follow-up of about 2 years in randomly assigned patients (April 2, 2010) irrespective of the available number of events. Adjusted for two interim analyses and the final number of progression-free survival events recorded, the significance boundary on the p-value scale at final analysis was 0·0246.

We assessed progression-free and overall survival with Kaplan-Meier methods and we compared study groups with log-rank tests. We calculated HRs and corresponding CIs with a Cox proportional hazards model. We used a prespecified marginal structural Cox proportional hazards model with the inverse probability of censoring weights (IPCW) method to assess for potential bias related to informative censoring (webappendix pp 249–251). We defined chromogranin A and 5-hydroxyindoleacetic acid responses as normalisation or a 50% or greater reduction from baseline. We described responses by treatment group, and we assessed changes from baseline over time with a mixed-effects model, including treatment, time, and the interaction term between time and treatment as fixed effects, baseline measurements as covariates, and patient as random effect. The protocol, including the statistical analysis plan, is available in the webappendix (pp 2–247). This study is registered at ClinicalTrials.gov, number NCT00412061.

Role of the funding source

The study was designed by the academic investigators and by representatives of the sponsor. Data were collected with the use of the sponsor's data management systems

For the **Common Terminology Criteria for Adverse Events** see http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

	Everolimus plus octreotide LAR group (n=216)	Placebo plus octreotide LAR group (n=213)
Median age, years (range)	60 (22–83)	60 (27–81)
Number of women	119 (55%)	89 (42%)
Number of men	97 (45%)	124 (58%)
WHO performance status*		
0	118 (55%)	140 (66%)
1	84 (39%)	62 (29%)
2	14 (6%)	10 (5%)
Primary site of cancer		
Small intestine	111 (51%)	113 (53%)
Lung	33 (15%)	11 (5%)
Colon	14 (6%)	14 (7%)
Pancreas	11 (5%)	15 (7%)
Liver	7 (3%)	11 (5%)
Other	40 (19%)	48 (23%)
Missing	0	1 (0·5%)
Histological grade		
Well differentiated	166 (77%)	175 (82%)
Moderately differentiated	38 (18%)	30 (14%)
Poorly differentiated	1 (0·5%)	1 (0·5%)
Unknown	11 (5%)	6 (3%)
Missing	0	1 (0·5%)
Current tumour-related symptoms†	170 (79%)	172 (81%)
Organ type involved‡		
Liver	198 (92%)	196 (92%)
Lymph nodes	80 (37%)	85 (40%)
Lung	64 (30%)	52 (24%)
Bone	35 (16%)	24 (11%)
Other	103 (48%)	103 (48%)
Time since initial diagnosis		
≤6 months	15 (7%)	23 (11%)
>6 months to ≤2 years	45 (21%)	53 (25%)
>2 years to ≤5 years	68 (31%)	51 (24%)
>5 years to ≤10 years	60 (28%)	61 (29%)
>10 years	27 (13%)	23 (11%)
Missing	1 (0·5%)	2 (1%)
History of previous somatostatin analogue therapy	173 (80%)	166 (78%)
History of previous octreotide therapy	169 (78%)	152 (71%)
Mean duration of previous somatostatin analogue exposure, years (SD; range)	2·6 (2·49; 0·0–11·7)	2·6 (2·39; 0·0–12·5)
Other systemic antitumour drugs	99 (46%)	82 (38%)
Chemotherapy	75 (35%)	55 (26%)
Immunotherapy	27 (13%)	20 (9%)
Targeted therapy	15 (7%)	16 (8%)
Other	21 (10%)	28 (13%)

Data are n (%) unless otherwise stated. *Data missing for one patient in the placebo plus octreotide LAR group. †Defined as diarrhoea, flushing, or both. ‡Organs as per target and non-target lesion locations recorded at baseline by investigator.

