Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Marianne E Pavel, Simron Singh*, Jonathan R Strosberg, Lida Bubuteishvili-Pacaud, Evgeny Degtyarev, Maureen P Neary, Carlo Carnaghi, Jiri Tomasek, Edward Wolin, Markus Raderer, Harald Lahner, Juan W Valle, Rodney Pommier, Eric Van Cutsem, Margot E T Tesselaar, Gianfranco Delle Fave, Roberto Buzzoni, Matthias Hunger, Jennifer Eriksson, David Cella, Jean-François Ricci, Nicola Fazio, Matthew H Kulke, James C Yao*

Summary

Background In the phase 3 RADIANT-4 trial, everolimus increased progression-free survival compared with placebo in patients with advanced, progressive, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (NETs). We now report the health-related quality of life (HRQOL) secondary endpoint.

Methods RADIANT-4 is a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial done in 97 centres in 25 countries worldwide. Adults (aged ≥18 years) were eligible for the study if they had pathologically confirmed, advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1 or 2) NETs of lung or gastrointestinal origin. Patients were randomly allocated (2:1) using block randomisation (block size of three) by an interactive voice response system to receive oral everolimus (10 mg per day) or placebo, both with best supportive care, with stratification by tumour origin, WHO performance status, and previous somatostatin analogue treatment. HRQOL was assessed with the Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire at baseline (visit 2, day 1), every 8 weeks (±1 week) during the study for the first 12 months after randomisation, and every 12 weeks thereafter until study drug discontinuation. The primary endpoint, reported previously, was progression-free survival assessed by central review; HRQOL was a prespecified secondary endpoint. The prespecified secondary outcome measure was time to definitive deterioration (≥7 points) in FACT-G total score. Analyses were done on the full analysis set, consisting of all randomised patients, by intention to treat. Only data obtained while receiving the randomly allocated treatment were included in this analysis. Enrolment for RADIANT-4 was completed on Aug 23, 2013, but the trial is ongoing pending final analysis of the key secondary endpoint of overall survival. This trial is registered with ClinicalTrials.gov, number NCT01524783.

Findings Between April 3, 2012, and Aug 23, 2013, 302 patients were enrolled; 205 were randomly allocated everolimus and 97 were assigned placebo. At baseline, 193 (94%) of 205 patients assigned everolimus and 95 (98%) of 97 allocated placebo had completed either fully or partly the FACT-G questionnaire; at week 48, 70 (83%) of 84 patients assigned everolimus and 22 (85%) of 26 allocated placebo completed FACT-G. Median time to definitive deterioration in FACT-G total score was 11·27 months (95% CI 9·27–19·35) with everolimus and 9·23 months (5·52–not estimable) with placebo (adjusted hazard ratio 0·81, 95% CI 0·55–1·21; log-rank p=0·31).

Interpretation HRQOL was maintained for patients with advanced, non-functional, gastrointestinal or lung NETs, with no relevant differences noted between the everolimus and placebo groups. In view of the previous RADIANT-4 findings of longer progression-free survival with everolimus, our findings suggest that everolimus delays disease progression while preserving overall HRQOL, even with the usual toxic effects related to active targeted drug treatment for cancer.

Funding Novartis Pharmaceuticals.

Introduction

Neuroendocrine tumours (NETs) are biologically and clinically heterogeneous tumours that arise from neuroendocrine cells throughout the body, mainly from the gastrointestinal tract and lungs. Most NETs are non-functional, meaning that they are not associated with symptoms of hormonal hypersecretion.[1] Most patients with NETs are diagnosed at a late stage of the disease.[2] Median overall survival for patients with metastatic well-differentiated NETs varies substantially by tumour origin, ranging from 14 months for cancers originating in the colon to 103 months for disease

Lancet Oncol 2017

Published Online
August 21, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30471-0

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(17)30618-6

*Co-primary authors

Department of Hepatology and Gastroenterology, Charité Universitätsmedizin Berlin, Campus Virchow-Klinikum, Berlin, Germany (M E Pavel MD); **Department of Medicine 1, Division of Endocrinology, Universitätsklinikum Erlangen, Erlangen, Germany** (M E Pavel); **Division of Medical Oncology & Hematology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada** (S Singh MD); **Department of Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, FL, USA** (J R Strosberg MD); **Novartis Pharma AG, Basel, Switzerland** (L Bubuteishvili-Pacaud MD, E Degtyarev MSc); **Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA** (M P Neary PhD); **Oncology Unit, Humanitas Clinical and Research Centre, Rozzano, Italy** (C Carnaghi MD); **Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Faculty of Medicine, Masaryk University, Brno, Czech Republic** (J Tomasek MD); **Department of Medical Oncology, Montefiore Einstein Center for Cancer Care, Bronx, NY, USA** (E Wolin MD); **Department of Internal Medicine I, Division of Oncology, Klinik f Innere Medizin I, AKH, Vienna, Austria** (M Raderer MD); **Klinik für**

Endokrinologie und Stoffwechselerkrankungen, Universitaetsklinikum Essen, Zentrum f Innere Medizin, Essen, Germany (H Lahner MD); **Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, and Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK** (J W Valle MD); **Division of Surgical Oncology, Oregon Health & Science University, Portland, OR, USA** (R Pommier MD); **University Hospitals Leuven, and KU Leuven, Digestive Oncology, Leuven, Belgium** (E Van Cutsem MD); **Department of Medical Oncology, Antoni van Leeuwenhoek, Amsterdam, Netherlands** (M E T Tesselaar MD); **Medical-Surgical Sciences and Translational Medicine, Azienda Ospedaliera Sant'Andrea – Università La Sapienza, Rome, Italy** (G Delle Fave MD); **S C Day Hospital e Terapia Ambulatoriale Oncologica, Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan, Italy** (R Buzzoni MD); **Mapi, Munich, Germany** (M Hunger PhD); **Mapi, Stockholm, Sweden** (J Eriksson MSc); **Department of Medical Social Sciences, Northwestern University, Chicago, IL, USA** (D Cella PhD); **Wellmera AG, Basel, Switzerland** (J-F Ricci PhD); **Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy** (N Fazio MD); **Medical Oncology and Solid Tumor Oncology, Dana Farber Cancer Institute, Boston, MA, USA** (M H Kulke MD); **and Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center, Houston, TX, USA** (J C Yao MD)

Correspondence to:
Dr Simron Singh, Division of Medical Oncology & Hematology, Sunnybrook Odette Cancer Center, Toronto, ON M4N 3M5, Canada
simron.singh@sunnybrook.ca

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 1990, and Jan 13, 2017, with the terms: "neuroendocrine tumors" OR "neuroendocrine tumours"; "health-related quality of life" OR "quality of life"; "EQ-5D"; "association" OR "correlation"; "disease progression" OR "progression-free survival"; AND "oncology" OR "cancer" OR "tumor" OR "tumour". Our search retrieved one study reporting health-related quality of life (HRQOL) and baseline and end-of-treatment utility values in patients with neuroendocrine tumours (NETs) treated with everolimus. However, the study had no control group; thus, it does not provide definite evidence on the effect of everolimus on HRQOL in NETs. Moreover, although three systematic literature reviews have been published on HRQOL in NETs, evidence is scant with respect to specific NET subtypes—eg, those of gastrointestinal and lung origin. We identified one publication on health status utilities for pre-progression and post-progression health states in NETs; however, these were derived from time trade-off experiments using health state vignettes rather than from HRQOL questionnaires administered to patients. We identified six further studies reporting that delayed disease progression is associated with improved HRQOL, but none were done in patients with NETs.

Added value of this study

We present a prespecified secondary analysis of HRQOL in the RADIANT-4 trial. To our knowledge, our analysis is the first to assess the effect of everolimus versus placebo on HRQOL in patients with NETs and the first to investigate the effect of disease progression on HRQOL and utilities in NETs. Time to definitive deterioration of the Functional Assessment of Cancer Therapy—General (FACT-G) total score (by ≥7 points) did not differ between the everolimus and placebo groups.

