# Efficacy and Safety of Everolimus in Elderly Patients With Metastatic Renal Cell Carcinoma: An Exploratory Analysis of the Outcomes of Elderly Patients in the RECORD-1 Trial

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## Abstract

**Background**—Elderly patients with metastatic renal cell carcinoma (mRCC) may require special treatment considerations, particularly when comorbidities are present. An understanding of the efficacy and safety of targeted agents in elderly patients with mRCC is essential to provide individualized therapy.

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**Objective**—To evaluate the efficacy and safety of everolimus in elderly patients (those 65 and 70 yr of age) enrolled in RECORD-1.

**Design, setting, and participants**—The multicenter randomized RECORD-1 phase 3 trial (Clinicaltrials.gov identifier, NCT00410124; http://www.clinicaltrials.gov) enrolled patients with mRCC who progressed during or within 6 mo of stopping sunitinib and/or sorafenib treatment (*n* = 416).

**Intervention**—Everolimus 10 mg once daily (*n* = 277) or placebo (*n* = 139) plus best supportive care. Treatment was continued until disease progression or unacceptable toxicity.

**Measurements**—Median progression-free survival (PFS), median overall survival (OS), and time to deterioration in Karnofsky performance status (TTD-KPS) were assessed using the Kaplan-Meier method; the log-rank test was used to compare treatment arms. Other outcomes evaluated included reduction in tumor burden, overall response rate (ORR), and safety.

**Results and limitations**—In RECORD-1, 36.8% of patients were 65 yr and 17.5% were 70 yr of age. PFS, OS, TTD-KPS, reduction in tumor burden, and ORR were similar in the elderly and the overall RECORD-1 population. Everolimus was generally well tolerated in elderly patients, and most adverse events were grade 1 or 2 in severity. The toxicity profile of everolimus was generally similar in older patients and the overall population; however, peripheral edema, cough, rash, and diarrhea were reported more frequently in the elderly regardless of treatment. The retrospective nature of the analyses was the major limitation.

**Conclusions**—Everolimus is effective and tolerable in elderly patients with mRCC. When selecting targeted therapies in these patients, the specific toxicity profile of each agent and any patient comorbidities should be considered.

## 1. Introduction

Over the last 5 yr, the treatment options available for the management of metastatic renal cell carcinoma (mRCC) have increased, with the approval of several agents targeting specific angiogenic or growth and proliferation pathways. Although these agents (ie, sunitinib, sorafenib, pazopanib, bevacizumab, temsirolimus, and everolimus) are now widely used in patients with mRCC, safety data continue to emerge from long-term follow-up and expanded access programs. Improved understanding of the efficacy and safety profiles of targeted agents in specific populations may enhance the ability of clinicians to provide individualized therapy and improve outcomes in mRCC.

Elderly patients constitute a large component of the mRCC population because the incidence of mRCC increases with age, with a median age of 62 yr at diagnosis [1]. Comorbid conditions are generally more prevalent in elderly patients compared with their younger counterparts. In a population-based study, serious concomitant diseases were present in 9%, 25%, 49%, and 60% of patients with newly diagnosed cancer <45, 45–59, 60–74, and 75 yr of age, respectively [2]. Another study reported the most prevalent comorbidities observed

in patients (*n* = 363) to be arthrosis-arthritis (31%), hypertension (29%), digestive diseases (23%), cardiac disease (21%), and vascular disease (19%) [3]. In addition, elderly patients with cancer are more likely to have a compromised performance status: In one study of 593 patients, a baseline Eastern Cooperative Oncology Group performance status 1 was observed in 30% of patients 70 yr of age versus 9% of patients <70 yr [4]. The presence of comorbidities and decreased performance status in an older patient may result in a decreased ability to tolerate cancer therapy and therefore to receive the intended dose intensity. An additional concern is that medications taken to manage comorbidities may interact with cancer treatments. Although clinical trials have not been performed directly comparing the safety and efficacy of targeted agents in the elderly population, retrospective analyses of outcomes in elderly subsets enrolled in large clinical trials may provide useful information about how age affects the efficacy and tolerability of individual targeted agents.

Everolimus is a mammalian target of rapamycin (mTOR) inhibitor approved in 65 countries for use in patients with mRCC who have failed prior vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy. The phase 3 RECORD-1 trial demonstrated a significant improvement in progression-free survival (PFS) with everolimus. Median PFS by independent central review was 4.9 mo with everolimus versus 1.9 mo with placebo ($p < 0.001$) [5,6]. Stomatitis, infection, asthenia, and fatigue, the most commonly reported adverse events (AEs) with everolimus, were manageable and mainly grade 1 or 2 in severity.

