Original Article

Phase 3 Trial of Everolimus for Metastatic Renal Cell Carcinoma

Final Results and Analysis of Prognostic Factors

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BACKGROUND: A phase 3 trial demonstrated superiority at interim analysis for everolimus over placebo in patients with metastatic renal cell carcinoma (mRCC) progressing on vascular endothelial growth factor receptor–tyrosine kinase inhibitors. Final results and analysis of prognostic factors are reported. **METHODS:** Patients with mRCC (N = 416) were randomized (2:1) to everolimus 10 mg/d (n = 277) or placebo (n = 139) plus best supportive care. Progression-free survival (PFS) and safety were assessed to the end of double-blind treatment. Mature overall survival (OS) data were analyzed, and prognostic factors for survival were investigated by multivariate analyses. A rank-preserving structural failure time model estimated the effect on OS, correcting for crossover from placebo to everolimus. **RESULTS:** The median PFS was 4.9 months (everolimus) versus 1.9 months (placebo) (hazard ratio [HR], 0.33; $P < .001$) by independent central review and 5.5 months (everolimus) versus 1.9 months (placebo) (HR, 0.32; $P < .001$) by investigators. Serious adverse events with everolimus, independent of causality, in $\geq 5\%$ of patients included infections (all types, 10%), dyspnea (7%), and fatigue (5%). The median OS was 14.8 months (everolimus) versus 14.4 months (placebo) (HR, 0.87; $P = .162$), with 80% of patients in the placebo arm crossed over to everolimus. By the rank-preserving structural failure time model, the survival corrected for crossover was 1.9-fold longer (95% confidence interval, 0.5-8.5) with everolimus compared with placebo only. Independent prognostic factors for shorter OS in the study included low performance status, high corrected calcium, low hemoglobin, and prior sunitinib ($P < .01$). **CONCLUSIONS:** These results established the efficacy and safety of everolimus in patients with mRCC after progression on sunitinib and/or sorafenib. *Cancer* 2010;116:4256–65. © *2010 American Cancer Society.*

KEYWORDS: everolimus, metastatic renal cell carcinoma, phase 3, prognostic factors, RAD001.

Everolimus is an orally administered inhibitor of mammalian target of rapamycin (mTOR), a component of an intracellular signaling pathway regulating cell growth and proliferation, metabolism, and angiogenesis. Abnormal functioning of the mTOR pathway may contribute to the pathogenesis of renal cell carcinoma (RCC).[1,2]

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The RECORD-1 (*Re*nal *C*ell cancer treatment with *O*ral *R*AD001 given *D*aily) trial assessed everolimus in patients with metastatic RCC (mRCC) who progressed on vascular endothelial growth factor receptor–tyrosine kinase inhibitor (VEGFR-TKI) therapy. A preplanned interim analysis reported that everolimus-treated patients had superior progression-free survival (PFS) compared with placebo-treated patients.[3] The independent data monitoring committee halted the trial, and the study was unblinded (end of double-blind treatment phase).

Herein, updated efficacy and safety results are reported until the end of double-blind treatment in the full data set of 416 patients. Efficacy data are also reported for patients who progressed on placebo, were unblinded, and crossed over to open-label everolimus. Mature overall survival (OS) data at 13 months after interim analysis data cutoff are presented. Exploratory OS analysis was performed to correct the treatment effect estimate for bias introduced by crossover from placebo to open-label everolimus after disease progression. Because the mRCC treatment paradigm has changed, assessment of pretreatment prognostic factors for PFS and OS in patients with VEGFR-TKI refractory tumors was undertaken. This is the first assessment of prognostic factors in this population.

MATERIALS AND METHODS
Patients and Study Design
Study design for RECORD-1 has been described.[3] The population comprised patients with clear-cell mRCC and disease progression during or within 6 months of stopping sunitinib and/or sorafenib. Prior therapy with cytokines and/or VEGF inhibitors (eg, bevacizumab) was permitted. Patients gave written informed consent.

In this prospective, randomized, double-blind, placebo-controlled, international, multicenter, phase 3 trial (Clinicaltrials.gov identifier: NCT00410124), eligible patients were randomized (2:1) to receive everolimus 10 mg/d orally plus best supportive care (BSC) or matching placebo plus BSC. Study drug was provided by Novartis Oncology (Florham Park, NJ), the trial sponsor. Randomization was stratified by Memorial Sloan-Kettering Cancer Center prognostic criteria for patients with previously treated mRCC (favorable, intermediate, or poor)[4] and prior VEGFR-TKI therapy (1 vs 2 prior VEGFR-TKIs). Blinded treatment was discontinued for progression, unacceptable toxicity, or study discontinuation. Investigators were blinded to study group assignments;

disclosure was permitted after documented Response Evaluation Criteria in Solid Tumors (RECIST) progression by investigator assessment. Patients who progressed by investigator assessment were unblinded, and those assigned to placebo were offered open-label everolimus.

Specific toxicities allowed dose interruption and reductions to 5 mg daily or every other day. Protocol and amendments were reviewed by local independent ethics committees or institutional review boards, and the study was conducted using established ethical principles.