Implications of all the available evidence

Approval of everolimus by the US Food and Drug Administration and the European Medicines Agency in 2016 for the treatment of patients with progressive, well-differentiated, non-functional NETs of gastrointestinal or lung origin that are unresectable, locally advanced, or metastatic was based on data from RADIANT-4, showing longer progression-free survival with everolimus than with placebo. Together with our secondary findings from RADIANT-4, we provide potentially practice-changing evidence that everolimus delays disease progression while preserving overall HRQOL, even with the usual toxic effects related to active targeted drug treatment for cancer. As more treatments become available for NETs, with no evidence for optimum sequencing, the decline in HRQOL and utility after disease progression shows the importance of considering HRQOL, along with progression-free survival, as a meaningful and patient-relevant endpoint in clinical trials of advanced NETs.

originating in the small intestine.[3] Treatment goals for patients with unresectable or metastatic NETs include control of secretory symptoms (if the tumour is functional), control of tumour growth, improvement in survival, and preservation of health-related quality of life (HRQOL) for as long as possible.[4]

In addition to clinical benefit, assessment of patient-reported outcomes such as HRQOL is recognised as important to capture treatment-related and disease-related outcomes that are experienced directly by patients. Treatment-related toxic effects and pain caused by metastases or progressive disease can contribute to deterioration of HRQOL.[4] As new treatment options emerge for non-curable advanced NETs, maintenance of HRQOL is an important treatment goal, and studies on HRQOL can aid in treatment selection. HRQOL is also important for health technology assessment agencies, because it can be used as an assessment of health status (utility) in cost-effectiveness evaluations of new interventions.

Although generally considered a gold-standard endpoint, overall survival in clinical trials of NETs might take a long time to assess because of long-term survival of patients with NETs post progression.[5] Progression-free survival, a surrogate endpoint, is accepted increasingly in trials of NETs and has been recommended as a primary endpoint in clinical trials.[6] In a review of published literature, an association was noted between progression-free survival and overall survival in NETs,[7,8] but no formal study has investigated the possible effect of disease progression on HRQOL. The relation between HRQOL, utility, and tumour progression has been assessed in several other malignant diseases suggesting that delayed progression results in superior HRQOL; however, this association has not been shown in NETs, in which patients often have indolent disease and, thus, good WHO performance status before initiation of treatment.

Everolimus is a potent oral inhibitor of mTOR.[9] In the phase 3 RADIANT-4 trial,[10] in patients with advanced, progressive, non-functional NETs of lung and gastrointestinal origin, everolimus resulted in longer progression-free survival than did placebo treatment. Based on safety and efficacy data from RADIANT-4, everolimus was approved for the treatment of advanced, progressive, non-functional, well-differentiated NETs of gastrointestinal or lung origin by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2016.

A secondary endpoint of the RADIANT-4 study was to compare HRQOL and WHO performance status between treatment groups. Here, we report the results of these analyses and those investigating the extent to which disease progression, irrespective of treatment

assignment, is associated with a decline in HRQOL and utility scores.

Methods

Study design and participants

RADIANT-4 is a multicentre, randomised, double-blind, placebo-controlled, phase 3 study done in 97 centres in 25 countries worldwide (appendix pp 4–7).[10] Adult patients (aged ≥18 years) were eligible for the study if they had pathologically confirmed, advanced (unresectable or metastatic), non-functional, well-differentiated (grade 1 or grade 2) NETs of lung or gastrointestinal origin. Additional key inclusion criteria included: WHO performance status 0 or 1; adequate bone marrow function (absolute neutrophil count ≥1·5×10⁹ cells per L, platelets ≥100×10⁹ per L, and haemoglobin >9 g/dL); adequate liver function (total serum bilirubin ≤2·0 mg/dL, alanine aminotransferase and aspartate aminotransferase ≤2·5×the upper limit of normal [ULN; ≤5×ULN in patients with liver metastases], and international normalised ratio [INR] ≤2); adequate renal function (serum creatinine ≤1·5×ULN); and fasting serum cholesterol 300 mg/dL or lower and fasting triglycerides 2·5×ULN or lower. 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 in the study 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. We excluded patients who had previously received more than one line of chemotherapy, had been treated with mTOR inhibitors (sirolimus, temsirolimus, or everolimus), had hepatic intra-arterial embolisation within 6 months of randomisation, had undergone cryoablation or radiofrequency ablation of hepatic metastases within 2 months of randomisation, or had received chronic treatment with corticosteroids or other immunosuppressive agents. Based on data from a similar patients' population, the median life expectancy of patients enrolled was 35·2 months.[11]

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

Patients were randomly allocated (2:1) to receive either oral everolimus or placebo. Randomisation was done using block randomisation (block size of three) stratified by previous somatostatin analogue treatment (yes *vs* no), WHO performance status (0 *vs* 1), and tumour origin, which was based on prognostic level and grouped into two strata (stratum A [better prognosis: appendix, caecum, jejunum, ileum, duodenum, or NET of unknown primary origin] *vs* stratum B [worse prognosis: lung, stomach, colon other than caecum, or rectum]).

The trial was supported by Interactive Response Technology (IRT) for randomisation and medication management (IRT is maintained by Cenduit, Allschwil, Switzerland). To ensure that treatment assignment was unbiased and concealed from patients, investigator staff, Novartis field monitors, and the Novartis trial team, a patient randomisation list was produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomisation numbers. These numbers were linked to the two treatment groups, which in turn were linked to medication pack numbers that appeared on the study drug package. A separate medication randomisation list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to medication packs containing each of the study treatments. Before dosing, all patients who fulfilled all inclusion criteria (and did not meet exclusion criteria) were randomly allocated via IRT to one of the treatment groups. The investigator or designee called or logged on to the IRT and confirmed that the patient fulfilled all the inclusion criteria. The IRT assigned a randomisation number to the patient, which was used to link the patient to a treatment group and specified a unique medication pack number for the first package of study treatment to be dispensed to the patient. The randomisation number was not communicated to the caller.

See Online for appendix

Patients, investigators, and the study funder 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

Patients were given daily oral doses of 10 mg everolimus (two 5 mg tablets) or matching placebo as study drug. In both treatment groups, the study drug was combined with best supportive care. We assessed disease progression using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) with central radiological review every 8 weeks (±1 week) for the first 12 months and every 12 weeks thereafter, until documented disease progression or start of new antineoplastic therapy, whichever occurred first. We did additional tumour assessments if symptomatic evidence suggested the possibility of disease progression based on clinical symptoms or physical examination.

We allowed dose reductions and treatment interruption for a maximum of 28 days for patients who did not tolerate therapy or to manage adverse events that were judged by the investigator to be related to study treatment. We

allowed two dose reductions: from 10 mg to 5 mg per day and, subsequently, to 5 mg every other day. The study did not have a fixed treatment duration; treatment continued until documented radiological disease progression, start of new cancer 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.