Table 1: **Baseline demographics and disease characteristics**

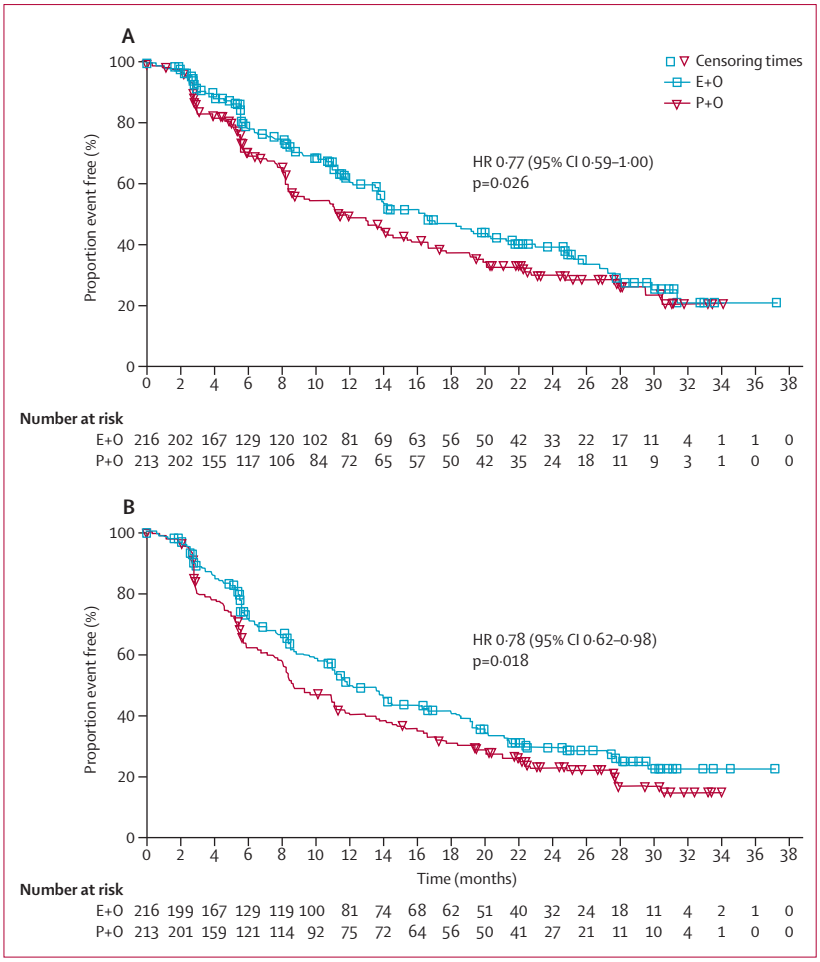


Figure 2: **Kaplan-Meier plots of progression-free events**
Assessed by central radiology review (A) and local investigator review (B). E+O=everolimus plus octreotide LAR. P+O=placebo plus octreotide LAR. HR=hazard ratio.

and were analysed by the sponsor's statistical team. All authors contributed to the interpretation of data and subsequent writing, reviewing, and amending of the report; the first draft of the report was prepared by the first author, the corresponding author, and a medical writer funded by Novartis. All authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan.

Results

Figure 1 shows the trial profile. 211 patients (98%) assigned to receive everolimus plus octreotide LAR and 204 (96%) assigned to receive placebo plus octreotide LAR had metastatic disease. There were imbalances in baseline demographic and disease characteristics favouring placebo plus octreotide LAR, including lung as primary tumour site, WHO performance status greater than 0, and previous use of chemotherapy (table 1). Both groups were similar with respect to history of previous treatment with somatostatin analogues given in accordance with site standard of care.

With a median follow-up of 28 months, the median duration of treatment was 37·0 weeks (range 1–163) in the everolimus plus octreotide LAR group and 36·6 (<1–152) in the placebo plus octreotide LAR group. Mean relative dose intensity (ratio of administered to planned doses) was 0·83 in the everolimus plus octreotide LAR group and 0·97 in the placebo plus octreotide LAR group. Dose reductions or temporary interruptions were needed by 140 patients (65%) in the everolimus plus octreotide LAR group and 74 (35%) in the placebo plus octreotide LAR group. At data cutoff, roughly equal proportions of patients in both groups remained on treatment; the primary reason for treatment discontinuation was disease progression (figure 1).