Efficacy and Safety Endpoints
The primary endpoint was PFS by central review. Secondary endpoints included safety, objective response rate, OS, and quality of life. Tumor response was assessed by RECIST,[5] with the use of imaging studies at scheduled intervals by treating physicians and an independent third-party core imaging laboratory.[3] Assessment of central review response was discontinued at double-blind treatment end (February 28, 2008), when the primary endpoint was met at the interim analysis and study treatment was unblinded.

Safety evaluations were performed as reported.[3] Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy–Kidney Symptom Index, Disease Related Symptoms questionnaire administered monthly on Day 1 of treatment cycle and at discontinuation. In this report, PFS, objective response rate, patient-reported outcomes, Karnofsky performance status (KPS), and safety data are provided through February 2008. Mature OS data are provided for data cut off of November 2008.

Statistical Analysis and Study Conduct
Original sample size (n = 362) was calculated using an unstratified 1-sided sequential log-rank score test with a cumulative type I error of $\alpha = .025$, and a cumulative power $1 - \beta = 90\%$ was used for a 3-look group sequential plan. Assuming a hazard ratio (HR) of 0.67 corresponding to median PFS of 4.5 (everolimus/BSC) and 3.0 months (placebo/BSC) and a 2:1 randomization, 290 PFS events were required for the final analysis. Two interim analyses were performed when approximately 30% and approximately 60% of the targeted 290 PFS events (per central radiology assessment) had been reached. The actual study data cutoff for the second interim analysis was October 15, 2007; data for 410 patients collected until this cutoff were analyzed in February 2008, and results were reviewed by an independent data monitoring

committee. The prespecified efficacy boundary for primary endpoint (O'Brien-Flemming type stopping rule) was crossed at this interim analysis, the study was unblinded, and the double-blind phase of the trial was terminated on February 28, 2008; 6 placebo-treated patients still on study were offered open-label everolimus.

In this analysis, 416 randomized patients were analyzed for efficacy (Full Analysis Set population) including an additional 6 Japanese patients enrolled between September 1 and November 5, 2007. These 6 patients were necessary to complete a commitment required by the Japanese Health Authority. The safety population (n = 411) included patients who received ≥1 dose of study drug with ≥1 valid postbaseline safety assessment. Data for this analysis were collected until the end of double-blind treatment (February 28, 2008) and based on 266 PFS events (vs 191 PFS events at the interim analysis), 6 additional accrued patients, and 4.5 months of additional blinded follow-up. The previously presented OS data cutoff was October 15, 2007, compared with November 15, 2008 for the analysis reported herein.

PFS and OS were compared between groups with a stratified, 1-sided, log-rank test adjusting for strata defined by Memorial Sloan-Kettering Cancer Center risk criteria. HRs were obtained from a stratified Cox model. Sensitivity and supportive evaluations of PFS included subgroup analyses and analyses of investigator assessments.

A post hoc exploratory OS analysis was performed using a rank-preserving structural failure time model to correct the treatment effect estimate for bias introduced by crossover from placebo to open-label everolimus after disease progression.[6,7] The rank-preserving structural failure time model provides a randomization-based estimate of treatment effect assuming a multiplicative effect of treatment on survival time.[7] The approach also allows reconstruction of the placebo survival curve as if all patients initially randomized to placebo never switched to everolimus. This is the first study to apply rank-preserving structural failure time modeling in RCC; however, this model has been used in a phase 3 trial of sunitinib in gastrointestinal stromal tumors.[8]

An analysis was performed investigating the impact of a prespecified set of prognostic factors (demographics, prior treatment, clinical features, specific laboratory values at baseline) on PFS and OS. Univariate and multivariate Cox proportional hazard models were applied, both stratified by randomized treatment (everolimus vs placebo), to adapt for treatment effect. Categorization of continuous factors was based on prespecified cutoff points. Model building started with the full model (all prespecified factors included); the final multivariate Cox model was obtained using backward variable elimination with selection level α = .05. Continuous factors were investigated assuming a linear effect and investigating for a potential nonlinear effect.[9,10]

RESULTS

Patient Characteristics and Disposition

Baseline characteristics were balanced between treatments (Table 1). The intent-to-treat population comprised 277 (everolimus) and 139 (placebo) patients (Fig. 1). Eighty-nine patients had received 1 prior systemic treatment, and 327 patients had received >1 treatment. Safety population included 274 (everolimus) and 137 (placebo) patients; 5 patients (3 everolimus, 2 placebo) were excluded because they did not receive study medication. At the end of the double-blind phase, 75 (27.1%) patients remained on everolimus, and only 6 (4.3%) patients remained on placebo.

Treatment Administration and Safety

Median treatment durations were 141 days for everolimus (range, 19-451 days) and 60 days for placebo (range, 21-195 days). At least 1 dose reduction occurred in 7% of everolimus-treated patients and 1% of placebo-treated patients. At least 1 treatment interruption occurred in 38% of everolimus-treated patients and 11% of placebo-treated patients. Interruptions were because of adverse events in 35% and 9%, and laboratory test abnormalities in 3% and 2% of everolimus- and placebo-treated patients, respectively.