In RECORD-1, age (<65 vs 65 yr) was not reported to have significant prognostic value for either PFS or overall survival (OS) [6]; however, a detailed subgroup analysis in elderly patients was not performed. Here we compare the outcomes and toxicities in patients 65 and 70 yr of age enrolled in RECORD-1 with those of the overall study population to further explore the tolerability and efficacy of everolimus in elderly patients.

## 2. Patients and methods

### 2.1. Eligibility and treatment

The study design of the randomized double-blind multicenter phase 3 RECORD-1 trial was previously reported [5,6]. Adult patients with metastatic clear cell RCC who experienced disease progression on or within 6 mo of stopping treatment with sunitinib, sorafenib, or both, were enrolled. Prior therapy with bevacizumab, interleukin-2, or interferon-α was allowed. Patients were assigned to receive everolimus 10 mg/d plus best supportive care (BSC) or placebo plus BSC. Randomization was stratified by Memorial Sloan-Kettering Cancer Center risk and number of prior VEGFr-TKI therapies (one vs two). Treatment continued until disease progression or unacceptable toxicity. Patients receiving placebo were allowed to cross over to the everolimus arm upon disease progression (during the blinded period of study) or at the end of the blinded study period.

### 2.2. Study design and outcome variables

Retrospective subgroup analyses compared efficacy and safety outcomes, including PFS, OS, reduction in tumor burden, time to deterioration of Karnofsky performance status

(KPS), and the frequency and severity of AEs, in patients 65 and 70 yr of age versus the overall RECORD-1 population. Tumor measurements were performed by calculating the sum of the longest diameter of all target lesions as assessed by computed tomography or magnetic resonance imaging at baseline and every 8 wk thereafter until study discontinuation. Disease progression was assessed by a blinded independent central review committee. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v.3.0.

### 2.3. Statistical analysis

Analyses were performed on the final RECORD-1 data set [6]. Subgroup analyses of efficacy were performed on the intent-to-treat population ($n = 416$). Subgroup analyses of safety were performed on the safety population ($n = 411$), which included patients who received one or more dose of the study drug with one or more valid postbaseline safety assessment. The Kaplan-Meier method was used to estimate PFS and median time to definitive worsening of KPS; the log-rank test was used to test the difference between the treatment arms. Descriptive statistics were used to compare safety outcomes. Definitive worsening was defined as a decrease in performance status by one or more Karnofsky category (ie, at least 10 points less) compared with baseline.

## 3. Results

### 3.1. Patients

Among the 416 patients enrolled in the RECORD-1 study, 36.8% were 65 yr and 17.5% were 70 yr of age. Of those 65 yr, 112 patients and 41 patients received everolimus or placebo, respectively. Of those 70 yr, 53 patients and 20 patients received everolimus or placebo, respectively. Table 1 summarizes the baseline characteristics.

### 3.2. Efficacy

Everolimus significantly improved PFS over placebo in elderly patients, to an extent consistent with that seen in the overall study population (Fig. 1). By central review, median PFS with everolimus and placebo, respectively, was 5.4 mo versus 2.2 mo in patients 65 yr of age (hazard ratio [HR]: 0.33; 95% confidence interval [CI], 0.21–0.51; $p < 0.001$), 5.1 mo versus 1.9 mo in patients 70 yr of age (HR: 0.19; 95% CI, 0.09–0.37; $p < 0.001$), and 4.9 mo versus 1.9 mo in the overall study population (HR: 0.33; 95% CI, 0.25–0.43; $p < 0.001$). Measurements of best percentage change in target lesion size from baseline were comparable in elderly patients and the overall study population (Fig. 2). In patients 65 yr, 70 yr, and in all patients, 44.1%, 52.1%, and 46.9% of everolimus-treated patients and 13.9%, 11.1%, and 10% of patients receiving placebo, respectively, had a decrease in tumor burden. Although statistically significant in the overall study population, in elderly patients there was no difference in the time to definitive deterioration of KPS with everolimus versus with placebo (Fig. 3; 6.5 mo vs 6.3 mo, >65 yr; 6.9 mo vs not reached, 70 yr).

Objective response rates were 2.7%, 3.8%, and 1.8% in patients 65 yr, 70 yr, and in all patients, respectively, with no responses observed in any group receiving placebo (Table 2). Consistent with the overall study population, no significant difference in median OS was

observed in everolimus-treated patients compared with those receiving placebo age 65 yr and 70 yr (Table 2).