We assessed HRQOL with the Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire, which comprises 27 items covering four dimensions of health: physical wellbeing, social or family wellbeing, emotional wellbeing, and functional wellbeing. Assessments were done at baseline (visit 2, day 1), every 8 weeks (±1 week) during the study for the first 12 months after randomisation, and every 12 weeks thereafter until study drug discontinuation.[12] Items are assessed on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very much) with a recall period of 7 days. To calculate FACT-G total and subscale scores, we followed scoring guidelines described elsewhere.[12] In brief, we calculated subscale scores by adding up the item responses for that subscale, and the FACT-G total score was the sum of the four subscale scores. We replaced missing item scores with the mean response for that subscale, as long as more than 50% of subscale items were completed. High scores reflect better HRQOL. The highest possible score is 28 for the physical, social or family, and functional scores, 24 for the emotional score, and 108 for the FACT-G total score. Clinically important differences have been reported for FACT-G total and subscale scores, but findings of a review concluded that clinically important differences are fairly stable for the FACT-G total score and subscale scores across publications and patient populations.[13] For each of the four subscale scores, the low end of a clinically important difference was established as a change of 2–3 points. For the FACT-G total score, the low end of the clinically important difference was estimated as 3–7 points.[13]

	Everolimus group (n=205)	Placebo group (n=97)
Age (years)	65 (22–86)	60 (24–83)
Sex		
Male	89 (43%)	53 (55%)
Female	116 (57%)	44 (45%)
Tumour grade		
Grade 1	129 (63%)	65 (67%)
Grade 2	75 (37%)	32 (33%)
Unknown or missing	1 (<1%)	0
FACT-G total score at baseline*	81·2 (15·5); n=189	82·6 (15·6); n=92
Physical wellbeing	23·5 (4·7); n=193	23·6 (5·0); n=94
Emotional wellbeing	17·0 (4·4); n=191	17·7 (4·5); n=94
Social wellbeing	22·0 (5·6); n=192	21·7 (5·5); n=93
Functional wellbeing	18·6 (6·3); n=191	19·6 (5·3); n=93
WHO performance status at baseline		
0	149 (73%)	73 (75%)
1	55 (27%)	24 (25%)
2	1 (<1%)	0
Treatment duration (weeks)†	40·4 (0·7–120·4)	19·6 (4·0–130·3)
Primary reason for end of treatment		
Disease progression	76 (37%)	70 (72%)
Adverse event	59 (29%)	7 (7%)
Patient withdrew consent	15 (7%)	5 (5%)
Death	4 (2%)	1 (1%)
Protocol deviation	1 (<1%)	1 (1%)
Treatment ongoing‡	48 (23%)	13 (13%)
Patient untreated	2 (1%)	0
Progression-free survival (months; median [95% CI])§	11·0 (9·2–13·3)	3·9 (3·6–7·4)
2-year overall survival (95% CI)‖	76·9% (70·0–82·4)	61·5% (50·0–71·1)
Adverse events of grade 3 or 4†	140 (69%)	28 (29%)

Data are median (range), number of patients (%), or mean (SD), unless otherwise stated. Patients in each treatment group also received best supportive care. FACT-G=Functional Assessment of Cancer Therapy—General. *Summary statistic is based on patients who completed >50% of subscale score responses. The highest possible score on physical, social, and functional FACT-G subscales is 28 and on the emotional subscale it is 24; the highest possible FACT-G total score is 108. †Safety set (analysed according to treatment actually received). ‡Patients with ongoing treatment at the time of data analysis cutoff (Nov 28, 2014). §Based on data analysis cutoff (Nov 28, 2014). ‖Based on data analysis cutoff (Nov 30, 2015).

Table 1: **Patients' characteristics**

Outcomes

The primary endpoint was progression-free survival, which has been reported elsewhere.[10] Here, we report data for the prespecified secondary endpoints of HRQOL and WHO performance status. The prespecified secondary outcome measures were time to definitive deterioration by 7 points or more in FACT-G total score (defined as either time from randomisation to a decrease in FACT-G score by at least 7 points compared with baseline, with no later increase above this threshold noted on treatment, or time to death that occurred before observation of deterioration) and time to definitive deterioration in WHO performance status (defined as an increase in performance status by at least one category of the score from baseline). We regarded death as worsening of both FACT-G and WHO performance status if it occurred on treatment and within the time of two planned assessments after the last available assessment. For the analyses of time to definitive deterioration, we only considered data obtained on study treatment and we censored patients receiving any further antineoplastic therapy before definitive worsening at the date of their last assessment on treatment before starting subsequent therapy.

Statistical analysis

We estimated the sample size 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.[10] We did not do a

sample size calculation based on time to definitive deterioration of FACT-G total score.

Analyses of time to definitive deterioration and change in FACT-G score over time were done in the full analysis set of all randomised patients, by intention to treat. Using Kaplan-Meier estimates, we obtained medians for each treatment group and 95% CIs. We used stratified Cox proportional hazard models to obtain hazard ratios (HRs) with 95% CIs considering the stratification factors at randomisation. To assess potential departure from non-proportionality, we added an interaction term between treatment (everolimus *vs* placebo) and time and tested it for significance.[14] Post-hoc exploratory analyses were done for time to definitive deterioration in FACT-G subscale scores by 3 points or more and analyses of FACT-G total and subscale scores over time.

We fitted linear mixed models (LMMs) for repeated measurements to analyse FACT-G total and subscale scores over time in the two treatment groups. These models used the continuous FACT-G scores as dependent variables and included as covariates the treatment group, stratification factors, baseline score, time as a categorical variable, and an interaction term for treatment by time. From the LMMs, we derived adjusted mean scores in the two treatment groups for each assessment together with 95% CIs. We obtained estimates through the restricted maximum likelihood method, and these are unbiased under the assumption that data are missing at random—ie, that patients who discontinue would have similar scores to patients in their treatment group and with the same covariates.[15] If a dropout is caused by death, LMMs implicitly impute data beyond the time of death. Thus, HRQOL scores estimated from LMMs are based on the assumption that all patients survive at least to the week 48 assessment.[16] The median duration of treatment on placebo was only 19·6 weeks,[10] therefore, only a few patients remained in the trial at later timepoints. Thus, all LMMs used data only up to week 48.

We did sensitivity analyses with a pattern mixture model based on the delta (δ) adjustment method to assess how severe departures from the missing-at-random assumption must be to alter conclusions from the primary analysis. We assumed that patients who discontinued treatment because of adverse events or withdrawal of consent had outcomes that were worse by some amount δ (varied between 7 and 28) than otherwise similar patients who remained in the study.[17]

Post-hoc analyses were done for the effect of adverse events on HRQOL by analysis of responses to the question "I am bothered by side-effects of treatment", an item of the FACT-G physical wellbeing domain, in the safety population—ie, according to treatment actually received. This question is correlated with the FACT-G total score and has been used previously in various studies in oncology.[18] To assess the effect of side-effects, we calculated the proportion of patients who felt "not at all", "a little bit", "somewhat", "quite a bit", and "very much" bothered by side-effects over time. To calculate patients' mean response to this question, we assigned 0 points for "not at all", 1 point for "a little bit", 2 points for "somewhat", 3 points for "quite a bit", and 4 points for "very much", and we plotted the mean response over time for each treatment.

We did additional assessments of FACT-G and WHO performance status as part of the end-of-treatment and 30-day safety follow-up visit. Using pooled data from all visits for patients in both randomised treatment groups, we were able to estimate the association between disease progression and HRQOL and utility in a post-hoc exploratory analysis. Utility is a summary measure of health status recorded on a scale from 1·0 (perfect health) to 0·0 (death). Utility values are used to assess the so-called quality weight together with survival in the calculation of quality-adjusted life-years (QALYs), which is an important outcome measure in funding decisions in publicly funded health-care systems—eg, in the UK.[19] Specific HRQOL methods (known as preference-based measures) can be used to calculate utility—eg, EuroQol EQ-5D.[20] Since we did not administer a preference-based measure for utility in the RADIANT-4 trial, we used

	Everolimus (n=205)		Placebo (n=97)		Mean difference (95% CI)	p value
	n/N (%)	Mean (95% CI)	n/N (%)	Mean (95% CI)		
Week 8	154/179 (86%)	79·5 (77·7 to 81·3)	82/88 (93%)	80·0 (77·6 to 82·5)	−0·5 (−3·5 to 2·5)	0·743
Week 16	134/158 (85%)	78·2 (76·1 to 80·3)	55/63 (87%)	80·2 (77·0 to 83·4)	−2·0 (−5·8 to 1·8)	0·294
Week 24	121/136 (89%)	77·7 (75·6 to 79·9)	40/44 (91%)	78·6 (75·1 to 82·0)	−0·8 (−4·9 to 3·2)	0·683
Week 32	99/121 (82%)	76·4 (74·1 to 78·7)	30/33 (91%)	77·5 (73·6 to 81·4)	−1·1 (−5·7 to 3·5)	0·637
Week 40	88/104 (85%)	76·2 (73·7 to 78·8)	23/26 (88%)	78·0 (73·4 to 82·5)	−1·7 (−6·9 to 3·5)	0·514
Week 48	70/84 (83%)	75·7 (73·2 to 78·2)	22/26 (85%)	77·8 (73·5 to 82·1)	−2·1 (−7·1 to 2·9)	0·408

Patients in each treatment group also received best supportive care. The highest possible FACT-G total score is 108. Adjusted mean scores are least square means from a linear mixed model including treatment arm, categorical time, and an interaction between categorical time and treatment arm as covariates. Additional covariates are tumour origin, WHO performance status, previous treatment with a somatostatin analogue, and baseline score. FACT-G=Functional Assessment of Cancer Therapy—General. n=patients with a valid FACT-G total score at that visit and a valid FACT-G baseline score. N=patients on study at that timepoint.