Safety profile was consistent with the second interim analysis (Table 2).[3] By investigator assessment and after a review of all respiratory adverse events (AEs), 37 (14%) patients had diagnoses consistent with noninfectious pneumonitis (grade 1 = 9, grade 2 = 18, grade 3 = 10). Descriptive statistics showed that median time to onset of pneumonitis was 108 days (range, 24-257 days). Grade 2 or higher noninfectious pneumonitis management included dose interruption and/or reduction and corticosteroid use in selected instances. Everolimus was discontinued for noninfectious pneumonitis in 3 and 7 patients, with grade 2 and 3 toxicity, respectively.

Everolimus exposure was 1.9-fold that of placebo exposure for patients during the double-blind period; the risk of infection associated with everolimus treatment was
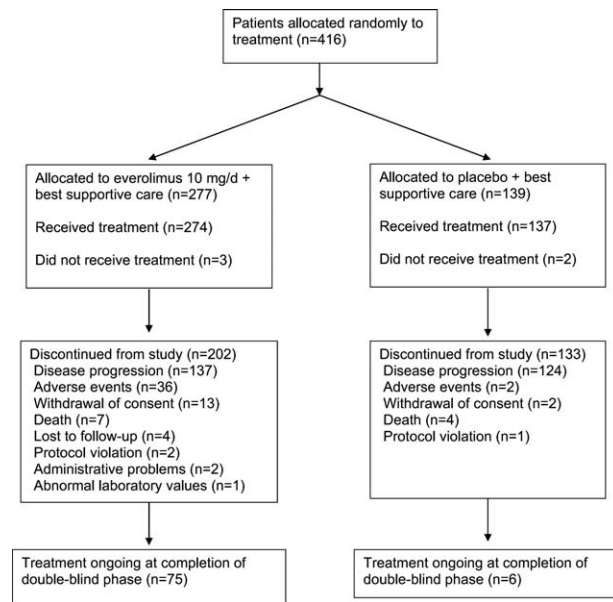
Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristic	Everolimus + BSC, n=277	Placebo + BSC, n=139
Median age, y (range)	61 (27-85)	60 (29-79)
Sex, No. (%)		
Men	216 (78)	106 (76)
Women	61 (22)	33 (24)
KPS, No. (%)		
100	78 (28)	41 (30)
90	98 (35)	53 (38)
80	72 (26)	30 (22)
70	28 (10)	15 (11)
Missing	1 (<1)	0
MSKCC risk, No. (%)[4]		
Favorable	81 (29)	39 (28)
Intermediate	156 (56)	79 (57)
Poor	40 (14)	21 (15)
Prior VEGFR-TKI therapy, No. (%)		
Sunitinib only	124 (45)	60 (43)
Sorafenib only	81 (29)	43 (31)
Sunitinib and sorafenib	72 (26)	36 (26)
Other previous systemic therapy, No. (%)		
Immunotherapy	179 (65)	93 (67)
Chemotherapy	37 (13)	22 (16)
Hormone therapy	5 (2)	5 (4)
Other	15 (5)	4 (3)
Prior radiotherapy, No. (%)	85 (31)	38 (27)
Prior nephrectomy, No. (%)	269 (97)	133 (96)
Disease sites, No. (%)		
1	24 (9)	13 (9)
2	68 (25)	36 (26)
≥3	182 (66)	88 (63)
Common sites of metastasis, No. (%)		
Lymph nodes	210 (76)	97 (70)
Lung	203 (73)	112 (81)
Bone	102 (37)	42 (30)
Liver	92 (33)	53 (38)
Other	140 (51)	59 (42)
Kidney	34 (12)	20 (14)
Brain	17 (6)	12 (9)

BSC indicates best supportive care; KPS, Karnofsky performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram is shown.

1.2-fold that of placebo, after adjustment for differences in exposure.

During the double-blind period, 4 patients died from causes other than disease progression alone; 3 of these deaths were infection-related: *Candida* pneumonia/sepsis with acute respiratory distress syndrome, sepsis (presumed bacterial), and recurrent bronchopulmonary aspergillosis. The fourth death was because of acute respi-ratory failure with disease progression; this patient had ongoing everolimus-related grade 3 interstitial lung disease.

Efficacy Assessment

By central radiology review, median PFS was 4.9 months (95% confidence interval [CI], 4.0-5.5 months) with everolimus and 1.9 months (95% CI, 1.8-1.9 months) with placebo (HR, 0.33; 95% CI, 0.25-0.43; $P < .001$) (Fig. 2A). By Kaplan-Meier analysis, the probability of remaining progression free 10 months after start of treatment was 25% in the everolimus arm. Sensitivity analyses indicated that benefit was maintained across subgroups and was consistent with the interim analysis (data not shown).[3]

Investigator-assessed data demonstrated a median PFS of 5.5 months (95% CI, 4.6-5.8 months) with everolimus versus 1.9 months (95% CI, 1.8-2.2 months) with placebo (HR, 0.32; 95% CI, 0.25-0.41; $P < .001$) (Fig. 2B).

Before ending the double-blind treatment, 106 (76.2%) of 139 patients who originally were randomized to placebo and showed progression had crossed over to everolimus. Median PFS after crossover was 5.1 months (95% CI, 3.7-7.6) by investigator's assessment (Fig. 2C).

