Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial

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Summary

Background Everolimus (RAD001) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), a therapeutic target for metastatic renal cell carcinoma. We did a phase III, randomised, double-blind, placebo-controlled trial of everolimus in patients with metastatic renal cell carcinoma whose disease had progressed on vascular endothelial growth factor-targeted therapy.

Methods Patients with metastatic renal cell carcinoma which had progressed on sunitinib, sorafenib, or both, were randomly assigned in a two to one ratio to receive everolimus 10 mg once daily (n=272) or placebo (n=138), in conjunction with best supportive care. Randomisation was done centrally via an interactive voice response system using a validated computer system, and was stratified by Memorial Sloan-Kettering Cancer Center prognostic score and previous anticancer therapy, with a permuted block size of six. The primary endpoint was progression-free survival, assessed via a blinded, independent central review. The study was designed to be terminated after 290 events of progression. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00410124.

Findings All randomised patients were included in efficacy analyses. The results of the second interim analysis indicated a significant difference in efficacy between arms and the trial was thus halted early after 191 progression events had been observed (101 [37%] events in the everolimus group, 90 [65%] in the placebo group; hazard ratio 0·30, 95% CI 0·22–0·40, p<0·0001; median progression-free survival 4·0 [95% CI 3·7–5·5] *vs* 1·9 [1·8–1·9] months). Stomatitis (107 [40%] patients in the everolimus group *vs* 11 [8%] in the placebo group), rash (66 [25%] *vs* six [4%]), and fatigue (53 [20%] *vs* 22 [16%]) were the most commonly reported adverse events, but were mostly mild or moderate in severity. Pneumonitis (any grade) was detected in 22 (8%) patients in the everolimus group, of whom eight had pneumonitis of grade 3 severity.

Interpretation Treatment with everolimus prolongs progression-free survival relative to placebo in patients with metastatic renal cell carcinoma that had progressed on other targeted therapies.

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Introduction

Everolimus (RAD001) is an orally administered inhibitor of the mammalian target of rapamycin (mTOR), a component of an intracellular signalling pathway that regulates cellular metabolism, growth, proliferation, and angiogenesis. Everolimus, a derivative of rapamycin, binds to an intracellular protein, FKBP-12, forming a complex that inhibits the mTOR serine-threonine kinase.

Abnormal functioning of signalling pathways is believed to contribute to the pathogenesis of many malignancies, and is particularly relevant to renal cancers. The pathogenesis of clear-cell renal cell carcinoma is linked to loss of the von Hippel-Lindau tumour suppressor gene, leading to accumulation of hypoxia-inducible factor 1 (HIF-1) and overexpression of HIF-1 target gene products, such as vascular endothelial growth factor (VEGF). VEGF and other factors induced by HIF-1 are thought to be the key drivers of tumour angiogenesis, permitting the growth and progression of renal cancers.[1] Activation of mTOR also leads to increased implicate mTOR as a valid target for treatment of renal cell carcinoma.[3,4]

Until recently, metastatic renal cell carcinoma was considered a cancer with a poor outlook, with treatment options limited to cytokines (interferon, interleukin 2).[5] Median survival averaged 13 months.[6] Two small molecules, sunitinib and sorafenib, which target the VEGF receptor (VEGF receptor tyrosine kinase inhibitors), temsirolimus, another mTOR inhibitor, and bevacizumab, a monoclonal antibody to VEGF, have shown clinical benefit for patients with treatment-naive or cytokine-pretreated renal cell carcinoma by prolonging progression-free or overall survival.[7–10] A systematic review of studies assessing targeted therapies for advanced renal cell carcinoma has recently been published.[11]

Drugs targeting these pathways have produced robust clinical effects in patients with advanced renal cell carcinoma. However, there now exists a high unmet medical need for patients who have failed therapy with

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approved therapeutic option exists for this recently established, pretreated population. An uncontrolled phase II trial of everolimus in pretreated patients showed a high proportion of durable disease stabilisation or tumour shrinkage in patients with metastatic renal cell carcinoma and progression of disease on cytokines.[12] Earlier studies had established a daily oral dosing schedule and the safety of everolimus in patients with various solid tumour malignancies.[13–15]

