

# Sorafenib for Older Patients With Renal Cell Carcinoma: Subset Analysis From a Randomized Trial

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- Background** The perception that older cancer patients may be at higher risk than younger patients of toxic effects from cancer therapy but may obtain less clinical benefit from it may be based on the underrepresentation of older patients in clinical trials and the known toxic effects of cytotoxic chemotherapy. It is not known how older patients respond to targeted therapy.
- Methods** This retrospective subgroup analysis of data from the phase 3, randomized Treatment Approach in Renal Cancer Global Evaluation Trial examined the safety and efficacy of sorafenib in older (age  $\geq 70$  years,  $n = 115$ ) and younger patients (age  $< 70$  years,  $n = 787$ ) who received treatment for advanced renal cell carcinoma. Patient demographics and progression-free survival were recorded. Best tumor response, clinical benefit rate (defined as complete response plus partial response plus stable disease), time to self-reported health status deterioration, and toxic effects were assessed by descriptive statistics. Health-related quality of life was assessed with a Cox proportional hazards model. Kaplan–Meier analyses were used to summarize time-to-event data.
- Results** Median progression-free survival was similar in sorafenib-treated younger patients (23.9 weeks; hazard ratio [HR] for progression compared with placebo = 0.55, 95% confidence interval [CI] = 0.47 to 0.66) and older patients (26.3 weeks; HR = 0.43, 95% CI = 0.26 to 0.69). Clinical benefit rates among younger and older sorafenib-treated patients were also similar (83.5% and 84.3%, respectively) and were superior to those of younger and older placebo-treated patients (53.8% and 62.2%, respectively). Adverse events were predictable and manageable regardless of age. Sorafenib treatment delayed the time to self-reported health status deterioration among both older patients (121 days with sorafenib vs 85 days with placebo; HR = 0.66, 95% CI = 0.43 to 1.03) and younger patients (90 days with sorafenib vs 52 days with placebo; HR = 0.69, 95% CI = 0.59 to 0.81) and improved quality of life over that time.
- Conclusions** Among patients with advanced renal cell carcinoma receiving sorafenib treatment, outcomes of older ( $\geq 70$  years) and younger ( $< 70$  years) patients were similar.

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Renal cell cancer, the 14th most common cancer worldwide (1), accounts for approximately 2% of all new cancer cases (2) and approximately 102 000 deaths worldwide (3). Rates have increased in Europe and the United States over the past 30 years, in part because of improved imaging technologies but also because of other factors (2). For example, cigarette smoking and obesity may each account for more than 20% of the cases of renal cell cancer. Increases in the incidence of renal cell carcinoma and in the average age of patients with advanced renal cell carcinoma are predicted because of the aging population (4). Although a higher risk of cancer is associated with advanced age, older patients are frequently underrepresented in oncology trials (5). Thus, there is a lack of detailed data on how this important subgroup of patients tolerates and responds to emerging cancer therapies.

The perception that older patients are at higher risk for toxicity and less likely to benefit from treatment has itself contributed to a lower accrual rate of older patients in these trials (6). Physician

surveys have found that comorbid conditions and toxic effects of treatment are the most frequently cited barriers to recruitment of

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older patients (7,8). A growing body of data, however, indicates that older patients with adequate organ function and a reasonable life expectancy should receive the same treatment as younger patients. A retrospective analysis (9) of 401 patients from 19 studies that evaluated 13 different molecularly targeted cancer therapies found similar frequencies of drug-related adverse events among patients who were younger than 65 years and those who were 65 years or older, regardless of whether the therapies were administered as monotherapy or in combination with chemotherapy. Similarly, older patients with non-small-cell lung cancer who were 70 years or older tolerated cisplatin-based regimens as well as younger patients, with response rates and time to progression similar to those of younger patients (10).