Best response by central review assessment of stable disease was achieved in 185 (66.8%) of 277 patients in the everolimus group versus 45 (32.4%) of 139 in the placebo

Table 2. Adverse Events, Irrespective of Relation to Treatment, and Laboratory Abnormalities Occurring in ≥10% of Patients in the Everolimus Group

Adverse Events/Abnormalities	Everolimus + BSC, n=274			Placebo + BSC, n=137		
	Overall Incidence	Grade 3	Grade 4	Overall Incidence	Grade 3	Grade 4
Adverse event, %						
Stomatitis[a]	44	4	<1	8	0	0
Infections[b]	37	7	3	18	1	0
Asthenia	33	3	<1	23	4	0
Fatigue	31	5	0	27	3	<1
Diarrhea	30	1	0	7	0	0
Cough	30	<1	0	16	0	0
Rash	29	1	0	7	0	0
Nausea	26	1	0	19	0	0
Anorexia	25	1	0	14	<1	0
Peripheral edema	25	<1	0	8	<1	0
Dyspnea	24	6	1	15	3	0
Vomiting	20	2	0	12	0	0
Pyrexia	20	<1	0	9	0	0
Mucosal inflammation	19	1	0	1	0	0
Headache	19	<1	<1	9	<1	0
Epistaxis	18	0	0	0	0	0
Pruritus	14	<1	0	7	0	0
Pneumonitis[c]	14	4	0	0	0	0
Dry skin	13	<1	0	5	0	0
Dysgeusia	10	0	0	2	0	0
Pain in extremity	10	1	0	7	0	0
Laboratory abnormality, %						
Hematology[d]						
Hemoglobin decreased	92	12	1	79	5	<1
Lymphocytes decreased	51	16	2	28	5	0
Platelets decreased	23	1	0	2	0	<1
Neutrophils decreased	14	0	<1	4	0	0
Clinical chemistry						
Cholesterol increased	77	4	0	35	0	0
Triglycerides increased	73	<1	0	34	0	0
Glucose increased	57	15	<1	25	1	0
Creatinine increased	50	1	0	34	0	0
Phosphate decreased	37	6	0	8	0	0
Aspartate transaminase increased	25	<1	<1	7	0	0
Alanine transaminase increased	21	1	0	4	0	0
Bilirubin increased	3	<1	<1	2	0	0

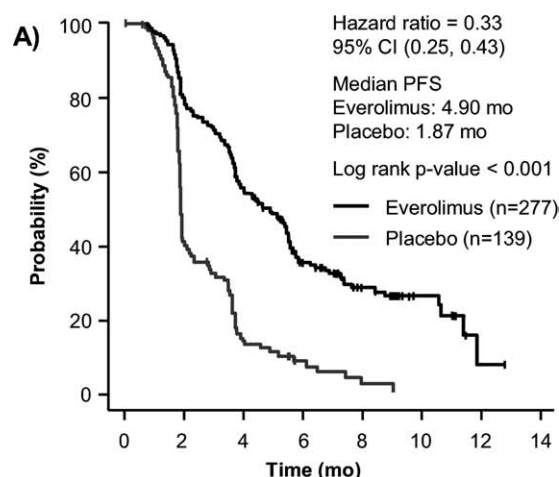BSC indicates best supportive care.
[a] Stomatitis (including aphthous stomatitis), mouth ulceration, and tongue ulceration.
[b] All infections reported, including pneumonia, aspergillosis, candidiasis, and sepsis.
[c] Includes interstitial lung disease, lung infiltration, pneumonitis, pulmonary alveolar hemorrhage, alveolitis, and pulmonary toxicity.
[d] Includes reports of anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, and thrombocytopenia.

group. No complete responses were observed; the partial response rate was 1.8% (n = 5) with everolimus and 0% with placebo. Decreases in tumor measurement from baseline as best percentage change from baseline were observed in 47% of patients treated with everolimus versus 10.0% with placebo (for waterfall plot, see Fig. 3). Analyses assessing time to definitive deterioration in KPS by 10% and time to definitive deterioration of Functional Assessment of Cancer Therapy–Kidney Symptom Index, Disease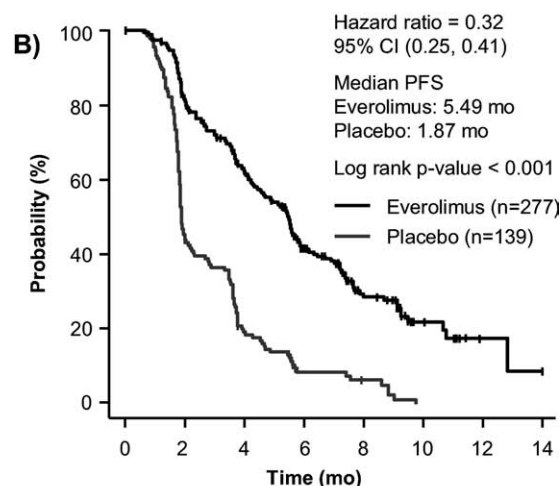 Related Symptoms by 2 score units showed improved outcome with everolimus over placebo (1-sided log-rank P values: $P = .004$ and $P = .053$, respectively) (Figs. 4 and 5).