### 3.3. Safety

Toxicities in elderly patients were similar to those in the overall study population. Stomatitis was the most common AE of any grade in everolimus-treated patients, including the elderly populations (Table 3). Some AEs, including peripheral edema, cough, rash, and diarrhea, occurred at higher rates in the elderly subgroups for both everolimus and placebo-treated patients compared with the overall study population. Rates of grade 3/4 AEs were low in the elderly and generally consistent with rates reported in all patients (Table 4). The most common grade 3/4 toxicities in patients 65 yr and 70 yr were anemia (14% and 12%, respectively), infection (11% and 12%, respectively), lymphopenia (9% and 10%, respectively), and hyperglycemia (8% in both subgroups).

Elderly patients did not experience a higher rate of noninfectious pneumonitis with everolimus: Pneumonitis of any grade was reported in 11% of patients age 65 yr and 10% of patients 70 yr, compared with 14% among all RECORD-1 patients. Grade 3 pneumonitis was reported in 2% of elderly patients (two patients 65 yr and one patient 70 yr) compared with 3.6% ($n = 10$) in the overall population. No grade 4 pneumonitis was observed in either elderly subpopulation. Regardless of study drug relationship, age did not affect the incidence of serious AEs (everolimus vs placebo, respectively; 65 yr: 37.8% vs 41.0%; 70 yr: 38.5% vs 35.0%; overall: 40.9% vs 47.4%). However, patients who were 70 yr of age had a greater occurrence of more than one dose reduction and/or interruption, as well as increased frequency of AEs resulting in dose reduction and/or interruption compared with patients 65 yr of age and the overall study population (Table 5). Consistent with this, the mean dose intensity was lower in everolimus-treated patients 70 yr compared with patients 65 yr and all patients. Nevertheless, median everolimus treatment duration appeared slightly longer in elderly patients. Elderly patients receiving everolimus were administered a slightly higher mean number of concomitant medications than the overall population.

## 4. Discussion

This retrospective study represents the first detailed report of efficacy and safety results with everolimus in elderly patients with mRCC. In RECORD-1, everolimus provided significant clinical benefit in patients 65 yr and 75 yr of age. Tumor burden reduction in elderly patients was improved with everolimus compared with placebo, consistent with the overall study population. Median PFS was prolonged and higher rates of disease stabilization were observed in patients treated with everolimus compared with placebo, regardless of age.

Retrospective analyses of other targeted therapies have reported an increase in the frequency of AEs in elderly patients with mRCC [7–9]; however, the specific AEs associated with each agent varied. The individual safety profile of an agent is an important consideration when making treatment decisions in elderly patients, especially when comorbidities are present. The toxicity profiles of VEGF-targeted therapies differ significantly from those of mTOR inhibitors. The most common grade 3/4 AEs associated with the VEGFr-TKI sunitinib in a

pivotal study were hypertension (8%), fatigue (7%), diarrhea (5%), and hand-foot syndrome (5%) [10]. In an expanded-access study, severe toxicity requiring dose reduction or discontinuation of sunitinib significantly correlated with increased age ($p = 0.006$) [7]. In a pivotal trial of sorafenib, the most common grade 3/4 AEs were hand-foot skin reaction (6%), hypertension (4%), diarrhea (3%), and fatigue (3%) [11]. A subgroup analysis of elderly patients in this study demonstrated higher rates of grade 3 AEs with sorafenib in patients 70 yr of age (40% vs 29% in patients <70 yr), although the incidence of grade 4 events was similar (6% vs 7%, respectively) [8]. However, in an expanded-access study, the incidence of grade 3/4 AEs associated with sorafenib was similar in patients 65 and <65 yr, although fatigue and rash/desquamation occurred more frequently in patients 65 yr (8% vs 4% and 6% vs 4% in patients <65 yr, respectively) [12]. In a trial of bevacizumab plus interferon-α, bevacizumab-associated grade 3/4 toxicity included hypertension (10%), anorexia (17%), fatigue (37%), and proteinuria (15%) [13], with serious AEs occurring more frequently in patients 65 yr (40%) versus <65 yr (23%) [9]. Not surprisingly, the safety profile of the mTOR inhibitor temsirolimus is similar to everolimus. The most common grade 3/4 AEs in temsirolimus-treated patients were anemia (20%), asthenia (11%), hyperglycemia (11%), and dyspnea (9%) [14]. Age had little effect on the incidence of grade 3/4 toxicities [15].

In RECORD-1, everolimus was well tolerated in the elderly, with a toxicity profile similar to that observed in younger patients. The most common grade 3/4 AEs were anemia (12% and 14% in patients 65 and 70 yr) and infection (11% and 12% in patients 65 and 70 yr). The frequency of several AEs including peripheral edema, cough, rash, and diarrhea were higher in the elderly; however, these AEs were more frequent both in patients receiving everolimus and placebo and were generally manageable. No increases in grade 3/4 AEs were observed in elderly patients compared with the overall population, and notably, elderly patients also did not appear to have an increased risk of developing noninfectious pneumonitis compared with younger patients.