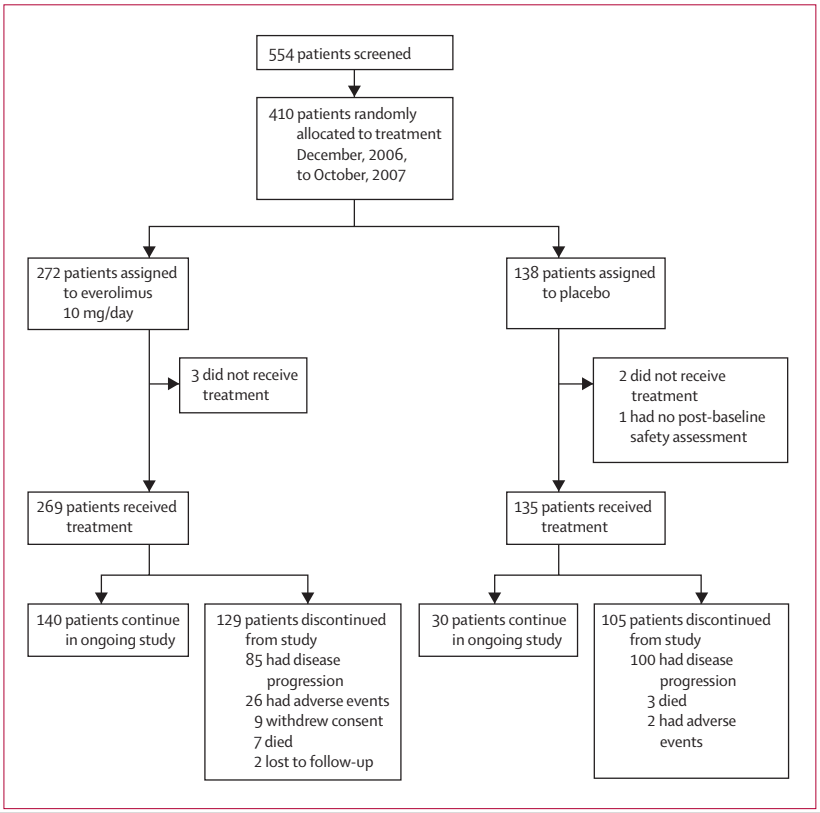
In this international, multicentre, double-blind, randomised phase III trial, everolimus was compared with placebo for the treatment of metastatic renal cell carcinoma in patients whose disease had progressed on treatment with VEGF receptor tyrosine kinase inhibitors.

Methods

Patients

This trial was done in 86 centres in Australia, Canada, Europe, Japan, and the USA. The study population consisted of adults (aged 18 years and above) with metastatic renal cell carcinoma that showed a clear-cell component, which had progressed on or within 6 months of stopping treatment with sunitinib or sorafenib, or both drugs. Previous therapy with bevacizumab, interleukin 2, or interferon alfa was also permitted. Key eligibility criteria included the presence of measurable disease (as per the Response Evaluation Criteria in Solid Tumours [RECIST][16]), a Karnofsky performance status score of 70% or more (on a scale of 0 to 100, with higher scores indicating better performance), and adequate bone marrow, hepatic, and renal function. Patients were ineligible if they had previously received mTOR inhibitor therapy (temsirolimus), had untreated CNS metastases, or uncontrolled medical conditions (eg, unstable angina pectoris, symptomatic congestive heart failure, recent myocardial infarction, or diabetes).

The protocol was approved by the institutional review boards of the participating institutions and the study was done in accordance with international standards of good clinical practice. All patients provided written informed consent.



Procedures

Patients were stratified according to a Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable *vs* intermediate *vs* poor risk) and previous anticancer therapy (one *vs* two previous VEGF receptor tyrosine kinase inhibitors).[17] Patients were randomly assigned in a two to one ratio to everolimus or placebo with the use of permuted blocks of six (four to everolimus, two to placebo) within each stratum. Patients received either continuous treatment with oral everolimus 10 mg once daily or placebo, both in conjunction with best supportive care. Study drugs (identical tablets of everolimus or placebo) were provided by the study sponsor, and were self-administered orally (two 5 mg tablets) daily in a fasting state or with a light fat-free meal. Each cycle was considered as 28 days of treatment; safety was assessed every 14 days for the first three cycles and every 4 weeks thereafter.