PFS (by central review) was compared for everolimus and placebo according to prior VEGFR-TKI. Median PFS for patients treated with everolimus versus placebo was as follows: prior sunitinib (n = 184 patients), 3.9 versus 1.8 months (HR, 0.34; 95% CI, 0.23-0.51); prior sorafenib (n = 124), 5.9 versus 2.8 months (HR, 0.25; 95% CI, 0.16-0.42); and prior sunitinib and
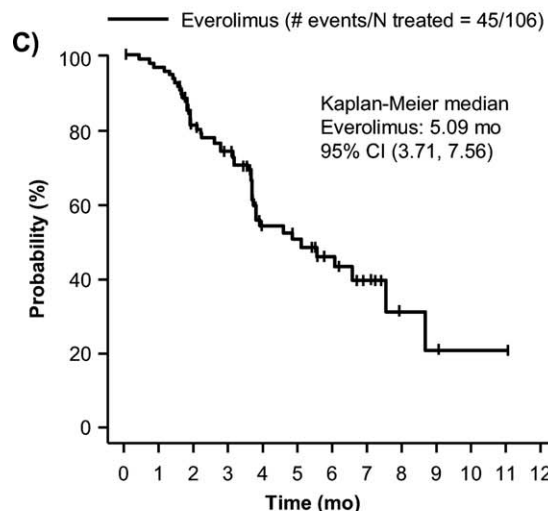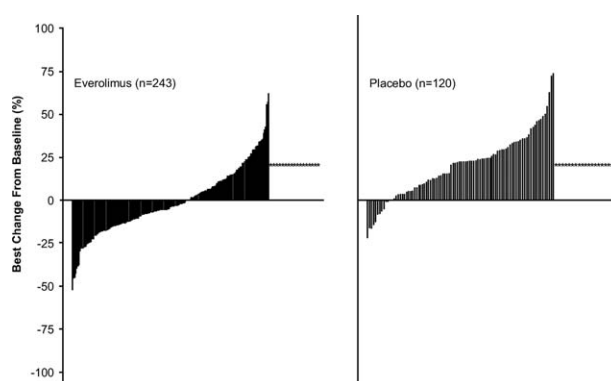
A)
Hazard ratio = 0.33
95% CI (0.25, 0.43)

Median PFS
Everolimus: 4.90 mo
Placebo: 1.87 mo

Log rank p-value < 0.001

— Everolimus (n=277)
— Placebo (n=139)

Number of patients at risk

Everolimus	277	192	115	51	26	10	1	0
Placebo	139	47	15	6	2	0	0	0

B)
Hazard ratio = 0.32
95% CI (0.25, 0.41)

Median PFS
Everolimus: 5.49 mo
Placebo: 1.87 mo

Log rank p-value < 0.001

— Everolimus (n=277)
— Placebo (n=139)

Number of patients at risk

Everolimus	277	210	149	76	33	11	2	0
Placebo	139	62	25	8	5	0	0	0

C)
— Everolimus (# events/N treated = 45/106)

Kaplan-Meier median
Everolimus: 5.09 mo
95% CI (3.71, 7.56)

Number of patients at risk

Everolimus	106	91	69	61	30	27	15	9	3	2	1	1	0

Figure 3. Best percentage change from baseline in sum of longest diameters based on central radiology review is shown. Thirty-four patients and 19 patients in the everolimus and placebo arms, respectively, for whom the best percent change in target lesions was not available or for whom the best percent change in target lesions was contradicted by unknown overall lesion response, were excluded from the analysis.

sorafenib (n = 108), 4.0 versus 1.8 months (HR, 0.32; 95% CI, 0.19-0.54).

Overall Survival

Median OS was 14.8 months in patients randomized to everolimus versus 14.4 months for patients randomized to placebo (HR, 0.87; 95% CI, 0.65-1.15; $P = .162$) (Fig. 6A). Before November 2008, 111 (80%) of 139 patients allocated to the placebo received open-label everolimus. Survival results likely were confounded by crossover to everolimus.

The exploratory rank-preserving structural failure time analysis estimates the relative survival treatment benefit of everolimus versus placebo. Adjusting for patients who switched therapy, the survival time if always treated with everolimus would be 1.9-fold longer (95% CI, 0.5-8.5) than if never treated with everolimus (ie, when receiving placebo only). The rank-preserving structural failure time approach was also used to reconstruct the placebo survival curve as if all patients initially randomized to placebo never switched over to everolimus; the reconstructed