This study has several limitations. Analyses were retrospective, and they were not designed to allow statistical comparison across the different elderly subpopulations. Patients were not stratified by age; thus an imbalance in subgroups is possible. Finally, selection of previous therapy was at the physician's discretion and may have been biased by previous experience with sorafenib and sunitinib in elderly patients.

## 5. Conclusions

In RECORD-1, everolimus provided clinical benefit over placebo in elderly patients and the overall study population. Age had no apparent detrimental effect on PFS or reduction in tumor burden observed with everolimus. Everolimus was well tolerated in elderly patients and the overall study population, with low rates of grade 3/4 AEs. Some toxicities including peripheral edema, cough, rash, and diarrhea were reported more frequently in elderly patients, irrespective of treatment; however, no increase in everolimus-related pneumonitis was observed compared with younger patients. Elderly patients have a higher obvious incidence of comorbidities, and many are unable to tolerate therapeutic regimens appropriate for the general mRCC population. With a favorable safety and efficacy profile, everolimus

may be considered a suitable targeted agent in the treatment of relatively healthy elderly patients with mRCC.

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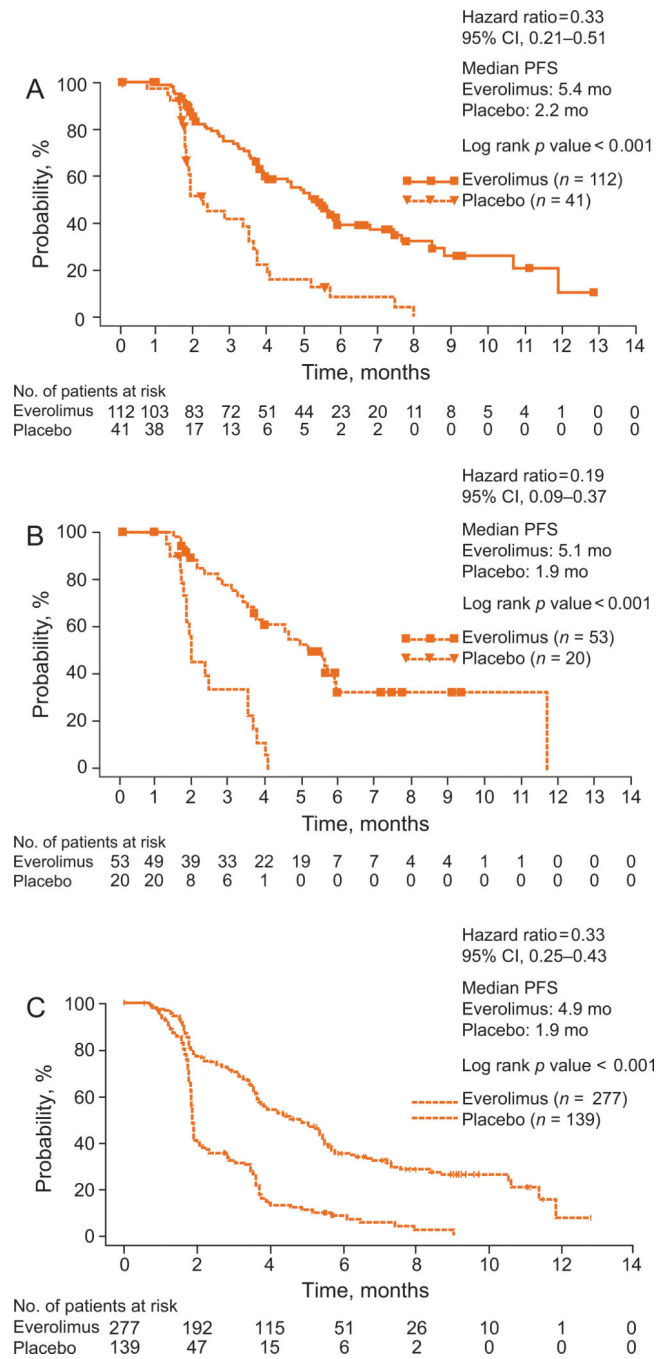
**Fig. 1.**
Kaplan-Meier estimates of progression-free survival (PFS) associated with everolimus versus placebo in (A) patients ≥65 yr, (B) patients ≥70 yr, and (C) the total study population as determined by central review. CI = confidence interval.
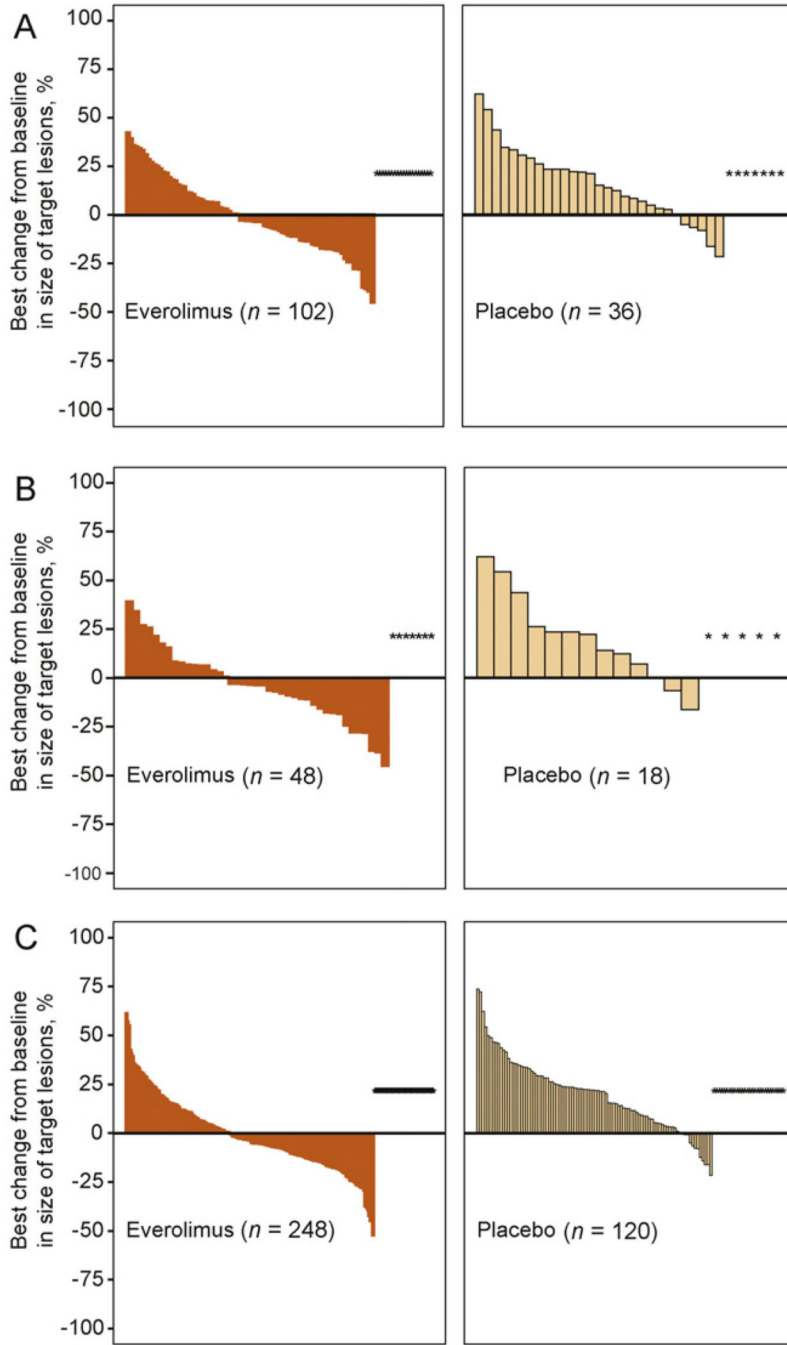
**Fig. 2.**
Best percentage change from baseline in sum of the longest tumor diameters ( SLD) based on central radiology review associated with the everolimus and placebo groups in (A) patients 65 yr of age, (B) patients 70 yr of age, and (C) the total study population. Patients for whom the best SLD was not available, or for whom the best SLD was contradicted by an unknown overall lesion response, were excluded from the analysis (everolimus vs placebo, respectively, in patients 70 yr [5 and 2 patients], patients 65 yr [10 and 5 patients], and the total study population [34 and 19 patients]. CI = confidence interval.
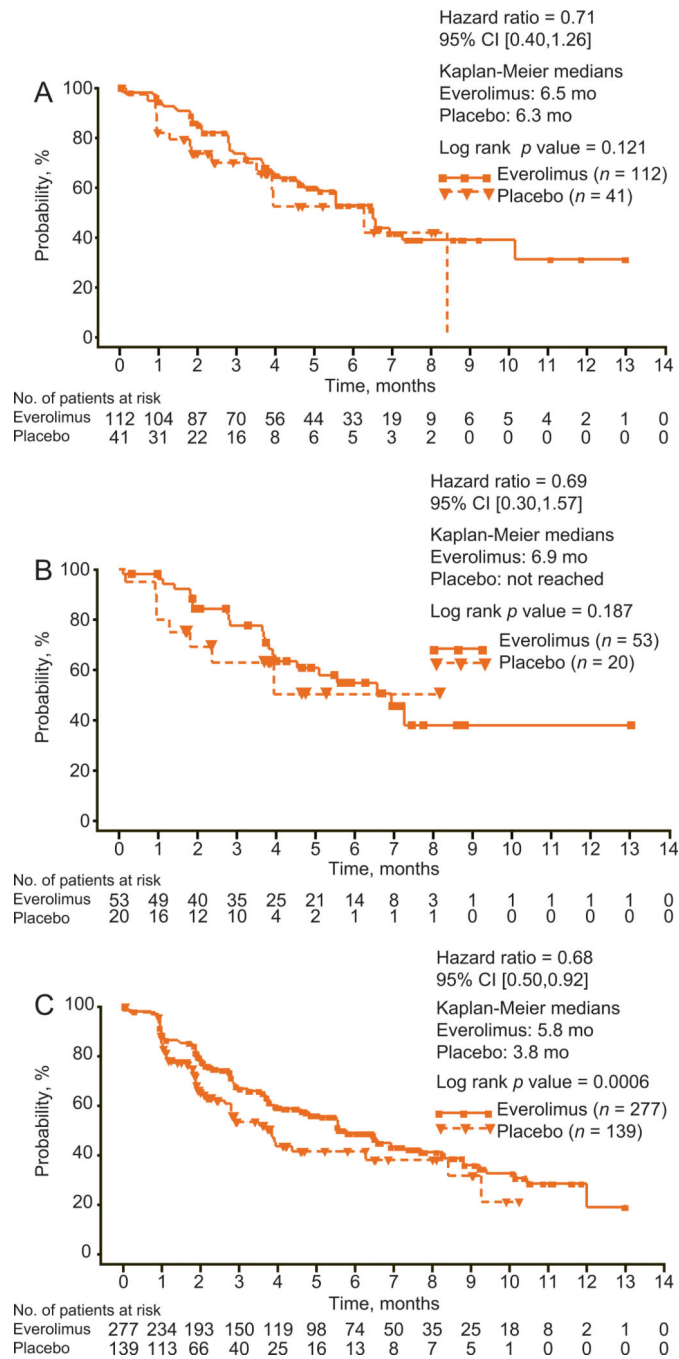
**Fig. 3.**
Kaplan-Meier estimates of time to deterioration of KPS with everolimus versus placebo in (A) patients 65 yr of age, (B) patients 70 yr of age, and (C) the total study population as determined by central review.