Median progression-free survival assessed by central review and based on 103 events in the everolimus plus octreotide LAR group and 120 in the placebo plus octreotide LAR group was 16·4 months (95% CI 13·7–21·2) in the everolimus plus octreotide LAR group and 11·3 (8·4–14·6) in the placebo plus octreotide LAR group. Everolimus plus octreotide LAR was associated with a 23% reduction in the estimated risk for progression (figure 2). Findings of the local investigator assessment, based on 128 events in the everolimus plus octreotide LAR group and 156 in the placebo plus octreotide LAR group), were consistent with the central review: 12·0 months (10·6–16·1) in the everolimus plus octreotide LAR group and 8·6 (8·1–11·1) in the placebo plus octreotide LAR group (figure 2). IPCW analysis confirmed the presence of informative censoring in the central assessment (treatment effect HR 0·60, 95% CI 0·44–0·84). Prespecified subgroup analyses showed a consistent benefit across most subgroups of patients. Treatment benefit with everolimus plus octreotide LAR was recorded irrespective of having or not having received previous chemotherapy and irrespective of WHO performance status, age, sex, tumour grade, and primary tumour site (figure 3). We also noted a benefit for everolimus plus octreotide LAR in the 47 patients in the everolimus plus octreotide LAR group and 61 in the placebo plus octreotide LAR group who had not been treated with octreotide LAR before study entry (median progression-free survival 25·2 months in the everolimus plus octreotide LAR group *vs* 11·3 in the placebo plus octreotide LAR group; HR 0·61, 95% CI 0·36–1·04). This might be attributable to a more substantial inhibition of the phosphoinositide 3-kinase/Akt/mTOR pathway, with everolimus and octreotide LAR inhibiting mTOR and the upstream insulin-like growth factor I autocrine loop, respectively.[15,16]

The combination of everolimus plus octreotide LAR offered patients with progressive advanced disease a 23% reduction in the relative risk of progression (HR 0·77; p=0·026). These findings were strongly supported by the local investigator-assessed analysis of progression-free

survival (HR 0·78; p=0·018) and IPCW analysis. Most adverse events associated with everolimus plus octreotide LAR were grade 1 or 2 and consistent with the known safety profile of these drugs.

Partial response as best overall response, assessed by central radiology review, was recorded in five patients in the everolimus plus octreotide LAR group and four patients in the placebo plus octreotide LAR group. Stable disease (best overall response) was evident in 182 patients (84%) in the everolimus plus octreotide LAR group and 172 (81%) in the placebo plus octreotide LAR group. Progressive disease was recorded in nine patients (4%) in the everolimus plus octreotide LAR group and 26 (12%) in the placebo plus octreotide LAR group. Of patients that could be assessed, 150 (75%) in the everolimus plus octreotide LAR group and 91 (45%) in the placebo plus octreotide LAR group experienced tumour shrinkage (figure 4).

Patients treated with everolimus plus octreotide LAR had higher proportions of chromogranin A and 5-hydroxyindoleacetic acid responses (75 [46%] of 164 and 85 [61%] of 140) compared with those treated with placebo plus octreotide LAR (53 [36%] of 146 and 76 [54%] of 141). Based on the mixed model, everolimus plus octreotide LAR resulted in greater reductions in serum chromogranin A (p treatment=0·0041) and urine 5-hydroxyindoleacetic acid (p treatment <0·0001) compared with placebo plus octreotide LAR (figure 5).

At disease progression, patients initially randomly assigned to receive placebo plus octreotide LAR were given the opportunity to cross over to open-label everolimus plus octreotide LAR, thus confounding a possible treatment-related survival benefit. 124 of the 213 patients initially assigned to receive placebo plus octreotide LAR crossed over. Of these patients, 123 (58%) also had an open-label safety assessment. Median overall survival was not reached at the time of our analysis, and we noted no significant difference between groups (HR 1·22, 95% CI 0·91–1·62). Adjusted for imbalances in baseline prognostic factors, the HR was 1·06 (0·79–1·43) (prespecified baseline covariates were age, sex, race, performance status, and previous somatostatin analogue use).

Most adverse events associated with everolimus plus octreotide LAR were grade 1 or 2 and consistent with the known safety profiles of these drugs (table 2). 18 patients in the everolimus plus octreotide LAR group and 11 in the placebo plus octreotide LAR group died within 28 days of the last intake of study drug. Of these deaths, six in the everolimus plus octreotide LAR group and six in the placebo plus octreotide LAR group were attributable to underlying cancer or disease progression. None of the remaining deaths (12 in the everolimus plus octreotide LAR group and five in the placebo plus octreotide LAR group) were deemed treatment related per investigator assessment. Drug-related adverse events led to study discontinuation in 40 patients (19%) in the everolimus plus octreotide LAR group and seven (3%) in the placebo plus octreotide LAR group.