Figure 2. (A) Kaplan-Meier estimates of progression-free survival (PFS) are shown by central radiology review. (B) Kaplan-Meier estimates of PFS are shown by investigator review. (C) Kaplan-Meier estimates of PFS on everolimus for patients who received placebo and were crossed over to everolimus are shown by investigator review. CI indicates confidence interval.
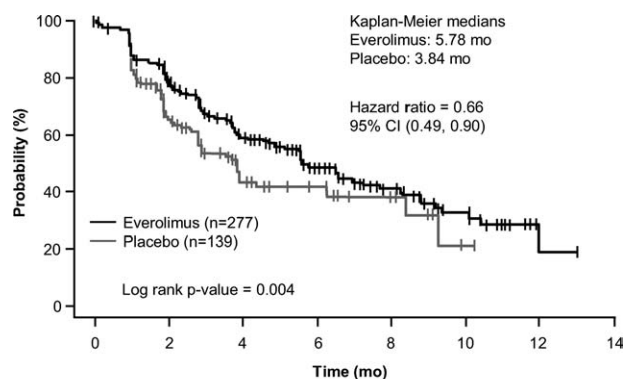
Figure 4. Time to definitive deterioration in Karnofsky performance status by 10% is shown. CI indicates confidence interval.
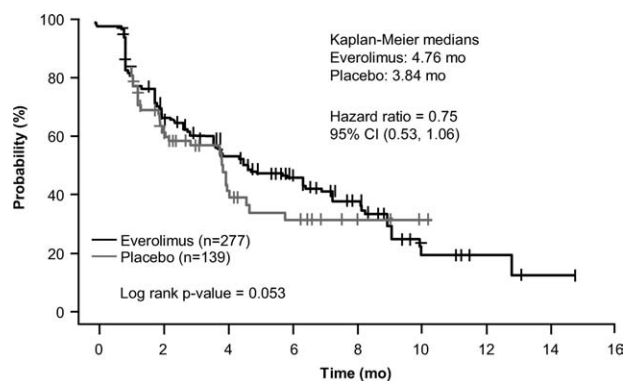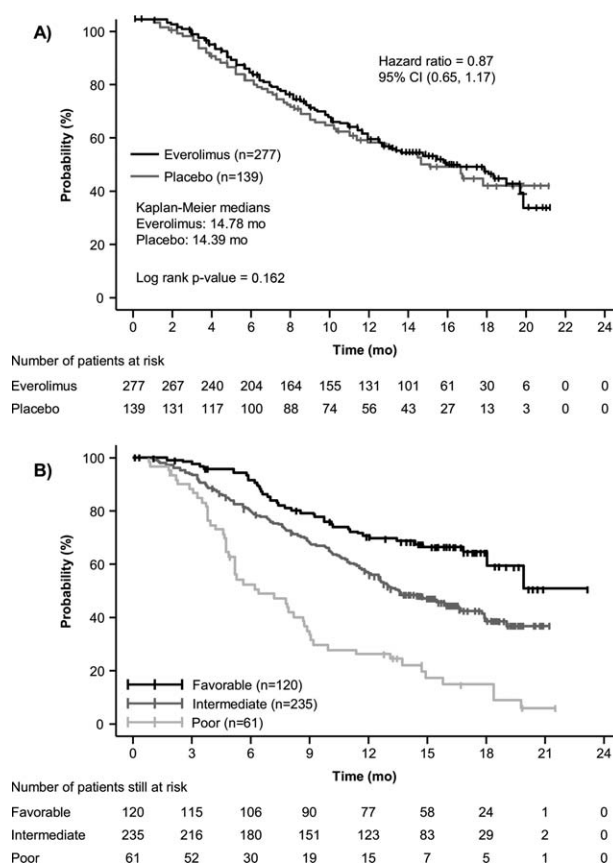

Figure 5. Time to definitive deterioration of the Functional Assessment of Cancer Therapy–Kidney Symptom Index, Disease Related Symptoms risk score by 2 U is shown. CI indicates confidence interval.

Figure 6. (A) Kaplan-Meier estimates of overall survival (OS) are shown by treatment group. (B) Kaplan-Meier estimates of OS are shown by MSKCC risk score.[4] CI indicates confidence interval.

median OS for placebo was 10.0 months, that is, 4.8 months shorter than the observed median OS with everolimus.

Pretreatment Prognostic Factors

In univariate analyses, a significant effect ($P < .05$) was obtained for many baseline features (Table 3). For example, the number of prior therapies, 1 (n = 89) versus >1 (n = 327), was associated with OS duration ($P = .0152$; median, 11.6 vs 16.6 months, respectively). Starting with the full model (all factors included) and using a significance level of $\alpha = .05$, factors were selected for the final multivariate model for PFS and OS.

The Memorial Sloan-Kettering Cancer Center risk model established in previously treated patients is redundant to 3 variables (KPS, corrected calcium, and hemoglobin). Therefore, the multivariate Cox proportional hazards models for OS were obtained using 2 strategies: 1) using Memorial Sloan-Kettering Cancer Center risk group (2 dummy variables comparing intermediate risk vs favorable risk and poor risk vs favorable risk) to investigate if this risk model is confirmed in the current study; and 2) using KPS, corrected calcium, and hemoglobin as individual variables to investigate whether these 3 factors have a prognostic value themselves. For PFS, the same final model is obtained with both strategies (Table 4). The final model obtained for OS with Strategy 1 includes the Memorial Sloan-Kettering Cancer Center risk score. In Strategy 2, all 3 individual variables of Memorial Sloan-Kettering Cancer Center risk score are included in the final OS model indicating the prognostic relevance of these factors (Table 4).