**Table 1**

Demographics and baseline characteristics of elderly patients and the total study population

| | Age 65 yr | | Age 70 yr | | All patients | |
|---|---|---|---|---|---|---|
| | Everolimus plus BSC (*n* = 112) | Placebo plus BSC (*n* = 41) | Everolimus plus BSC (*n* = 53) | Placebo plus BSC (*n* = 20) | Everolimus plus BSC (*n* =277) | Placebo plus BSC (*n* = 139) |
| Age, yr, median (range) | 69.0 (65–85) | 69.0 (65–79) | 74.0 (70–85) | 72.5 (70–79) | 61.0 (27–85) | 60.0 (29–79) |
| MSKCC risk, *n* (%) | | | | | | |
| Favorable | 25 (22) | 10 (24) | 13 (25) | 3 (15) | 81 (29) | 39 (28) |
| Intermediate | 70 (63) | 24 (59) | 33 (62) | 14 (70) | 156 (56) | 79 (57) |
| Poor | 17 (15) | 7 (17) | 7 (13) | 3 (15) | 40 (14) | 21 (15) |
| Prior VEGFr-TKI, *n* (%) | | | | | | |
| Sorafenib only | 42 (38) | 17 (42) | 18 (34) | 11 (55) | 81 (29) | 43 (31) |
| Sunitinib only | 40 (36) | 14 (34) | 17 (32) | 4 (20) | 124 (45) | 60 (43) |
| Sorafenib and sunitinib | 30 (27) | 10 (24) | 18 (34) | 5 (25) | 72 (26) | 36 (26) |
| Other prior systemic therapy, *n* (%) | | | | | | |
| Immunotherapy | 71 (63) | 29 (71) | 33 (62) | 15 (75) | 179 (65) | 93 (67) |
| Chemotherapy | 13 (12) | 7 (17) | 5 (9) | 4 (20) | 37 (13) | 22 (16) |
| Hormonal therapy | 3 (3) | 2 (5) | 2 (4) | 2 (10) | 5 (2) | 5 (4) |
| Prior surgery (nephrectomy), *n* (%) | 107 (96) | 40 (98) | 51 (96) | 20 (100) | 269 (97) | 133 (96) |

BSC = best supportive care; MSKCC = Memorial-Sloan Kettering Cancer Center; VEGFr-TKI = vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