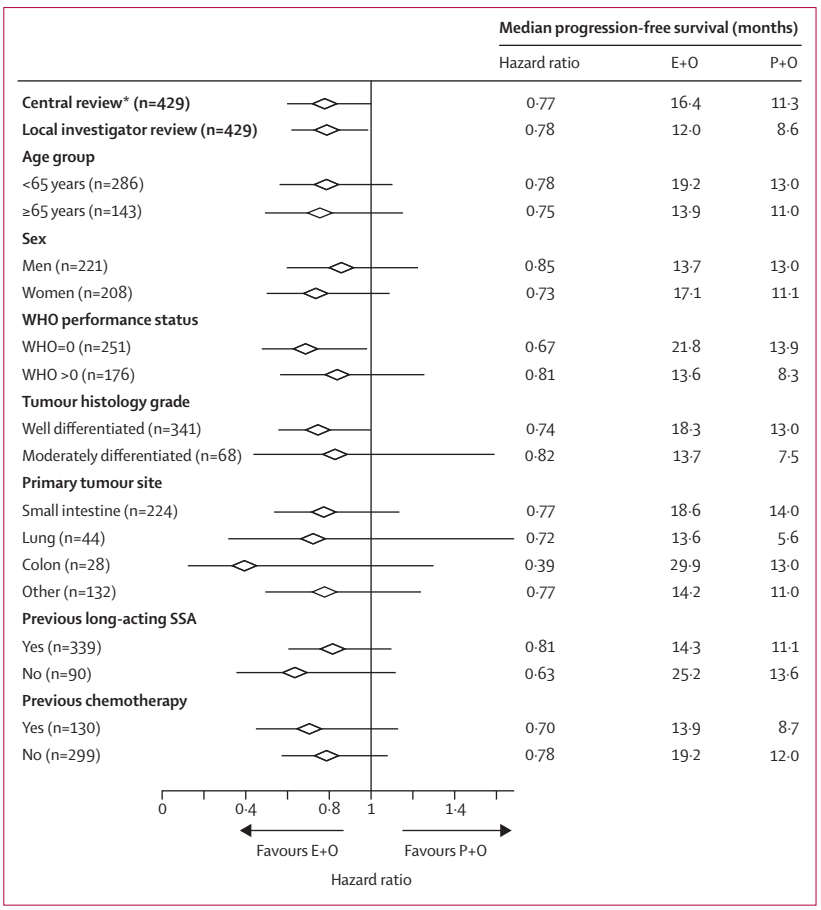
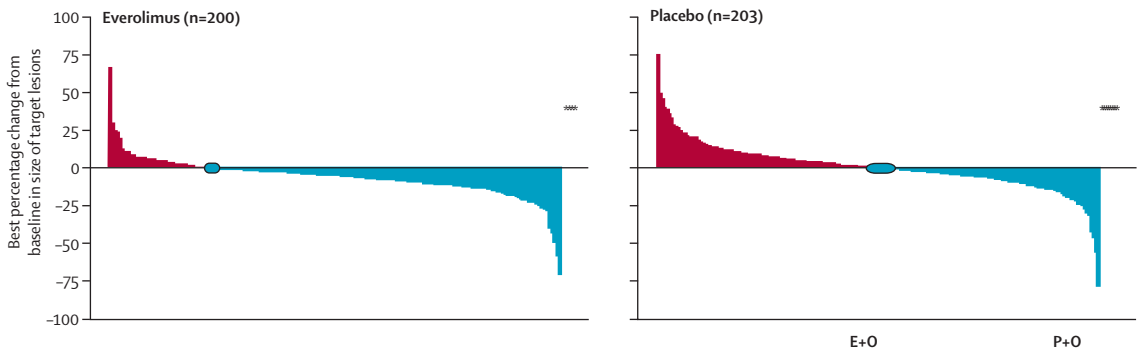


Figure 3: **Effect of study treatment on progression-free survival by subgroup**
Hazard ratio is everolimus plus octreotide LAR over placebo plus octreotide LAR, obtained by unstratified Cox model. E+O=everolimus plus octreotide LAR. P+O=placebo plus octreotide LAR. SSA=somatostatin analogue. *Independent adjudicated central review.