Table 2: **Adjusted mean FACT-G total scores by treatment arm and time in study**

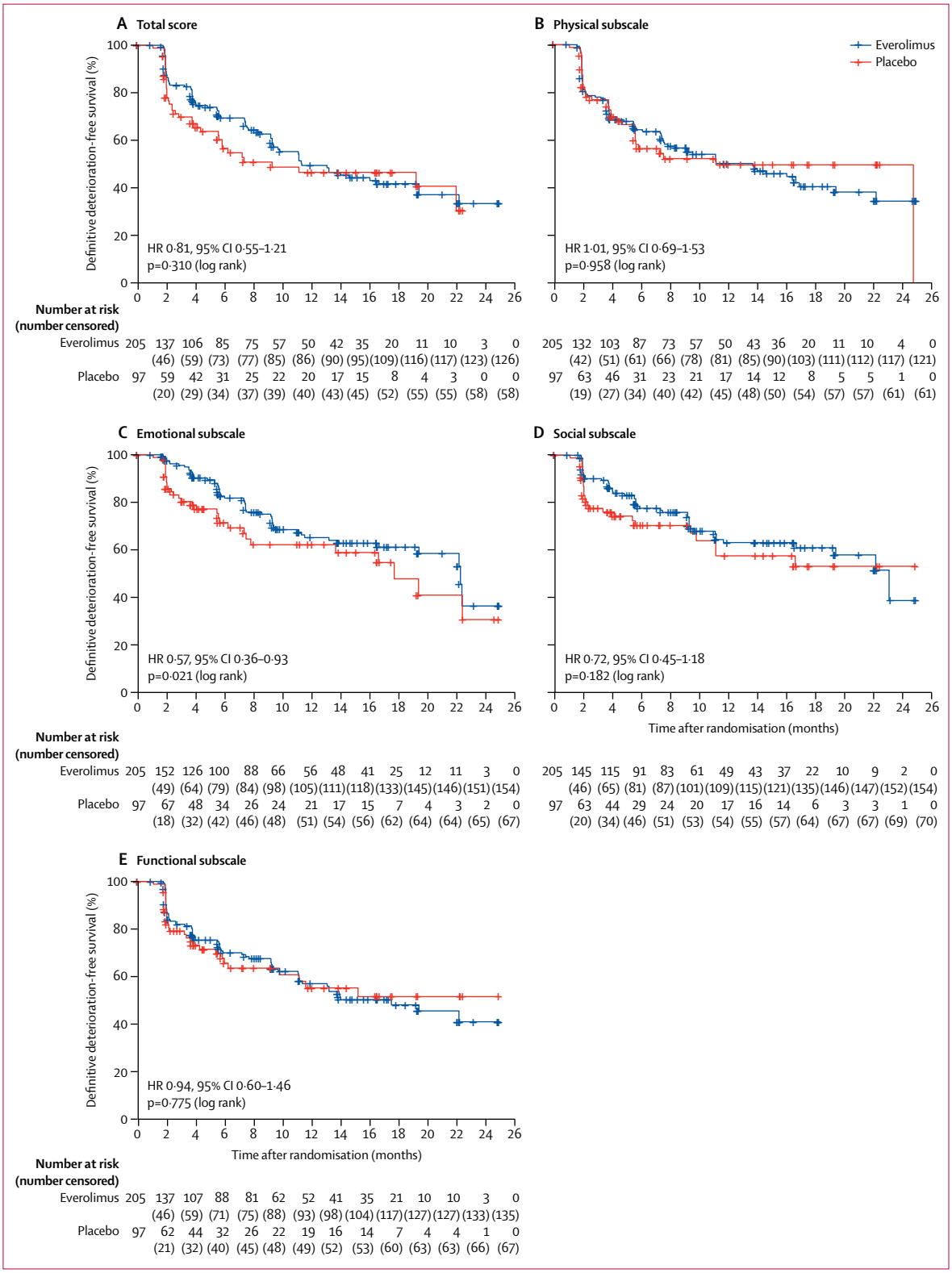

Figure 1: **Kaplan-Meier plots showing time to definitive deterioration of FACT-G total score by at least 7 points (A) and subscale scores by at least 3 points (B–E)**
HRs should be interpreted with caution since proportional hazard assumption might not be met for all subscales. FACT-G=Functional Assessment of Cancer Therapy—General. HR=hazard ratio.

mapping algorithms entailing regression modelling to link the responses on FACT-G (a disease-specific questionnaire) to EQ-5D utilities. This alternative approach is an acceptable and commonly used means to derive utilities when they have not been obtained directly in a trial.[21] Using two mapping algorithms published by Young and colleagues[22] and Teckle and colleagues,[23] we converted FACT-G values to EQ-5D utility scores. We did a thorough appraisal of all published mapping algorithms to select the most appropriate algorithms (appendix pp 1–2).[24]

We used all HRQOL assessments that took place before or at the date of the latest tumour assessment before disease progression to estimate HRQOL or utilities pre-progression. We used all HRQOL measurements at the same visit of documented disease progression or thereafter until the start of new anticancer treatments to estimate HRQOL or utilities post progression. We used a HRQOL assessment that took place between the date of the latest tumour assessment before disease progression and the date of documented disease progression either to estimate post-progression or pre-progression HRQOL or utilities, depending on whether the assessment was done nearer to the date of documented disease progression or to the previous tumour assessment, respectively. We fitted repeated-measurements LMMs to FACT-G total and subscale scores and utility scores. The regression models included response status (pre-progression and post-progression based on central radiology review) as a single time-dependent categorical covariate. We included patients as random effects. We used regression models to generate adjusted mean FACT-G scores and adjusted mean utilities for pre-progression and post-progression together with 95% CIs.

All analyses presented in this paper are based on the cutoff for the primary analyses (Nov 28, 2014)—ie, before crossover was permitted. We did all analyses with SAS version 9.4. The p values provided are nominal (threshold for significance $p<0·05$); we made no multiplicity adjustment.

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

Role of the funding source

The funder contributed to study design, data collection, data analysis, and data interpretation, in collaboration with the investigators and other authors. Funds for writing support were provided by the funder. LB-P, ED, MH, and JE had access to raw data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between April 3, 2012, and Aug 23, 2013, 302 patients were enrolled to the study; 205 patients were allocated everolimus and 97 patients were assigned placebo. Table 1 presents baseline and disease characteristics of patients, which are reported in more detail elsewhere.[10] The median age of all patients was 63 years (range 22–86).

At baseline, 193 (94%) of 205 patients assigned everolimus and 95 (98%) of 97 patients allocated placebo completed either fully or partly the FACT-G questionnaire. Overall compliance remained high in both treatment groups at the first post-baseline assessment and was above 80% throughout the first year of treatment (table 2). The mean FACT-G total score at baseline was 81·2 (SD 15·5) for patients assigned everolimus and 82·6 (15·6) for those allocated placebo (table 1).