**Table 2**

Best overall tumor response and median overall survival in elderly patients and the total study population

| | Patient population | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Age ≥65 yr | | Age ≥70 yr | | All patients | |
| | Everolimus plus BSC (*n* = 112) | Placebo plus BSC (*n* = 41) | Everolimus plus BSC (*n* = 53) | Placebo plus BSC (*n* = 20) | Everolimus plus BSC (*n* = 277) | Placebo plus BSC (*n* = 139) |
| Best overall tumor response, *n* (%) | | | | | | |
| CR | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| PR | 3 (2.7) | 0 (0.0) | 2 (3.8) | 0 (0.0) | 5 (1.8) | 0 (0.0) |
| SD | 77 (68.8) | 18 (43.9) | 38 (71.7) | 7 (35.0) | 185 (66.8) | 45 (32.4) |
| PD | 21 (18.8) | 18 (43.9) | 8 (15.1) | 11 (55.0) | 57 (20.6) | 74 (53.2) |
| Unknown | 11 (9.8) | 5 (12.2) | 5 (9.4) | 2 (10.0) | 30 (10.8) | 20 (14.4) |
| ORR | 3 (2.7) | 0 (0.0) | 2 (3.8) | 0 (0.0) | 5 (1.8) | 0 (0.0) |
| Overall survival, mo, median (95% CI) | 14.78 (11.96–20.27) | 16.13 (8.48–22.93) | 13.57 (9.82–21.82) | 13.63 (5.09–22.93) | 13.57 (11.96–17.87) | 13.01 (10.09–16.66) |
| HR (95% CI) | 1.07 (0.69–1.67) | | 0.85 (0.47–1.55) | | 0.9 (0.71–1.14) | |
| *p* value | 0.381 | | 0.301 | | 0.183 | |

BSC = best supportive care; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; ORR = overall response rate; ORR = CR plus PR; CI = confidence interval; HR = hazard ratio.

**Table 3**

Incidence in elderly patients and the total study population of adverse events and laboratory abnormalities (all grades)[*]

| | Age ≥65 yr | | Age ≥70 yr | | All patients | |
|---|---|---|---|---|---|---|
| | Everolimus plus BSC (n = 111) | Placebo plus BSC (n = 39) | Everolimus plus BSC (n = 52) | Placebo plus BSC (n = 20) | Everolimus plus BSC (n = 274) | Placebo plus BSC (n = 137) |
| **Adverse event, %** | | | | | | |
| Stomatitis | 42 | 5 | 46 | 0 | 44 | 8 |
| Cough | 36 | 21 | 40 | 20 | 30 | 16 |
| Infection | 36 | 15 | 33 | 10 | 37 | 18 |
| Asthenia | 33 | 26 | 37 | 25 | 33 | 23 |
| Rash | 32 | 13 | 33 | 0 | 29 | 7 |
| Peripheral edema | 32 | 10 | 37 | 20 | 25 | 8 |
| Diarrhea | 32 | 8 | 38 | 10 | 30 | 7 |
| Fatigue | 29 | 26 | 37 | 20 | 31 | 27 |
| Anorexia | 28 | 10 | 27 | 10 | 25 | 14 |
| Nausea | 25 | 13 | 27 | 15 | 26 | 19 |
| Dyspnea | 23 | 8 | 23 | 5 | 24 | 15 |
| Pyrexia | 22 | 5 | 27 | 0 | 20 | 9 |
| Vomiting | 21 | 10 | 21 | 15 | 20 | 12 |
| Mucosal inflammation | 21 | 0 | 25 | 0 | 19 | 1 |
| Headache | 16 | 5 | 15 | 0 | 19 | 9 |
| Epistaxis | 16 | 0 | 15 | 0 | 18 | 0 |
| Dysgeusia | 14 | 3 | 17 | 5 | 10 | 2 |
| Pneumonitis | 11 | 0 | 10 | 0 | 14 | 0 |
| Pain in extremity | 10 | 13 | 14 | 15 | 10 | 7 |
| Pruritus | 10 | 10 | 10 | 15 | 14 | 7 |
| Dry skin | 9 | 3 | 8 | 5 | 13 | 5 |
| **Laboratory abnormality, %** | | | | | | |
| Hemoglobin decreased | 88 | 56 | 92 | 55 | 92 | 79 |
| Cholesterol increased | 71 | 39 | 71 | 30 | 77 | 35 |
| Triglycerides increased | 69 | 26 | 73 | 20 | 73 | 34 |