Doses were delayed or reduced if patients had clinically significant haematological or other adverse events that were deemed to be related to everolimus, according to a nomogram described in the protocol. In such cases, doses were reduced to 5 mg once daily.

Treatment in both groups was continued until disease progression, unacceptable toxicity, death, or discontinuation for any other reason. Investigators were unaware of the study group assignments, but disclosure was permitted after documented progression on the basis of investigator assessment. Patients who were initially randomised to placebo were then able to crossover to receive open-label everolimus. This element of the study design was incorporated to address both ethical and recruitment considerations.

Progression-free survival, documented with RECIST and assessed via a blinded, independent central review, was the primary endpoint, defined as the time from randomisation to the first documentation of disease progression or death (from any cause). Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms, and

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All randomly assigned patients were assessable for efficacy (intention-to-treat analysis). Tumour measurements (assessed by CT or MRI scans) were done at screening and were subsequently repeated every 8 weeks for the remainder of the study, as well as on discontinuation of study drug. Additional scans were done as warranted to confirm response (no sooner than 4 weeks and no later than 6 weeks after its initial observation), or whenever disease progression was suspected. Selection of target lesions and tumour assessments by the blinded central review were done independently of investigator evaluations.

All patients who received at least one dose of study drug and had follow-up were assessed for safety. Safety assessments consisted of monitoring and recording of all adverse events, regular monitoring of haematology and clinical chemistry measurements (laboratory evaluations), regular measurement of vital signs, performance of physical examinations, and recording of all concomitant medications and therapies. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.

Health-related quality-of-life was assessed with the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30[18] and Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms (FKSI-DRS) questionnaires.[19] These questionnaires were administered before randomisation, on day one of each cycle, and on discontinuation from the study.

Statistical analysis

The sample size was calculated on the basis of the primary endpoint. A clinically meaningful improvement was defined as a 33% risk reduction (hazard ratio 0·67), corresponding to a 50% prolongation in median progression-free survival, from 3·0 months for the placebo arm to 4·5 months for patients receiving everolimus. With the two to one randomisation and assuming a one-sided cumulative α of 0·025, we calculated that a total of 290 events as per central radiology review were required to achieve 90% power for the three-look group sequential plan. With a scheduled recruitment period of 16 months and additional follow-up of 5 months, we estimated that we would need to enrol about 362 patients (assuming that around 10% of patients would be lost to follow-up) to observe the required number of events.

The first and second interim analyses were planned after observing about 30% and 60%, respectively, of the targeted 290 events required for the final statistical analysis. These interim analyses allowed the study to be stopped on the basis of safety, or futility or efficacy (second analysis only). The final analysis was to be done when 290 progression events had been observed, if the

	Everolimus group (N=272)	Placebo group (N=138)
Age (years)	61 (27–85)	60 (29–79)
Sex		
Male	212 (78%)	105 (76%)
Female	60 (22%)	33 (24%)
Karnofsky performance status		
100	75 (28%)	40 (29%)
90	98 (36%)	53 (38%)
80	70 (26%)	30 (22%)
70	28 (10%)	15 (11%)
Missing	1 (<1%)	0
MSKCC risk factors for second-line therapy*		
Favourable	79 (29%)	39 (28%)
Intermediate	153 (56%)	78 (57%)
Poor	40 (15%)	21 (15%)
Previous treatment with VEGF receptor tyrosine kinase inhibitors		
Sunitinib only	124 (46%)	60 (43%)
Sorafenib only	77 (28%)	42 (30%)
Both sunitinib and sorafenib	71 (26%)	36 (26%)
Other previous systemic therapy		
Interferon	138 (51%)	72 (52%)
Interleukin 2	60 (22%)	33 (24%)
Chemotherapy	36 (13%)	22 (16%)
Bevacizumab	24 (9%)	14 (10%)
Previous surgery (nephrectomy)	262 (96%)	131 (95%)
Previous radiotherapy	83 (31%)	38 (28%)
Common sites of metastases		
Lymph nodes	203 (75%)	98 (71%)
Lung	199 (73%)	112 (81%)
Bone	100 (37%)	43 (31%)
Liver	94 (35%)	49 (36%)
Number of disease sites†		
1	26 (10%)	14 (10%)
2	67 (25%)	35 (25%)
3	87 (32%)	41 (30%)
≥4	88 (32%)	45 (33%)