79 (39%) of 205 patients assigned everolimus and 39 (40%) of 97 allocated placebo had a decrease in FACT-G total score of at least 7 points. Time to definitive deterioration in FACT-G total score did not differ between treatment groups (figure 1A), with an estimated median time to definitive deterioration of 11·27 months (95% CI 9·27–19·35) for everolimus and 9·23 months (5·52–not estimable [NE]) for placebo (adjusted HR 0·81, 95% CI 0·55–1·21; log-rank p=0·31).

The post-hoc analysis of time to definitive deterioration in FACT-G subscale scores showed a significant difference between the everolimus and placebo arms in emotional wellbeing (median 22·21 months [95% CI 19·35–NE] *vs* 17·64 months [7·75–NE]), with 51 (25%) of 205 patients assigned everolimus and 30 (31%) of 97 allocated placebo having a decrease in the emotional subscale score of at least 3 points (figure 1C). No differences were recorded in median time to definitive deterioration between the everolimus and placebo arms for physical wellbeing (13·63 months [95% CI 7·79–16·82] *vs* 11·10 months [5·55–24·67]; figure 1B), social wellbeing (23·03 months [19·35–NE] *vs* NE [9·72–NE]; figure 1D), or functional wellbeing (17·45 months [11·07–NE] *vs* NE [9·72–NE]; figure 1E). A decrease of at least 3 points was noted in 84 (41%) of 205 patients assigned everolimus and 36 (37%) of 97 allocated placebo for the FACT-G physical

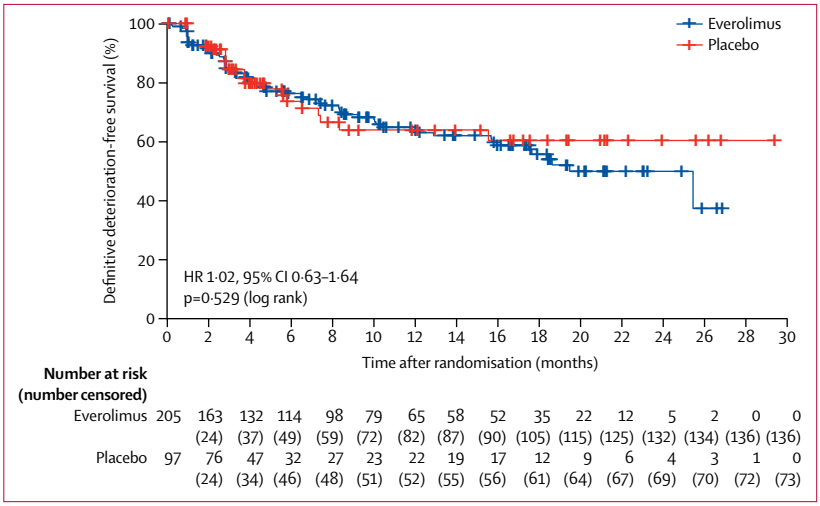

Figure 2: **Kaplan-Meier plot showing time to definitive deterioration of WHO performance status by at least one category**
HR=hazard ratio.

subscale score, 51 (25%) and 27 (28%) for the social wellbeing subscale score, and 69 (34%) and 30 (31%) for the functional subscale score.

Adding interaction terms between treatment group and time in the stratified Cox models did not significantly alter the findings of the proportional hazard assumption (p=0·056 for FACT-G total score; p=0·14 for physical wellbeing; p=0·49 for emotional wellbeing; p=0·37 for social wellbeing; p=0·12 for functional wellbeing).

69 (34%) of 205 patients assigned everolimus and 24 (25%) of 97 allocated placebo had a decrease in WHO performance status of at least one category. Time to definitive deterioration in WHO performance status did not differ between treatment groups (median 25·46 months [95% CI 17·54–NE] with everolimus *vs* NE [8·31–NE] with placebo; figure 2).

Table 2 presents the post-hoc analysis of adjusted mean FACT-G total scores over time, and figure 3 shows the change over time in adjusted mean FACT-G subscale scores. In general, FACT-G total and subscale scores were maintained over the study period, with small non-significant differences between the everolimus and placebo groups at some timepoints. No clinically relevant declines were noted at any of the timepoints for FACT-G total or subscale scores. Results of the pattern mixture model showed that for any δ tested, mean FACT-G total scores did not differ between treatment groups, supporting the robustness of results from the primary analysis.[25] Results for subgroups of lung and gastrointestinal patients have been published elsewhere.[26,27]

Table 3 presents data for the post-hoc analysis of answers to the question "I am bothered by side-effects of treatment". The proportion of patients who reported that they were "not at all" or "a little bit" bothered by side-effects ranged from 94 (58%) of 162 patients at week 8 to 50 (68%) of 74 patients at week 48 in the everolimus group, and from 66 (81%) of 81 patients at week 8 to 24 (100%) of 24 patients at week 48 in the placebo group (table 3; appendix p 3).

Adjusted mean FACT-G scores and utility values pre-progression and post progression for the whole population regardless of treatment allocation are presented in