Although more data are needed, current evidence indicates that age has a minimal influence on the nature and treatment of advanced renal cell carcinoma. Older (>70 years) and younger ( $\leq 70$  years) patients diagnosed with renal cell carcinoma present with similar clinical and laboratory features, incidences of nephrectomy, and probabilities of survival (11). A moderately greater mortality rate has been observed in some older patient populations with advanced renal cell carcinoma, perhaps because older patients in these studies were at a more advanced stage at diagnosis (12). In another analysis (13), older patients ( $\geq 60$  years;  $n = 174$ ) with advanced renal cell carcinoma who received subcutaneous cytokine-based therapy (either interleukin-2 or interferon- $2\alpha$  therapy) had similar objective response rates (27% vs 31%), median overall survival (22 vs 19 months), and median progression-free survival (6 vs 5 months), as younger patients (<60 years;  $n = 251$ ).

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals, Montville, NJ) is a novel multikinase inhibitor with antiangiogenic and proapoptotic activity. Sorafenib inhibits such tyrosine kinases as vascular endothelial growth factor receptor-1, -2, and -3; platelet-derived growth factor receptor- $\beta$ ; c-Kit; and Flt-3 (14). Sorafenib, an oral agent, was approved as a treatment for renal cell carcinoma in the United States in December 2005 on the basis of results of the pivotal phase 3 Treatment Approach in Renal Cancer Global Evaluation Trial (TARGET), the largest randomized placebo-controlled trial in renal cell carcinoma to date. The final independently assessed analysis (15), as of January 2005, found a statistically significant doubling of progression-free survival from 2.8 to 5.5 months ( $P < .001$ ) for sorafenib-treated patients and a clinically meaningful trend toward improved overall survival (median = 14.7 months in the placebo group compared with median not reached in sorafenib group; hazard ratio [HR] of death from any cause = 0.72,  $P = .018$ ). Because of the statistically significantly improved progression-free survival, trend toward improved overall survival, and manageable toxicity profile, the trial was stopped early and patients who had been randomly assigned to receive placebo were allowed to cross over to treatment with sorafenib. The final progression-free survival data supported global approval of sorafenib, the first systemic agent approved for renal cell carcinoma in over a decade. In this retrospective analysis of data collected before placebo patients were allowed to cross over to sorafenib therapy, we evaluated the association of age with results of treatment with sorafenib in patients with advanced renal cell carcinoma by comparing outcomes

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## CONTEXT AND CAVEATS

### Prior knowledge

It was not known how older patients would respond to molecularly targeted therapy.

### Study design

Retrospective subgroup analysis of data from a phase 3 randomized trial that examined the safety and efficacy of sorafenib in 115 older (age  $\geq 70$  years) and 787 younger (age <70 years) patients with advanced renal cell carcinoma.

### Contribution

Median progression-free survival and clinical benefit rates (ie, complete response + partial response + stable disease) were similar in younger and older sorafenib-treated patients and better than those of younger and older placebo-treated patients. Adverse effects were predictable and manageable regardless of age. Sorafenib treatment delayed the time to self-reported health status deterioration in both groups and improved quality of life over that time.

### Implications

Results of this study support the use of sorafenib as a treatment for advanced renal cell carcinoma in all age groups.

### Limitations

The study was not designed to test for statistically significant differences between treatment effects in younger and older subgroups. The sample size in the older group was limited, and there was an imbalance in treatment assignments in the older group. Older patients who participate in clinical trials are generally healthier than those who do not participate, and so results of this study may not be generalizable.

*From the Editors*

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between younger (<70 years) and older ( $\geq 70$  years) patients enrolled in TARGET.

## Materials and Methods

### Eligibility

The study population in TARGET consisted of patients who were at least 18 years of age with histologically confirmed metastatic renal cell carcinoma. Patients with disease progression after they received at least one systemic treatment for metastatic renal cell carcinoma (within the previous 8 months) were enrolled in the study. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0 or 1; a Memorial Sloan-Kettering Cancer Center prognostic score indicating low or intermediate risk; and adequate bone marrow, liver, pancreatic, and renal function. Patients with brain metastases were excluded from the study. All patients provided written informed consent before study entry in accordance with the institutional review board of each participating institution.