Data are median (range) or n (%). *Risk factors associated with shorter survival in second-line therapy were low serum haemoglobin, raised corrected serum calcium, and poor performance status; favourable=no risk factors, intermediate=one risk factor, poor=two or more risk factors.[14] †As per baseline assessment for independent central radiology review; seven patients did not have centrally reviewed tumour assessments.

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

After the second interim analysis, the study steering committee, on the recommendation of the independent data monitoring committee, decided to terminate the trial early because the pre-specified efficacy stopping boundary (p≤0·0057, determined according to the method of Lan and DeMets with O'Brien-Fleming-type stopping rules[20,21]) was crossed, the null hypothesis rejected, and the criteria for a positive study met. This second interim analysis was designed to have 45% probability of detecting an effective treatment under

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	Everolimus group (N=272)	Placebo group (N=138)
Progression-free survival		
Number of progression events (independent central review)	101 (37%)	90 (65%)
Progression	85 (31%)	82 (59%)
Death	16 (6%)	8 (6%)
Censored	171 (63%)	48 (35%)
Best objective response (independent central review)		
Partial response rate	3 (1%)	0
Disease stabilisation*	171 (63%)	44 (32%)
Progressive disease	53 (19%)	63 (46%)
Disease could not be assessed	45 (17%)	31 (22%)
Overall survival		
Number of deaths	42 (15%)	26 (19%)

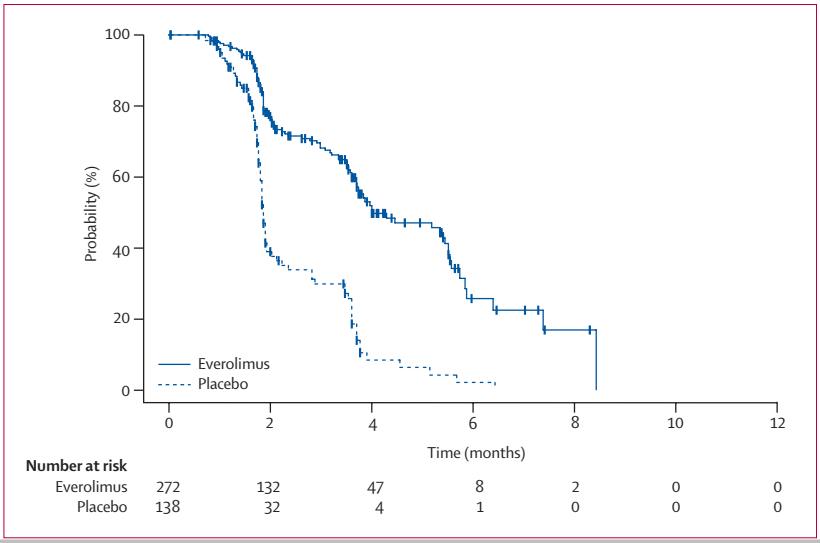
*Stable disease was defined as disease that remained unchanged for at least 56 days.

Table 2: **Summary of efficacy measures**

protocol, this second interim analysis was planned after observing about 60% of the targeted 290 progression-free survival events (per central radiology); however, because this central assessment was not done in real time and the number of events needed was unknown, the cutoff date (Oct 15, 2007) was determined using a statistical prediction model based on events per the investigator. The actual number of centrally assessed progression-free survival events observed as of the cutoff date and included in the analysis was 191 (or 66% of the targeted 290 events).

Patients without tumour progression or death at the time of the data cutoff for the analysis or at the time of receiving an additional anticancer therapy were censored at their last date of adequate tumour evaluation.

Progression-free and overall survival curves were estimated with Kaplan-Meier methodology; treatment arms were compared with a stratified log-rank test adjusting for strata defined by MSKCC prognostic score and the hazard ratio estimated by use of a stratified Cox proportional hazards model.