| | Age ≤65 yr | | Age ≥70 yr | | All patients | |
|---|---|---|---|---|---|---|
| | Everolimus plus BSC (n = 111) | Placebo plus BSC (n = 39) | Everolimus plus BSC (n = 52) | Placebo plus BSC (n = 20) | Everolimus plus BSC (n = 274) | Placebo plus BSC (n = 137) |
| Creatinine increased | 65 | 36 | 71 | 30 | 50 | 34 |
| Lymphocytes decreased | 63 | 26 | 62 | 20 | 51 | 28 |
| Glucose increased | 60 | 26 | 54 | 40 | 57 | 25 |
| Phosphate decreased | 33 | 10 | 31 | 5 | 37 | 8 |
| Platelets decreased | 31 | 0 | 27 | 0 | 23 | 2 |
| Alanine transaminase increased | 20 | 3 | 17 | 0 | 21 | 4 |
| Aspartate transaminase increased | 18 | 5 | 17 | 5 | 25 | 7 |
| Neutrophils decreased | 17 | 3 | 12 | 5 | 14 | 4 |

BSC = best supportive care.

*
Regardless of relation to treatment, occurring in >10% of all patients in the everolimus arm.

**Table 4**

Incidence of grades 3 and 4 adverse events in elderly patients and the total study population[*]

| | Age ≥65 yr | | Age ≥70 yr | | All patients | |
|---|---|---|---|---|---|---|
| | Everolimus plus BSC (n = 111) | Placebo plus BSC (n = 39) | Everolimus plus BSC (n = 52) | Placebo plus BSC (n = 20) | Everolimus plus BSC (n = 274) | Placebo plus BSC (n = 137) |
| Adverse event, % | | | | | | |
| Anemia | 14 | 3 | 12 | 0 | 10 | 5 |
| Infection | 11 | 3 | 12 | 0 | 10 | 1 |
| Lymphopenia | 9 | 0 | 10 | 0 | 4 | 0 |
| Hyperglycemia | 8 | 3 | 8 | 5 | 6 | 2 |
| Stomatitis | 6 | 0 | 4 | 0 | 4 | 0 |
| Fatigue | 3 | 3 | 6 | 0 | 5 | 3 |

BSC = best supportive care.

[*] Adverse events with combined grades 3 and 4 incidence of >5% in the everolimus arm of either elderly subpopulation are shown.

**Table 5**

Dose reductions, dose interruptions, and concomitant medications in elderly patients and the total study population

| | Age 65 yr | | Age 70 yr | | All patients | |
|---|---|---|---|---|---|---|
| | Everolimus plus BSC (*n* = 111) | Placebo plus BSC (*n* = 39) | Everolimus plus BSC (*n* = 52) | Placebo plus BSC (*n* = 20) | Everolimus plus BSC (*n* = 274) | Placebo plus BSC (*n* = 137) |
| No. of dose reductions/interruptions, % | | | | | | |
| 0 | 56 (50.5) | 34 (87.2) | 23 (44.2) | 18 (90.0) | 147 (53.6) | 116 (84.7) |
| 1 | 30 (27.0) | 5 (12.8) | 13 (25.0) | 2 (10.0) | 75 (27.4) | 15 (10.9) |
| >1 | 25 (22.5) | 0 | 16 (30.8) | 0 | 52 (19.0) | 6 (4.4) |
| Reasons for dose reduction/interruption, % | | | | | | |
| Adverse event | 44 (39.6) | 3 (7.7) | 27 (51.9) | 2 (10.0) | 107 (39.1) | 12 (8.8) |
| Dosing error | 13 (11.7) | 1 (2.6) | 4 (7.7) | 0 | 27 (9.9) | 7 (5.1) |
| Laboratory test abnormality | 6 (5.4) | 1 (2.6) | 3 (5.8) | 0 | 7 (2.6) | 3 (2.2) |
| Scheduling conflict | 2 (1.8) | 0 | 2 (3.8) | 0 | 7 (2.6) | 1 (0.7) |
| Treatment duration, d | | | | | | |
| Median (min, max) | 157.0 (20, 451) | 84.0 (21, 284) | 150.0 (28, 402) | 111.0 (25, 237) | 141.0 (19, 451) | 60.00 (21, 295) |
| Dose intensity, mg/d | | | | | | |
| Mean (min, max) | 9.03 (2.7, 10.0) | 9.96 (9.3, 10.0) | 8.69 (2.7, 10.0) | 9.97 (9.4, 10.0) | 9.18 (2.7, 10.0) | 10.01 (5.0, 20.0) |
| No. of concomitant medications* | | | | | | |
| Mean | 15.1 | 13.3 | 15.2 | 12.0 | 13.8 | 14.2 |
| Median (min, max) | 14 (2, 41) | 11 (2, 34) | 14 (4, 39) | 11.5 (2, 27) | 12 (1, 46) | 12 (1, 55) |

*
Used by each patient after the start of the study drug.