The most common drug-related adverse events of any grade were stomatitis, rash, fatigue, and diarrhoea (table 2). The most common grade 3 or 4 drug-related adverse events were stomatitis, fatigue, diarrhoea, hyperglycaemia, thrombocytopenia, and infections. The incidence of drug-related pneumonitis, a known issue with everolimus treatment, was 8% (18 patients) in the everolimus plus octreotide LAR group versus 0% in the placebo plus octreotide LAR group. Metabolic-related adverse events (drug related) included hyperglycaemia (table 2) and hypercholesterolaemia (12 patients [6%] in the everolimus plus octreotide LAR group *vs* three [1%] in the placebo plus octreotide LAR group). Serious adverse events were reported in 122 patients (57%) in the everolimus plus octreotide LAR group versus 73 (35%) in the placebo plus octreotide LAR group, and, of these patients, 41 (19%) versus nine (4%) reported treatment-related effects. The most commonly reported drug-related serious adverse events included diarrhoea (four patients



	E+O	P+O
Increase in size of target lesions from baseline	43 (22%)	94 (46%)
No change in size of target lesions from baseline	3 (2%)	10 (5%)
Decrease in size of target lesions from baseline	150 (75%)	91 (45%)
Change in size of target lesion was available but contradicted by overall lesion response of progressive disease	4 (2%)	8 (4%)

Figure 4: **Best percentage change from baseline in size of target lesion**
We did not include data on 16 patients in the everolimus plus octreotide group and 10 in the placebo plus octreotide LAR group in our analysis because one patient in the everolimus group showed a change in the available target lesion, although the overall response was unknown, and because change in the target lesion could not be assessed in 15 patients in the everolimus plus octreotide LAR group and 10 in the placebo plus octreotide LAR group. Additionally, four patients in the everolimus plus octreotide LAR group (2%) and eight in the placebo plus octreotide LAR group (4%) showed changes in the available target lesion contradicted by progressive disease as overall response (marked as * in the graph). E+O=everolimus plus octreotide LAR. P+O=placebo plus octreotide LAR.

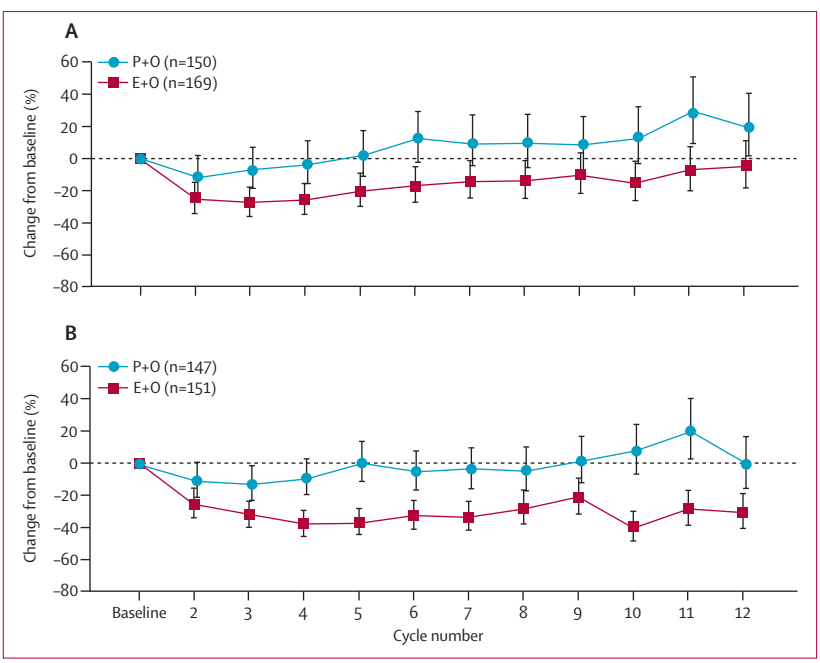


Figure 5: **Changes in biomarker concentrations over time by treatment group**
Least square estimated fold changes over baseline and associated 95% CIs derived from a mixed model are shown for serum chromogranin A (A) and 24 h urinary 5-hydroxyindoleacetic acid concentrations (B). We include only patients with raised biomarker concentrations (ie, greater than the upper limit of normal) at baseline. E+O=everolimus plus octreotide LAR. P+O=placebo plus octreotide LAR.