East version 3.1 was used to calculate the sample size and stopping boundaries; all other statistical analyses were done with SAS version 8.2. This trial is registered with ClinicalTrials.gov with the identifier NCT00410124.

Role of the funding source

The study sponsor contributed to the design, conduct, data collection, and data analysis. The corresponding author had access to all data and takes responsibility for the accuracy and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

The trial profile is shown in figure 1. Baseline demographic and disease characteristics were much the same in the two groups (table 1). Details of previous treatment for renal cell carcinoma are shown in table 1. 193 (71%) patients in the everolimus group and 109 (79%) in the placebo group had progressed while receiving previous therapy.

The median duration of treatment was 95 (range 12–315) days in the everolimus group and 57 (21–237) days in the placebo group. Treatment was ongoing for 140 (51%) patients in the everolimus group and 30 (22%) patients in the placebo group at the time of data cutoff for this analysis. The main reasons for treatment discontinuation included disease progression, adverse events, death, and withdrawal of consent (figure 1).

At the time of data cutoff, progression-free survival, as assessed by independent central review, was significantly prolonged in the everolimus group compared with the placebo group (hazard ratio 0·30, 95% CI 0·22–0·40; p<0·0001; table 2 and figure 2). Median progression-free survival was 4·0 (95% CI 3·7–5·5) months in the everolimus group and 1·9 (1·8–1·9) months for placebo. The probability of being progression-free at 6 months was 26% (95% CI 14–37) for patients receiving everolimus compared with 2% (0–6) for patients in the placebo group.

Analyses of progression-free survival using investigator assessments of disease status, rather than central review, were consistent with those of the primary efficacy analysis (median progression-free survival 4·6 months, 95% CI 3·9–5·5 in the everolimus group *vs* 1·8 months, 1·8–1·9; hazard ratio 0·31, 95% CI 0·24–0·41; p<0·0001).

Sensitivity analyses of potential confounding factors (including stratification factors at baseline and missing data or loss to follow-up) confirmed the robustness of the results for the primary efficacy analysis. Predefined subset analyses (MSKCC risk classification) plus a series of exploratory analyses designed to investigate the homogeneity of the treatment effect across relevant patient subgroups (number of previous VEGF receptor

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region) indicated that benefit was maintained across subgroups (figure 3).

Confirmed objective tumour responses (all partial responses) assessed by independent central review were seen in three (1%) patients receiving everolimus and none in the placebo group. The effect of everolimus on progression-free survival is thus probably the result of disease stabilisation (table 2).

At the time of the analysis, median overall survival had not been reached for the everolimus group and was 8·8 (95% CI 7·9–not available) months for the placebo group. There was no significant difference between groups in terms of overall survival (hazard ratio 0·83, 95% CI 0·50–1·37; p=0·23; figure 4), probably due to confounding by crossover: of the 98 patients in the placebo group who progressed as per investigator assessment, 79 crossed over to open-label everolimus after disease progression. 60 of these 79 patients had progressed within 8 weeks of enrolment.

No significant differences were evident between the two treatment groups in the time to definitive deterioration of patient-reported outcomes, as determined by pre-established criteria for clinically meaningful changes (EORTC QLQ-C30: physical functioning scale hazard ratio 0·94, 95% CI 0·64–1·39; global health status/quality-of-life score 1·02, 0·70–1·50; FKSI-DRS risk score: 0·82, 0·57–1·18). Longitudinal mean scores for the FKSI-DRS and the physical functioning, global health status/quality-of-life, role functioning, emotional functioning, cognitive functioning, social functioning, and symptoms scales of the EORTC QLQ-C30 questionnaire indicated that quality of life was sustained during treatment with everolimus relative to placebo, irrespective of the adverse effects that might be expected from the toxicities associated with an active treatment (data not shown).