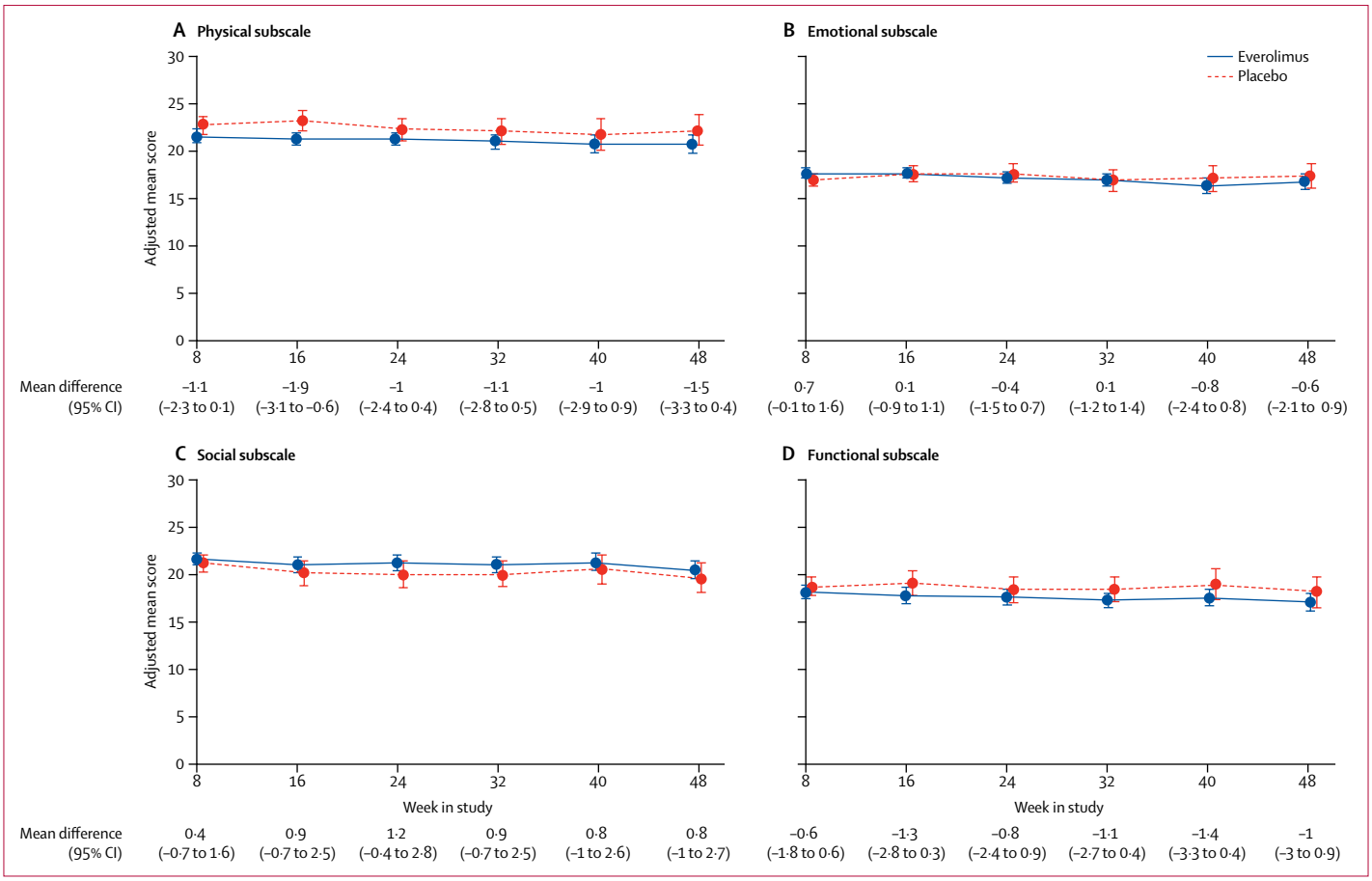

Figure 3: **Adjusted mean FACT-G subscale scores by treatment group over time**
The highest possible score on the physical, social, and functional FACT-G subscales is 28 and on the emotional subscale score it is 24. Adjusted mean scores are least square means from a linear mixed model including treatment arm, categorical time, and an interaction between categorical time and treatment group as covariates. Additional covariates are tumour origin, WHO performance status, previous treatment with a somatostatin analogue, and baseline score. Circles denote mean score and error bars show 95% CI. FACT-G=Functional Assessment of Cancer Therapy—General.

	Not at all	A little bit	Somewhat	Quite a bit	Very much	Mean (SD)	Difference (everolimus–placebo)
Everolimus							
Baseline (n=173)	134 (77%)	19 (11%)	10 (6%)	7 (4%)	3 (2%)	0·42 (0·90)	0·10 (0·86)
Week 8 (n=162)	42 (26%)	52 (32%)	37 (23%)	22 (14%)	9 (6%)	1·41 (1·17)	0·70 (1·09)
Week 16 (n=141)	37 (26%)	48 (34%)	35 (25%)	16 (11%)	5 (4%)	1·32 (1·09)	0·80 (1·04)
Week 24 (n=124)	32 (26%)	43 (35%)	33 (27%)	16 (13%)	0	1·27 (0·99)	0·77 (0·95)
Week 32 (n=101)	25 (25%)	38 (38%)	26 (26%)	11 (11%)	1 (%)	1·26 (0·99)	0·93 (0·91)
Week 40 (n=91)	30 (33%)	29 (32%)	21 (23%)	10 (11%)	1 (1%)	1·15 (1·04)	0·82 (0·97)
Week 48 (n=74)	20 (27%)	30 (41%)	15 (20%)	8 (11%)	1 (1%)	1·19 (1·00)	0·98 (0·90)
Placebo							
Baseline (n=91)	74 (81%)	9 (10%)	6 (7%)	0	2 (2%)	0·32 (0·79)	..
Week 8 (n=81)	44 (54%)	22 (27%)	10 (12%)	5 (6%)	0	0·70 (0·91)	..
Week 16 (n=54)	36 (67%)	11 (20%)	5 (9%)	1 (2%)	1 (2%)	0·52 (0·89)	..
Week 24 (n=42)	29 (69%)	5 (12%)	8 (19%)	0	0	0·50 (0·80)	..
Week 32 (n=29)	20 (69%)	8 (28%)	1 (3%)	0	0	0·34 (0·55)	..
Week 40 (n=24)	18 (75%)	4 (17%)	2 (8%)	0	0	0·33 (0·64)	..
Week 48 (n=24)	19 (79%)	5 (21%)	0	0	0	0·21 (0·42)	..

Data are number of patients (%) or mean (SD). 0 points were given for the category "not at all", 1 point for "a little bit", 2 points for "somewhat", 3 points for "quite a bit", and 4 points for "very much".

Table 3: **Summary of item "I am bothered by side-effects of treatment"**

table 4. Disease progression resulted in a decline in FACT-G total score of 4·91 (95% CI 3·71–6·11) post progression, and a decrease in all subscale scores. Disease progression was associated with a decline of 0·030 (95% CI 0·023–0·038; Teckle,[23] p<0·0001) and 0·054 (0·041–0·068; Young,[22] p<0·0001) in utility.

	Pre-progression	Post progression	Mean difference (95% CI)
FACT-G total score (mean, 95% CI)	79·71 (77·91–81·50)	74·80 (72·81–76·78)	4·91 (3·71–6·11)
Physical wellbeing	22·38 (21·83–22·92)	20·88 (20·24–21·51)	1·50 (1·05–1·95)
Emotional wellbeing	17·58 (17·12–18·04)	16·44 (15·92–16·97)	1·14 (0·78–1·49)
Social wellbeing	21·55 (20·93–22·17)	20·86 (20·17–21·55)	0·69 (0·24–1·14)
Functional wellbeing	18·19 (17·54–18·85)	16·85 (16·12–17·59)	1·34 (0·86–1·82)
Mean utility (95% CI; Teckle mapping algorithm)[23]	0·826 (0·815–0·836)	0·795 (0·783– 0·807)	0·030 (0·023–0·038)
Mean utility (95% CI; Young mapping algorithm)[22]	0·779 (0·763–0·796)	0·725 (0·706–0·744)	0·054 (0·041–0·068)

The highest possible score on the physical, social, and functional FACT-G subscales is 28 and on the emotional subscale score it is 24; the highest possible FACT-G total score is 108. The number of FACT-G assessments ranged from 1118 to 1155 pre-progression and 381 to 392 post progression, depending on the outcome considered. Differences in the number of observations are caused by different scoring rules and how they deal with missing values in FACT-G items; not all scales require non-missing data in all FACT-G items. Unit of analysis is the HRQOL assessment; because of repeated assessments over time, the number of observations is larger than the number of patients. FACT-G=Functional Assessment of Cancer Therapy—General. HRQOL=health-related quality of life.

Table 4: **Association of disease progression with HRQOL and utility**

Discussion

The analysis of FACT-G total scores in patients with advanced, progressive, non-functional NETs of lung or gastrointestinal origin who were enrolled in the randomised, phase 3 RADIANT-4 trial shows that despite toxic effects of active cancer treatment (eg, adverse events with some risk for grade 3–4 adverse events and discontinuations because of adverse events), HRQOL is maintained in patients treated with everolimus, with no statistically or clinically relevant differences compared with patients treated with placebo. Indeed, toxic effects seem to be counterbalanced by the higher efficacy (longer progression-free survival) and potentially fewer disease-related symptoms with everolimus than with placebo. This finding was confirmed in analyses of WHO performance status and post-hoc analyses of FACT-G subscale scores. Analyses of the association between HRQOL and disease progression irrespective of treatment assignment showed a decline in FACT-G scores and utility after disease progression.

Time to definitive deterioration has become a familiar endpoint in the analysis of longitudinal HRQOL data in oncology.[28] It was a prespecified secondary endpoint in the RADIANT-4 trial and no differences were noted in time to definitive deterioration of the FACT-G total score between patients treated with everolimus and those treated with placebo. Analyses of time to definitive deterioration for most FACT-G subscale scores and the WHO performance status showed similar results. It is noteworthy that everolimus improved scores on the emotional wellbeing subscale; a possible interpretation is that some patients assigned everolimus might have had the perception of receiving treatment because of

the presence of adverse events. This sort of unmasking, however, does not invalidate the patients' responses per se, or the noted difference in emotional wellbeing. Another reason could be that longer progression-free survival in patients assigned everolimus than those assigned placebo has a positive effect on emotional status.