### Study Design

This was a retrospective analysis of outcomes in patients younger than 70 years or 70 years or older who were a part of the pivotal phase 3 double-blind international randomized parallel-group

multicenter TARGET, which compared sorafenib treatment with placebo treatment in patients with advanced renal cell carcinoma who had received one previous regimen of systemic therapy. The details of the TARGET trial design are reported elsewhere (15). Briefly, from November 24, 2003, when the first patient was assessed for eligibility, until March 31, 2005, when enrollment closed, 903 patients were enrolled and randomly assigned to receive either sorafenib or placebo treatment. There were 451 patients in the sorafenib group and 452 in the placebo group. Baseline disease characteristics (*see* Table 1) were collected at the time of study entry in the clinic and recorded on the study case report forms in conjunction with treatment group randomization. Patients were stratified by country and Memorial Sloan-Kettering Cancer Center prognostic score and then were randomly assigned to treatment with 400 mg of sorafenib twice daily or with placebo (in 6-week cycles for the first 24 weeks and 8-week cycles thereafter) in a continuous dosing fashion until progressive disease or unacceptable toxicity was encountered.

Because 115 patients in this study were aged 70 years or older, this population provided a rare opportunity to assess the benefits and side effects of treatment in the elderly. Consultations with clinicians in the field of geriatrics indicated that 70 years was the age beyond which individuals tend to be classified as elderly.

A single planned, independently assessed analysis of progression-free survival in January 2005 (15) found that sorafenib was associated with a statistically significant increase in progression-free survival (HR for disease progression = 0.44, 95% confidence interval [CI] = 0.35 to 0.55,  $P < .001$ , with the median progression-free survival of the sorafenib group being double that of the placebo group—ie, 24 vs 12 weeks, respectively). Consequently, crossover from placebo to sorafenib was permitted beginning in May 2005. The data in this report are from an updated descriptive analysis of progression-free survival as of May 2005, after the trial was fully accrued but before crossover was allowed.

## Outcome Variables

The outcome variables for this retrospective analysis included progression-free survival, best tumor response, clinical benefit rate, and quality of life. A complete response was defined as disappearance of all target lesions. A partial response was defined as a 30% decrease in the sum of the longest diameter of target lesions. Stable disease was defined as small changes in lesions that did not meet criteria for complete response, partial response, or progressive disease. Progression-free survival was defined as the time from randomization to disease progression (as detected radiologically or clinically, whichever was earlier) or death (if death occurred before progression). Tumor assessments by computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis were performed before treatment, on day 1 of cycle 2, and at every cycle thereafter until the end of treatment. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (16). Clinical benefit rate was defined as the proportion of patients with a complete response, a partial response, or stable disease.

Patient-reported quality of life outcomes were assessed by use of the Functional Assessment of Cancer Therapy–Kidney Symptom Index (FKSI) and the Physical Well-Being (PWB) domain of the Functional Assessment of Cancer Therapy–General version

(FACT-G) (17,18). FKSI measures patient-reported kidney cancer-related symptoms and concerns. The PWB domain of FACT-G measures the physical functioning aspect of quality of life. In general, higher scores mean a better quality of life, with a change in an individual's score of 4 points considered a meaningful difference. The questionnaires were administered on day 1 of each cycle and at the end of treatment visit.

Safety analysis measured treatment-related adverse events; it distinguished between drug-related vs non-drug-related events. Adverse events were graded by use of the Common Terminology Criteria for Adverse Events from the National Cancer Institute. Quality of life data were obtained during the first five cycles of treatment.