As anticipated, adverse events were more frequently reported within the everolimus treatment group than in the placebo group (table 3); these events were mostly grade 1 or 2. The most common events were stomatitis, rash, fatigue or asthenia, and diarrhoea. The proportion of grade 3 or 4 events was low for both groups. Patients receiving everolimus had higher rates of grade 3 or 4 stomatitis, infections, and non-infectious pneumonitis than did those in the placebo group (table 3). Of the eight patients with grade 3 pneumonitis, six discontinued everolimus therapy. Four showed complete clinical resolution, and three improvement to grade 2 or less. Grade 3 or 4 lymphopenia, grade 3 hyperglycaemia, grade 3 hypophosphataemia, and grade 3 hypercholesterolaemia occurred more often in patients receiving everolimus than in those administered placebo (table 3).

Study drug toxicity led to treatment discontinuation for 28 (10%) patients receiving everolimus (with pneumonitis, dyspnoea, lung disorder, and fatigue the most common reasons) and for five (4%) patients in the

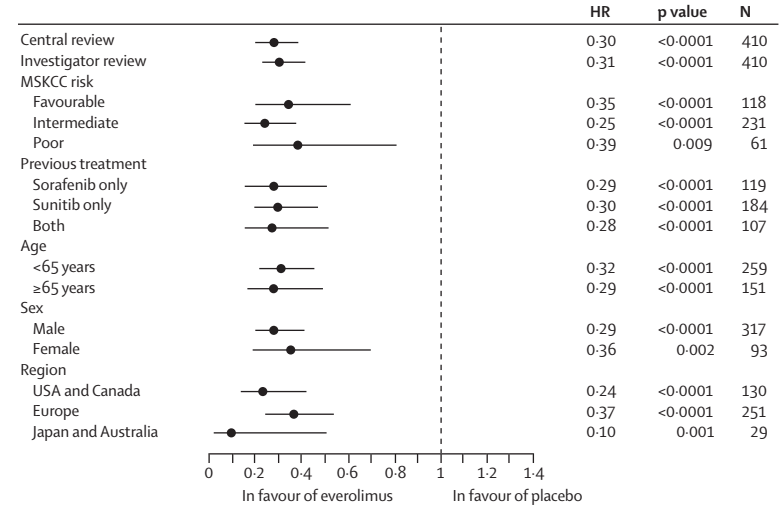
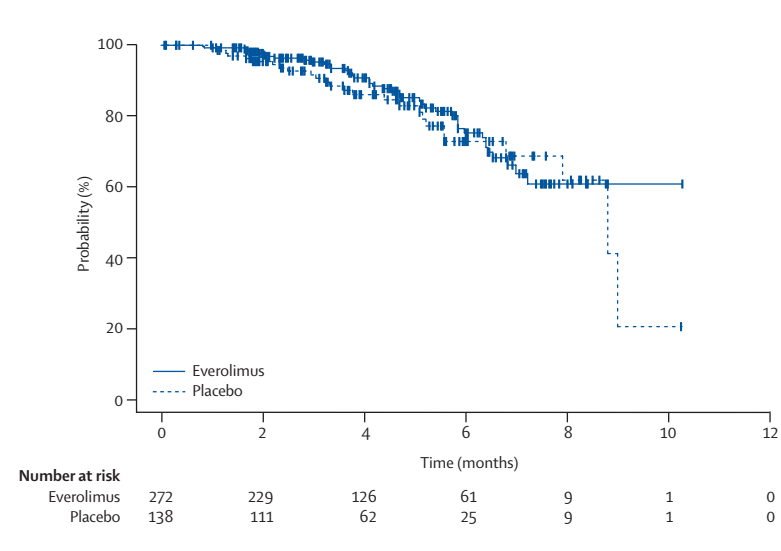


***Figure 3*: Progression-free survival in sensitivity analyses and predefined subgroups (independent central review)**

p values for subgroup analyses based on unstratified log-rank test. HR=hazard ratio.

group and 20 (15%) in the placebo group required a dose interruption, whereas 14 (5%) in the everolimus group and one (<1%) in the placebo group had a dose reduction with no previous interruption.

14 (5%) patients receiving everolimus therapy and six (4%) in the placebo group died within 28 days of their last dose (all causes). One patient in the everolimus group died from overwhelming candidal sepsis, complicated by acute respiratory failure, and which might have been attributable to study drug, and one patient receiving placebo died from myocardial infarction; all of the remaining deaths were attributed to the underlying malignancy.



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