The improvements in time to definitive deterioration outcomes for the FACT-G total score among patients receiving everolimus were noted despite a higher incidence of grade 3 or 4 toxic effects and discontinuations because of adverse events in this treatment group.[10] Protocol-defined adverse event management strategies might have led to an attenuation of HRQOL deterioration. In fact, most patients in both treatment groups (roughly 60% of those assigned everolimus and 80% of those allocated placebo at each post-baseline assessment) reported that they were "not at all" or "a little bit" bothered by side-effects from treatment. The number of patients who felt "quite a bit" or "very much" bothered was low (10–19% of those assigned everolimus and 2–6% of those allocated placebo). Although more patients assigned everolimus felt bothered by side-effects, such level of discomfort did not produce significant differences in overall HRQOL. Notably, 37 (46%) of 81 patients who were treated with placebo also reported some degree of bother with side-effects at week 8, and the proportion of patients continuing to report some degree of bother from side-effects with placebo remained greater than 30% in subsequent assessments; as such, the disease and symptoms themselves led to some degree of discomfort. To assess the effect of side-effects, responses to the FACT-G item "I am bothered by side-effects of treatment" were analysed. Alternatively, one could also estimate the effect on FACT-G scores of adverse events reported in the trial. However, a limitation of this approach would be that adverse events are continuously reported and not necessarily aligned at the same timepoints as the quality-of-life assessments, so this approach would limit the analysis to adverse events that were ongoing at the time of the HRQOL measurement. Also, actions taken followed by adverse events—eg, use of concomitant medication—are confounding factors, which makes it difficult to compare the results.

Moreover, it is likely that other factors—eg, longer progression-free survival—might also have contributed to HRQOL in patients receiving everolimus. Analyses of the association between HRQOL and disease progression showed a significant decline in the total FACT-G score after disease progression, which was within the clinically relevant difference range of 3–7 points.[13] Similar declines were noted for the FACT-G subscale scores and the magnitude of decline in HRQOL is consistent with findings of studies in other cancers.[29,30] Similarly, disease progression was associated with a significant decline in utility of 0·03 (Teckle)[23] and 0·05 (Young).[22] Although statistically significant, the clinical significance of this finding is not clear. Based on published clinically important differences for utility measures of 0·06,[31] 0·07,[32] and 0·09,[31,32] this study's difference in utility after disease progression might fall short of what one would confidently consider clinically meaningful. However, the utility difference was comparable with results from other studies in advanced lung cancer, with a decline in utility of 0·056,[30] and advanced gastrointestinal stromal tumours, with a decline of utility of 0·03.[33]

To estimate utilities in the RADIANT-4 trial, we used two published mapping algorithms to derive utilities from FACT-G responses. The FACT-G questionnaire provides a reasonable alternative to direct use of a health utility method because it is a generic HRQOL questionnaire that has been validated in patients with cancer and is used widely in oncology.[21] In this study, a general questionnaire such as FACT-G was judged more appropriate than NET-specific questionnaires (eg, the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire for neuroendocrine tumours of gastrointestinal origin [QLQ-GINET21] or the Norfolk quality-of-life tool)[34] because the study population was restricted to patients with non-functional tumours. Regarding the choice between FACT-G and EORTC QLQ-C30, both have proven validity in a range of cancer settings, but the fewer subscale scores for FACT-G decreases problems of endpoint multiplicity.[35] Overall, HRQOL in our study was somewhat lower when compared with reference values reported for a general US adult population and similar to an adult population of patients with cancer,[36] which is consistent with findings of another study[37] in which HRQOL in patients with NETs was somewhat impaired compared with the general population, although evidence in NETs of lung and gastrointestinal origin, specifically, is limited.[38–40] In an open-label expanded access study in patients with advanced NETs (pancreatic and non-pancreatic NETs) who received everolimus, HRQOL was not affected adversely in pancreatic NETs, but deteriorations were noted in some QLQ-C30 subscale scores over time for non-pancreatic NETs. However, the confidence intervals were very wide, and there was no control group, which makes the results inconclusive.[41] Findings of the effect of everolimus on HRQOL in our study are similar to those reported in advanced breast cancer, for which additional treatment with everolimus did not have a deleterious effect on HRQOL.[42] Findings of maintenance of HRQOL have also been noted in pancreatic NETs in patients treated with sunitinib.[43]

A limitation of our study is the extent of missing HRQOL questionnaire data after treatment discontinuation. Although compliance with questionnaire completion was more than 80% among patients on treatment, the amount of missing data increased over time because of treatment discontinuations followed by initiation of new antineoplastic therapy. Although we used statistical methods to account for potential worsening of HRQOL after dropout, a

conclusive statement on the effect of missing data cannot be made. On the other hand, median treatment duration in the everolimus group was twice as long as in the placebo group and the main reason for early discontinuations under placebo was disease progression. If HRQOL continues to deteriorate after disease progression (ie, at timepoints when data were scarce), the relative HRQOL benefit of everolimus caused by longer progression-free survival might be even larger than indicated by this study.

In conclusion, although analysis of the RADIANT-4 primary endpoint showed that disease progression is delayed with everolimus compared with placebo in patients with advanced non-functional gastrointestinal or lung NETs, findings of the secondary prespecified and post-hoc exploratory HRQOL analyses suggest that overall HRQOL in FACT-G total and subscale scores is preserved even with the usual toxic effects related to active targeted drug treatment for cancer. The decline in HRQOL and utility after disease progression shows the importance of considering HRQOL as an endpoint in clinical trials. Furthermore, these results support the use of progression-free survival as a primary endpoint in clinical trials in patients with NETs of lung and gastrointestinal origin because our results show the real-life health effect of disease progression on the patient.

Contributors

MH and ED contributed to data curation. MEP, SS, JRS, CC, JT, EW, MR, HL, JWV, RP, EVC, METT, GDF, RB, NF, MHK, JCY, and LB-P contributed to study implementation. MH, JE, MPN, and J-FR had the idea for the study. MH, JE, MPN, J-FR, ED, and DC contributed to the study methodology. MH, ED, and DC contributed to the formal analysis. All authors contributed equally to writing, review, and editing of the report. JE and MPN contributed to project administration.

Declaration of interests

MEP received grants from Novartis and Ipsen, outside the submitted work; and personal fees from Novartis, Ipsen, Pfizer, and Lexicon, outside the submitted work. SS has received honoraria, travel expenses, and research funding from Novartis, Ipsen, and Pfizer, outside the submitted work. JRS received personal fees from Ipsen, Lexicon, and Novartis, outside the submitted work. ED, LB-P, and MPN are employees of Novartis. JT received consulting fees from Bayer, Amgen, and Roche, outside the submitted work; and payments for lectures from Amgen, Merck, Bayer, Roche, Servier, and Novartis, outside the submitted work. EW is an advisory board member for Ipsen and Advanced Accelerator Applications, outside the submitted work. MR received grants from Novartis, during the conduct of the study; and personal fees from Novartis and Ipsen, outside the submitted work. HL received grants, personal fees, and non-financial support from Novartis; personal fees and non-financial support from Ipsen; and personal fees and non-financial support from Pfizer, during the conduct of the study. RP is a paid consultant to Novartis Oncology Pharmaceuticals and Ipsen; and is on the speaker's bureau for Novartis Oncology. EVC received grants for research funding from Amgen, Bayer, Boehringer, Celgene, Ipsen, Lilly, Merck Serono, Novartis, Roche, and Sanofi, outside the submitted work. JWV reports grants and personal fees from Novartis, during the conduct of the study; personal fees from Abbott, AstraZeneca, Baxalta, Celgene, Ipsen, Lilly, Merck, and Pfizer, outside the submitted work; and non-financial support from Celgene, outside the submitted work. MH and JE received grants from Novartis, during the conduct of the study. DC received personal fees from Novartis, outside the submitted work. J-FR received consulting fees from Wellmera AG, during the conduct of the study and outside the submitted work. NF received consulting fees from Ipsen and Pfizer, outside the submitted work; and research funding from Novartis (to their institution), outside the submitted work. MHK received personal fees from Lexicon, Novartis, and Ipsen, outside the submitted work. JCY received grants from the National Cancer Institute, during the conduct of the study; and consultant fees from Novartis, Ipsen, Merck, and Nektar, outside the submitted work. METT, RB, CC, and GDF declare no competing interests.