## Statistical Methods

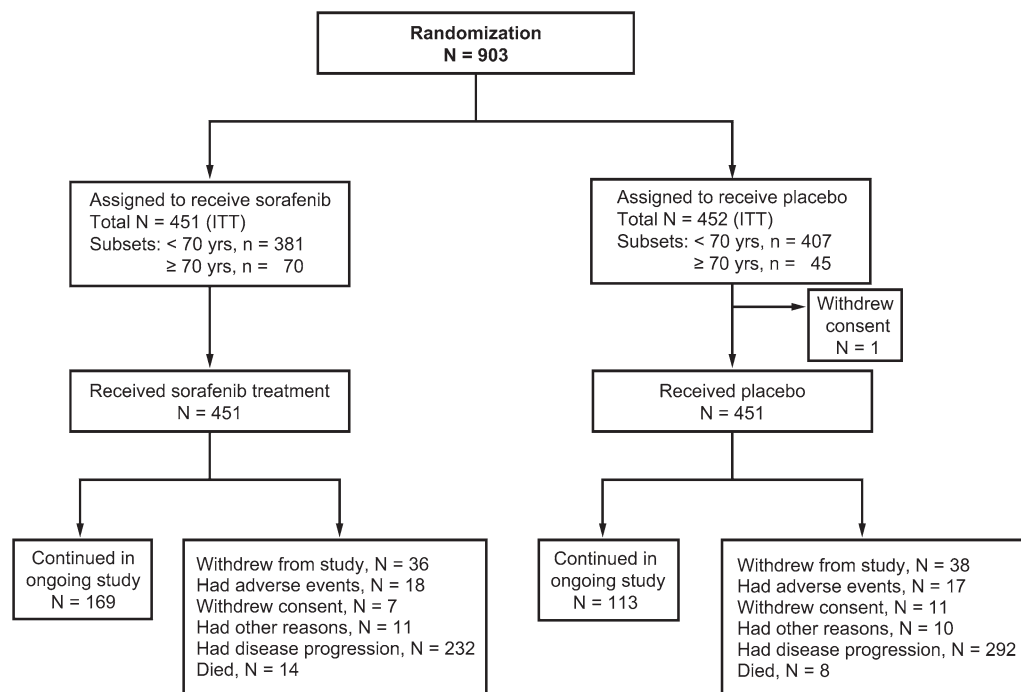
The subgroup analyses were conducted among the intent-to-treat older and younger subgroups and included data obtained through May 2005. Statistical analyses were performed in an exploratory fashion and their results are mainly descriptive in nature. Toxic effects were evaluated by use of the Common Terminology Criteria for Adverse Events version 3.0, and all events referred to were treatment related. Descriptive statistics were used to describe patient characteristics, best tumor response, clinical benefit rate, and safety for patients who were younger than 70 years or 70 years or older by treatment group. Kaplan–Meier estimates and curves were used to summarize time-to-event data, such as the analysis of progression-free survival. Treatment-related differences in response were evaluated by the Cochran–Mantel–Haenszel test. Progression-free survival was compared by the log-rank test (stratified by prognostic group and country).

The median time to health status deterioration was calculated for FKSI and the PWB domain of FACT-G by use of the Cox proportional hazards model. Schoenfeld residual plots were used to evaluate the proportional hazard assumption. For FKSI and PWB, the median time to health status deterioration was defined as a 4-point drop in total score from FKSI-15 or PWB or as clinical progression, or death if the FKSI-15 or PWB score was missing. A 4-point drop in total score was chosen to be consistent with published data on what constitutes a clinically significant deterioration. Details of the number of assessments completed at each time point and the mean scores for FKSI-15 and PWB have been described elsewhere (17). In addition, the condition of patients was rated as improved, no change, or worsened, according to how their scores compared with baseline for each cycle, on the basis of a 4-point change for total score of FKSI-15 and PWB scores. All reported  $P$  values are two-sided.