[2%] *vs* one [1%]), interstitial lung disease (three [1%] *vs* none), and thrombocytopenia (three [1%] *vs* none). The most commonly reported adverse events leading to discontinuation of treatment with everolimus plus octreotide LAR were fatigue (five patients; 2%), diarrhoea (four; 2%), general physical health deterioration (four; 2%), interstitial lung disease (four; 2%), and pneumonia (four; 2%).

	Everolimus plus octreotide LAR group (n=215)		Placebo plus octreotide LAR group (n=211)	
	All grades	Grades 3 and 4	All grades	Grades 3 and 4
Stomatitis*	133 (62%)	14 (7%)	29 (14%)	0
Rash	80 (37%)	2 (1%)	26 (12%)	0
Fatigue	67 (31%)	14 (7%)	49 (23%)	6 (3%)
Diarrhoea	59 (27%)	13 (6%)	33 (16%)	5 (2%)
Nausea	42 (20%)	1 (0·5%)	34 (16%)	2 (1%)
Infections†	42 (20%)	11 (5%)	13 (6%)	1 (0·5%)
Dysgeusia	36 (17%)	1 (0·5%)	7 (3%)	0
Anaemia	33 (15%)	3 (1%)	10 (5%)	0
Decreased weight	32 (15%)	1 (0·5%)	7 (3%)	0
Thrombocytopenia	30 (14%)	10 (5%)	0	0
Decreased appetite	29 (13%)	0	13 (6%)	0
Peripheral oedema	28 (13%)	0	7 (3%)	0
Hyperglycaemia	26 (12%)	11 (5%)	4 (2%)	1 (0·5%)
Dyspnoea	26 (12%)	4 (2%)	3 (1%)	0
Pulmonary events‡	25 (12%)	5 (2%)	0	0
Vomiting	23 (11%)	1 (0·5%)	11 (5%)	1 (0·5%)
Pruritus	23 (11%)	0	8 (4%)	0
Asthenia	22 (10%)	2 (1%)	14 (7%)	1 (0·5%)

*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †Includes all infections. ‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 2: **Drug-related adverse events in at least 10% of patients (safety set)**

Discussion

Our findings show that median progression-free survival was greater in the everolimus plus octreotide LAR group than the placebo plus octreotide LAR group. Treatment

of advanced neuroendocrine tumours remains a clinical challenge because of the lack of effective options and the absence of well controlled randomised clinical trial data to support evidence-based practice. With few exceptions, chemotherapeutic drugs are not active in advanced non-pancreatic neuroendocrine tumours and are associated with substantial toxic effects. Thus, there is a need for new treatment options (panel).

Neuroendocrine tumours arise from various primary sites: primarily the small intestine, other sites of the gastrointestinal tract, and the lung.[19,20] The variable clinical course of advanced neuroendocrine tumours presents a major challenge for designing studies of appropriate power and duration.[21] Patients with neuroendocrine tumours often develop many metastases. Variability in the assessment of these metastases and potential differences in target lesion selection can result in discrepancies between local and central reviews,[22] presenting a challenge in assessing tumour response or progression during clinical trials. Discrepancies in radiological assessment between local and central reviews have resulted in loss of events and informative censoring in our trial. Informative censoring violates assumptions underlying the standard time-to-event analysis method and might obscure the progression-free survival treatment-effect estimate by central review.[23,24] The findings of our prespecified IPCW analysis done to assess this issue suggested that there was informative censoring, confounding the statistical interpretation of our primary endpoint analysis.

We previously showed that everolimus, with or without octreotide LAR, can be safely given to patients with advanced pancreatic neuroendocrine tumours.[12–14] Our present findings show that everolimus plus octreotide LAR compared with placebo plus octreotide LAR was associated with a clinically meaningful 5·1 month increase in median progression-free survival in patients with progressive advanced neuroendocrine tumours associated with a history of secretory symptoms. Consistent with these findings, treatment with everolimus plus octreotide LAR was associated with tumour shrinkage and stabilisation and significant reduction in biochemical markers of neuroendocrine tumours.