Acknowledgments

This study was funded by Novartis Pharmaceuticals Corporation.
We thank the patients and investigators for their participation in the RADIANT-4 study; and the worldwide network of research nurses, trial coordinators, and operations staff for their contributions.
We acknowledge Jennifer Beaumont (MS of Northwestern University, Chicago, IL, USA) for technical review of health-related quality of life and statistical evaluations; and Daniela Capsa (Mapi Group, Stockholm, Sweden) for writing assistance.

References

1 Oberstein PE, Saif MW. Update on prognostic and predictive biomarkers for pancreatic neuroendocrine tumors. *JOP* 2012; **13:** 368–71.
2 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.
3 Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017; published online April 27. DOI:10.1001/jamaoncol.2017.0589.
4 Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev* 2004; **25:** 458–511.
5 Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst* 2009; **101:** 1642–49.
6 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.
7 Singh S, Wang X, Law C. Association between time to disease progression end points and overall survival in patients with neuroendocrine tumors. *Gastrointest Cancer* 2014; **4:** 103–13.
8 Ter-Minassian M, Brooks NV, Brais LK, et al. Association of progression-free survival with overall survival (OS) in patients (pts) with neuroendocrine tumor (NET) treated with somatostatin analogs. *Proc Am Soc Clin Oncol* 2015; **33** (15 suppl)**:** abstr 4090.
9 Lebwohl D, Anak O, Sahmoud T, et al. Development of everolimus, a novel oral mTOR inhibitor, across a spectrum of diseases. *Ann NY Acad Sci* 2013; **1291:** 14–32.
10 Yao JC, Fazio N, Singh S, et al, for the RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387:** 968–77.
11 Yao JC, Guthrie KA, Moran C, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *J Clin Oncol* 2017; **35:** 1695–703.
12 Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. *Health Qual Life Outcomes* 2003; **1:** 79.
13 Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof* 2005; **28:** 172–91.
14 Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pelissier S. Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. *BMC Med Res Methodol* 2010; **10:** 20.
15 Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: a review. *Test (Madr)* 2009; **18:** 1–43.
16 Kurland BF, Johnson LL, Egleston BL, Diehr PH. Longitudinal data with follow-up truncated by death: match the analysis method to research aims. *Stat Sci* 2009; **24:** 211.

17 Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. *Pharm Stat* 2013; **12:** 337–47.

18 Cella D, Escudier B, Rini B, et al. Patient-reported outcomes for axitinib *vs* sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. *Br J Cancer* 2013; **108:** 1571–78.

19 National Institute for Health and Care Excellence. Guide to the methods of technology appraisal, 2013. April, 2013. http://nice.org.uk/process/pmg9 (accessed Feb 24, 2016).

20 Brooks R. EuroQol: the current state of play. *Health Policy* 1996; **37:** 53–72.

21 Longworth L, Rowen D. Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. *Value Health* 2013; **16:** 202–10.

22 Young TA, Mukuria C, Rowen D, Brazier JE, Longworth L. Mapping functions in health-related quality of life: mapping from two cancer-specific health-related quality-of-life instruments to EQ-5D-3L. *Med Decis Making* 2015; **35:** 912–26.

23 Teckle P, McTaggart-Cowan H, Van der Hoek K, et al. Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D. *Health Qual Life Outcomes* 2013; **11:** 203.

24 Singh S, Pavel E, Strosberg J, et al. Association of disease progression, health-related quality of life, and utility in patients with advanced, nonfunctional, well-differentiated gastrointestinal or lung neuroendocrine tumors in the phase 3 RADIANT-4 trial. *Med Decis Making* 2016; **36:** E448–609.

25 Pavel ME, Strosberg JR, Bubuteishvili-Pacaud L, et al. Health-related quality of life (HRQoL) in patients with advanced, nonfunctional, well-differentiated gastrointestinal (GI) or lung neuroendocrine tumors (NET) in the phase 3 RADIANT-4 trial. 2016. https://www.nanets.net/nanets_cd/2016/pdfs/P11.pdf (accessed May 30, 2017).

26 Pavel ME, Strosberg JR, Pacaud L, et al. Health-related quality of life (HRQoL) in patients with advanced neuroendocrine tumors (NET) by tumor origin in the phase 3 RADIANT-4 trial. 2016. https://www.nanets.net/nanets_cd/2016/pdfs/P12.pdf (accessed May 30, 2017).

27 Singh S, Strosberg JR, Bubuteishvili-Pacaud L, et al. Health-related quality of life (HRQoL) in patients with advanced neuroendocrine tumors (NET) of gastrointestinal origin in the phase 3 RADIANT-4 trial. *Proc Am Soc Clin Oncol* 2017; **35** (4 suppl)**:** abstr 285.

28 Anota A, Hamidou Z, Paget-Bailly S, et al. Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: do we need RECIST for quality of life to achieve standardization? *Qual Life Res* 2015; **24:** 5–18.

29 Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. *Eur J Cancer* 2012; **48:** 311–23.

30 Griebsch I, Palmer M, Fayers PM, Ellis S. Is progression-free survival associated with a better health-related quality of life in patients with lung cancer? Evidence from two randomised trials with afatinib. *BMJ Open* 2014; **4:** e005762.

31 Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007; **5:** 70.

32 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005; **14:** 1523–32.

33 Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. *Gastric Cancer* 2015; **18:** 627–34.

34 Vinik E, Carlton CA, Silva MP, Vinik AI. Development of the Norfolk quality of life tool for assessing patients with neuroendocrine tumors. *Pancreas* 2009; **38:** e87–95.

35 Luckett T, King MT, Butow PN, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of life in cancer clinical research: issues, evidence and recommendations. *Ann Oncol* 2011; **22:** 2179–90.

36 Pearman T, Yanez B, Peipert J, Wortman K, Beaumont J, Cella D. Ambulatory cancer and US general population reference values and cutoff scores for the functional assessment of cancer therapy. *Cancer* 2014; **120:** 2902–09.

37 Haugland T, Vatn MH, Veenstra M, Wahl AK, Natvig GK. Health related quality of life in patients with neuroendocrine tumors compared with the general Norwegian population. *Qual Life Res* 2009; **18:** 719–26.

38 Chau I, Casciano R, Willet J, Wang X, Yao JC. Quality of life, resource utilisation and health economics assessment in advanced neuroendocrine tumours: a systematic review. *Eur J Cancer Care (Engl)* 2013; **22:** 714–25.

39 Jimenez-Fonseca P, Carmona-Bayonas A, Martin-Perez E, et al. Health-related quality of life in well-differentiated metastatic gastroenteropancreatic neuroendocrine tumors. *Cancer Metastasis Rev* 2015; **34:** 381–400.

40 Martini C, Gamper EM, Wintner L, et al. Systematic review reveals lack of quality in reporting health-related quality of life in patients with gastroenteropancreatic neuroendocrine tumours. *Health Qual Life Outcomes* 2016; **14:** 127.

41 Pavel M, Unger N, Borbath I, et al. Safety and QOL in patients with advanced NET in a phase 3b expanded access study of everolimus. *Target Oncol* 2016; **11:** 667–75.

42 Burris HA III, Lebrun F, Rugo HS, et al. Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial. *Cancer* 2013; **119:** 1908–15.

43 Vinik A, Bottomley A, Korytowsky B, et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumors: results from an international phase III trial. *Target Oncol* 2016; **11:** 815–24.