Table 3. Results of Univariate Analysis for All Predefined Prognostic Factors

Factor	*P* <.05 on Univariate Analysis[a]	
	PFS	OS
KPS (<80 vs ≥80)[b]		x
Sex		
Age (<65 vs ≥65 years)		
MSKCC risk score[c]	x	x
Time from initial diagnosis (<1 vs ≥1 year)		x
No. of organs involved (1 vs >1)[d]	x	x
Liver metastases	x	x
Lung metastases		
Bone metastases	x	x
Lymph nodes involved	x	
CNS metastases	x	x
Prior radiation		x
No. of prior medications (1 vs >1)[d,e]		x
Prior sunitinib	x	x
Prior sorafenib		x
Prior bevacizumab		x
Prior interferon		x
Prior interleukin		
Corrected calcium (≤2.5 mmol/L vs >2.5 mmol/L)[b]	x	x
Alkaline phosphatase (≤ULN vs >ULN)	x	x
LDH (≤1.5 × ULN >1.5 × ULN)		x
Hemoglobin (<LLN vs ≥LLN)[b]	x	x
Platelets (<LLN vs ≥LLN)		
Neutrophils (≤ULN vs >ULN)	x	x

PFS indicates progression-free survival; OS, overall survival; KPS, Karnofsky performance status; MSKCC, Memorial Sloan-Kettering Cancer Center; CNS, central nervous system; ULN, upper limit of normal; LDH, lactate dehydrogenase; LLN, lower limit of normal.

[a] Likelihood ratio test, stratified by study treatment.
[b] Excluded from multivariate model for Strategy 1 only.
[c] Excluded from multivariate model for Strategy 2 only.
[d] Excluded from multivariate model; single factors used instead.
[e] Patients received a median of 2 prior antineoplastic medications. Eighty-nine patients (21%) had received 1 prior medication, 141 (34%) had received 2 medications, 104 (25%) had received 3 medications, and 82 (20%) had received ≥4 medications.

For OS, additional models were constructed using the continuous form rather than the categorized form where applicable. Assuming a linear effect of all continuous variables, the selected model included nearly the same variables as shown in Table 3. In addition, the resulting models included the variables *time since initial diagnosis* and *lactate dehydrogenase* (LDH). Further investigation of continuous covariates suggests a nonlinear effect for LDH (results not shown).

Overall results confirm the capability of Memorial Sloan-Kettering Cancer Center risk score to distinguish different prognosis for OS. The probability of being alive at 12 months for the favorable, intermediate, and poor risk groups was 70% (95% CI, 62-79%), 56%

(95% CI, 50-63%), and 26% (95% CI, 15-37%), respectively (Fig. 6B). In the final multivariate Cox model, risk was significantly increased for patients with an intermediate (HR, 1.54; 95% CI, 1.08-2.19) or poor risk score (HR, 3.38; 95% CI, 2.21-5.16) compared with patients with a favorable risk score. The analysis also demonstrated that patients with liver or bone metastases, elevated neutrophils, or prior treatment with sunitinib had decreased PFS and OS (Table 4), indicating prognostic relevance.

DISCUSSION

Everolimus provided a significant benefit in PFS for patients with mRCC who progressed on sunitinib and/or sorafenib. Risk of progression was reduced by 67% for the everolimus group compared with the placebo group. Median PFS by central review and investigator assessment was 4.9 and 5.5 months, respectively, compared with 1.9 months for placebo (*P* < .001). In patients who crossed over to open-label everolimus after progression by RECIST on placebo, the median PFS was 5.1 months (95% CI, 3.7-7.6). A clinical benefit for everolimus in this setting is supported by quality of life and performance status analyses.

The safety profile of everolimus is acceptable. Grade 3 or 4 AEs were low, and 7% required dose modification. Thirty-six (13%) of 274 patients receiving everolimus had treatment discontinued for AEs. Grade 3 noninfectious pneumonitis occurred in 10 (4%) patients in the everolimus group. Noninfectious pneumonitis is an adverse reaction associated with rapamycin and rapamycin analogues.[11] Awareness of this toxicity and appropriate diagnostic and medical management is important to optimize patient safety.

The adverse event profile of everolimus differs from that of VEGFR-TKIs.[12,13] This may be an advantage in patients showing intolerance to sorafenib or sunitinib and could avoid potential for cumulative toxicity associated with sequential VEGFR-TKI treatment. For example, hypertension, cardiac events, hypothyroidism, and hand-foot skin reaction, which may be problematic with VEGFR-TKIs, are not observed commonly with everolimus.