We did not collect outcomes reported by patients because we did not require them to have refractory symptoms at the time of study entry, as evidenced by the high number of patients who had a WHO performance status of 0 at the time of study entry, and because patients were allowed to receive octreotide LAR during the study for symptom control. Our study was not designed to assess the effect of everolimus on carcinoid-related symptoms.

Our study was affected by several factors, including inherent radiological challenges associated with the assessment of advanced neuroendocrine tumours, biological and clinical diversity of the population of patients, imbalances in baseline factors, and crossover design. Imbalances between study groups were noted in important prognostic baseline covariates, including primary tumour site, WHO performance status, and previous use of chemotherapy, all of which favoured the placebo plus octreotide LAR group and probably affected the primary outcome results. Despite this imbalance, everolimus was associated with a benefit on progression-free survival overall and across patient subgroups.

Our findings showing the efficacy of everolimus plus octreotide LAR in advanced neuroendocrine tumours are important because of the lack of effective anticancer treatment options. Efficacy of everolimus in this population will need confirmation in a future study. Together with clear evidence of benefit from the recently completed RADIANT-3[14] trial of everolimus in patients with advanced pancreatic neuroendocrine tumours, our data support the efficacy of everolimus in a broad spectrum of advanced neuroendocrine tumours.

Panel: Research in context

Systematic review

We searched Medline for reports on clinical trials in advanced neuroendocrine tumours, with "mTOR" and "NET" as our primary search terms. We did not limit our search by date. We identified no previous randomised studies of mTOR inhibitors in the present population.

Interpretation

Evidence-based treatment of neuroendocrine tumours is a challenge to clinicians because of the lack of reliable data from large clinical trials. No approved antitumour drugs are available for treating progressive disease in patients with gastrointestinal or lung neuroendocrine tumours, consequently affecting the survival of patients. Therefore, our findings that show the efficacy of the mTOR inhibitor everolimus plus octreotide LAR in advanced neuroendocrine tumours are important. These data support the efficacy of everolimus for the treatment of patients with a broad spectrum of advanced neuroendocrine tumours.

Contributors

MEP, JDH, and EB recruited patients, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. MP interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. DH provided substantial clinical data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. REW served as medical monitor, collected the data, analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. JK and VJ analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. DL designed the study, analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. EMW designed the study, recruited patients, collected the data, analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. KO designed the study, analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. EVC recruited patients, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft. JCY conceived and designed the study, recruited patients, collected the data, analysed the data, interpreted the data, wrote the report, reviewed the drafts, and approved the final draft.

Trial investigators

Australia D Morris, P Mainwaring, D Wyld, T Price; *Belgium* I Borbath, J-L Van Laethem; *Canada* J Maroun, L Siu, L Sideris, M Moore, R Letourneau; *Czech Republic* P Vitek, O Louthan, J Novotny; *Finland* M Valimaki; *France* G Cadiot, J A Chayvialle, S Dominguez, B Goichot, R Guimbaud, C Lepage, P Rougier, P Ruszniewski, J F Seitz, M Ychou; *Germany* C Auernhammer, M Blaker, J Schmoll, B Wiedenmann; *Greece* G Kaltsas, G Nikou; *Israel* D Gross, I Shimon; *Italy* E Bajetta, P Tomassetti, N Fazio, G Luppi, S Ricci, S Siena, F Santeusanio; *Netherlands* E De Vries, W W De Herder; *Slovakia* S Kinova; *Spain* D Castellano, J Sastre; *Sweden* B Eriksson; *Turkey* S Yalcin, N Aykan; *USA* J Beck, J Brell, T Dragovich, G Eckhardt, T Hobday, N LoConte, L Kvols, A Maniam, A Montero, T O'Dorisio, J Picus, S Williamson, E Chiorean, J Hamm, M Pipas, J Hecht, D Slater, T Larimore, S DelPrete, T Ryan, M Morse, P Byeff, B Baltz, P Engstrom, C Becerra, D Richards, L White Jr, A Cohn, N Neubauer, L DeMarco, P Conkling, W Edenfield, B Hellerstedt, D Loesch, R Raju, D Smith, R Ruxer, T Cartwright.

Conflicts of interest

MEP has served as a consultant and has received honoraria and research funding from Novartis. EB has received honoraria or research funding from Novartis. MP has received research funding and is on the speaker's bureau for Novartis. DH is a consultant to and has received honoraria and research funding from Novartis. REW, JK, DL, and VJ are employees of and own shares in Novartis. EMW is a consultant to Novartis. KO serves on advisory boards of and receives honoraria from Novartis, Pfizer, and Ipsen. EVC has received research funding from Novartis. JCY is a consultant to Novartis and has received research funding from Novartis. JDH declares no conflicts of interest.

Acknowledgments

We thank the participating patients and their families; the worldwide network of research nurses, trial coordinators, and operations staff for their contributions; and Zenta Tsuchihashi, Jeremie Lebrec, and Azzeddine Cherfi for biomarker analyses, and Kathy Covino for assistance with the preparation of the report.

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 Saltz L, Trochanowski B, Buckley M, et al. Octreotide as an antineoplastic agent in the treatment of functional and nonfunctional neuroendocrine tumors. *Cancer* 1993; **72:** 244–48.

3 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.

4 O'Reilly T, McSheehy PM. Biomarker development for the clinical activity of the mTOR inhibitor everolimus (RAD001): processes, limitations, and further proposals. *Translational Oncol* 2010; **3:** 65–79.

5 Meric-Bernstam F, Gonzalez-Angulo AM. Targeting the mTOR signaling network for cancer therapy. *J Clin Oncol* 2009; **27:** 2278–87.

6 Faivre S, Kroemer G, Raymond E. Current development of mTOR inhibitors as anticancer agents. *Nat Rev Drug Discov* 2006; **5:** 671–88.

7 Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer* 2004; **4:** 335–48.

8 von Wichert G, Jehle PM, Hoeflich A, et al. Insulin-like growth factor-I is an autocrine regulator of chromogranin A secretion and growth in human neuroendocrine tumor cells. *Cancer Res* 2000; **60:** 4573–81.

9 Moreno A, Akcakanat A, Munsell MF, Soni A, Yao JC, Meric-Bernstam F. Antitumor activity of rapamycin and octreotide as single agents or in combination in neuroendocrine tumors. *Endocr Relat Cancer* 2008; **15:** 257–66.

10 Missiaglia E, Dalai I, Barbi S, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. *J Clin Oncol* 2010; **28:** 245–55.

11 Zatelli MC, Minoia M, Martini C, et al. Everolimus as a new potential antiproliferative agent in aggressive human bronchial carcinoids. *Endocr Relat Cancer* 2010; **17:** 719–29.

12 Yao JC, Lombard-Bohas C, Baudin E, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. *J Clin Oncol* 2010; **28:** 69–76.

13 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 trial. *J Clin Oncol* 2008; **26:** 4311–18.

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

15 O'Reilly KE, Rojo F, She QB, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. *Cancer Res* 2006; **66:** 1500–08.

16 Pollak MN, Polychronakos C, Guyda H. Somatostatin analogue SMS 201-995 reduces serum IGF-I levels in patients with neoplasms potentially dependent on IGF-I. *Anticancer Res* 1989; **9:** 889–91.

17 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.

18 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5:** 649–55.

19 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 disgestive system, 4th edn. Lyon: International Agency for Research on Cancer, 2010: 13–14.

20 Asamura H, Kameya T, Matsuno Y, et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. *J Clin Oncol* 2006; **24:** 70–76.

21 Durante C, Boukheris H, Dromain C, et al. Prognostic factors influencing survival from metastatic (stage IV) gastroenteropancreatic well-differentiated endocrine carcinoma. *Endocr Relat Cancer* 2009; **16:** 585–97.

22 Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. *J Clin Oncol* 2011; **29:** 934–43.

23 Dodd LE, Korn EL, Freidlin B, et al. Blinded independent central review of progression-free survival in phase III clinical trials: important design element or unnecessary expense? *J Clin Oncol* 2008; **26:** 3791–96.

24 Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. *J Clin Oncol* 2009; **27:** 2874–80.