The OS analysis was likely confounded by crossover to open-label everolimus for most participants assigned to placebo. Crossover from placebo to open-label everolimus was implemented in the trial design based on ethical and practical considerations. Mature survival results show that the median OS was 14.8 months for patients treated with everolimus. A beneficial effect on survival for everolimus

Table 4. Final Multivariate Cox Proportional Hazards Models for PFS and OS[a]

Prognostic Factor	*P*	HR	95% CI
PFS (Strategies 1 and 2)			
Prior sunitinib (yes vs no)	<.001	1.87	1.42-2.48
Liver metastases (yes vs no)	<.001	1.64	1.26-2.12
Bone metastases (yes vs no)	<.001	2.30	1.76-3.01
Lymph nodes involved (yes vs no)	.009	1.48	1.10-1.98
Neutrophils (>ULN vs ≤ULN)	<.001	2.04	1.39-2.98
OS (Strategy 1)			
MSKCC[b]			
Intermediate vs favorable	.018	1.54	1.08-2.19
Poor vs favorable	<.001	3.38	2.21-5.16
Prior sunitinib (yes vs no)	<.001	1.92	1.39-2.67
Prior interferon (yes vs no)	.011	0.71	0.54-0.92
Liver metastases (yes vs no)	.016	1.42	1.07-1.88
Bone metastases (yes vs no)	<.001	1.64	1.25-2.16
Alkaline phosphatase (>ULN vs ≤ULN)	<.001	1.92	1.41-2.61
Neutrophils (>ULN vs ≤ULN)	<.001	3.14	2.16-4.57
OS (Strategy 2)			
KPS (<80 vs ≥80)	<.001	2.13	1.43-3.16
Corrected calcium (>2.5 mol/L vs ≤2.5 mol/L)	<.001	2.01	1.47-2.74
Hemoglobin (<LLN vs ≥LLN)	.005	1.66	1.17-2.37
Prior sunitinib (yes vs no)	<.001	1.97	1.42-2.75
Prior interferon (yes vs no)	.003	0.65	0.50-0.86
Liver metastases (yes vs no)	<.001	1.64	1.24-2.19
Bone metastases (yes vs no)	<.001	1.76	1.32-2.35
Alkaline phosphatase (>ULN vs ≤ULN)	.014	1.52	1.09-2.12
Neutrophils (>ULN vs ≤ULN)	<.001	2.61	1.76-3.87

PFS indicates progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ULN, upper limit of normal; MSKCC, Memorial Sloan-Kettering Cancer Center; KPS, Karnofsky performance status; LLN, lower limit of normal.

[a] Final models were obtained by backward variable elimination using selection level $\alpha = .05$ and stratified by randomized treatment. For Strategy 1, MSKCC risk groups were included using the favorable group as the reference. For Strategy 2, single factors of the MSKCC score (KPS, corrected calcium, and hemoglobin) were included.

[b] MSKCC risk status in previously treated patients.[4] Dummy coding was performed with 2 binary variables using the favorable risk group as a reference category.

was supported by outcome from an exploratory analysis that accounted for this crossover effect. According to that analysis, the estimated median survival for patients on the placebo arm in the absence of crossover to everolimus is 10.0 months instead of the observed 14.4 months.

Earlier independent prognostic factors established for patients with mRCC previously treated with cytokines or chemotherapy,[4] including high corrected calcium, low KPS, and low hemoglobin, were implemented in the resulting Memorial Sloan-Kettering Cancer Center risk model used for stratification in the RECORD-1 trial. Because the treatment paradigm has changed, assessment of prognostic factors in patients with VEGFR-TKI refractory tumors was undertaken.

In developing the Cox proportional hazards model for this prognostic factor analysis, stratification by randomized treatment (everolimus vs placebo) was used

to adapt for the treatment effect. All 3 prognostic factors of the Memorial Sloan-Kettering Cancer Center score were independent predictors of OS, and confirmed the capability of Memorial Sloan-Kettering Cancer Center risk score to separate patients into prognostic subgroups and the relevance of these factors for the risk score. Other risk factors, such as presence of liver or bone metastases, or prior treatment with sunitinib, were associated with decreased OS and PFS. These prognostic factors relate to survival after VEGFR-TKIs and are not predictive of response to everolimus. Clinical benefit with everolimus was observed for all patient subsets in each Memorial Sloan-Kettering Cancer Center risk group[4] and regardless of which prior VEGFR-TKI was received.

The observation that patients who received prior sunitinib treatment had a poorer prognosis (whereas prior

sorafenib treatment did not) is intriguing. The difference in median PFS of patients on the placebo arm who were previously treated with sunitinib or sorafenib but not both, 1.8 months versus 2.8 months, respectively, suggests that there may have been a bias in the selection of VEGFR-TKI or that resistance to sunitinib is associated with a more aggressive tumor biology.

Optimal sequencing of targeted agents in second- and third-line therapy was not fully addressed in this trial because of practical considerations. Among patients enrolled, 21% (89 of 416) had prior treatment limited to 1 prior VEGFR-TKI, 53% (219 of 416) had received 1 VEGFR-TKI and at least 1 other prior therapy (most commonly a cytokine), and 26% (108 of 416) had received both VEGFR-TKIs with or without additional prior therapy. As such, everolimus is the only drug to show a PFS benefit in a randomized phase 3 trial in patients who progressed on a VEGFR-TKI.

In summary, the benefit and safety of everolimus is established in patients with mRCC after progression on VEGFR-TKI therapy. Previously reported Memorial Sloan-Kettering Cancer Center risk features maintained prognostic value in this new clinical setting. Ongoing and future trials with everolimus include clinical studies in combination with bevacizumab and other targeted agents in the front-line setting and sequencing studies with sunitinib and everolimus.[14,15]

CONFLICT OF INTEREST DISCLOSURES

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