## Results

From November 24, 2003, through March 31, 2005, 903 patients were randomly assigned to receive treatment with sorafenib ( $n = 451$ ) or placebo ( $n = 452$ ). Of these 903 patients, 902 received a study drug and were evaluated for safety in this analysis. Of the 115 patients who were 70 years or older, 70 were randomly assigned to receive sorafenib and 45 were assigned to placebo. Of the 788 patients who were younger than 70 years, 381 were randomly assigned to sorafenib and 407 were assigned to placebo (Figure 1).

**Figure 1.** CONSORT trial flow diagram. Patient enrollment and outcomes are shown for all patients with renal cell carcinoma (aged <70 or ≥70 y) who were randomly assigned to treatment with sorafenib or placebo. An intent-to-treat analysis was used.



Baseline characteristics for the two age groups are listed in Table 1. The median age of older sorafenib-treated patients was 72 years (range = 70–86 years) and that of older placebo-treated patients was 73 years (range = 70–84 years). There were no clinically significant differences in baseline characteristics between sorafenib arms, except that older patients had a higher proportion of female patients, an increased proportion of patients with Eastern Cooperative Oncology Group performance scores of 1 or 2, and more patients with an intermediate risk according to the Memorial Sloan-Kettering Cancer Center criteria. At baseline, older sorafenib-treated patients had higher incidences of vascular hypertensive disorders (66% vs 36%), diabetes mellitus (20% vs 11%), coronary artery disorders (7% vs 6%), anemias (14% vs 7%), and breathing abnormalities (16% vs 9%) than younger sorafenib-treated patients.

### Efficacy

The best tumor response was determined among patients by age and treatment (Table 2). Among 381 younger patients randomly assigned to receive sorafenib, 33 (8.7%) had a partial response and 285 (74%) had stable disease. Among younger patients randomly assigned to receive placebo, six (1.5%) had a partial response and 213 (52%) had stable disease. Among the 70 older sorafenib-treated patients, one (1.4%) had a complete response, 10 (14%) had a partial response, and 48 (69%) had stable disease. The difference in overall response rates (complete response plus partial response) between the treatment groups for younger patients (8.7% in the sorafenib-treated group and 1.5% in the placebo-treated group; difference = 7.2%, 95% CI = 4.3% to 11%) was lower than that for older patients (15.7% in the sorafenib-treated group and 4.4% in the placebo-treated group; difference = 11.3%, 95% CI = 10.5% to 17%), as calculated by the Cochran–Mantel–Haenszel test. Among older patients who were randomly assigned to receive placebo, two (4.4%) had partial response and 26 (58%) had stable disease. The clinical benefit rate (complete response + partial response + stable

disease) for older and younger patients receiving sorafenib (84.3% and 83.5%, respectively) was substantially higher than in those receiving placebo (62.2% and 53.8%, respectively).

Progression-free survival among sorafenib-treated patients was approximately double that observed among placebo-treated patients, regardless of age (Figure 2). Among older sorafenib-treated patients, the median progression-free survival was 26.3 weeks, and among older placebo-treated patients, the median was 13.9 weeks (HR of progression = 0.43; 95% CI = 0.26 to 0.69). Median progression-free survival among sorafenib-treated younger patients was 23.9 weeks and that among younger placebo-treated patients was 11.9 weeks (HR = 0.55, 95% CI = 0.47 to 0.66). The progression-free survival outcomes for older sorafenib-treated patients were thus consistent with the results in younger patients and in the overall TARGET population (15).

Progression-free survival benefits should be considered in the context of the cost to the patient of achieving such benefits. One way to estimate the net degree of patient benefit is to compare the length of therapy among patient and treatment groups estimated from the start to the end of study drug therapy. Among patients younger than 70 years, the median duration of sorafenib therapy was 25.6 weeks and of placebo treatment was 15.7 weeks (difference = 9.9 weeks; 95% CI = 9.83 to 9.97 weeks). Among patients who were 70 years or older, the median duration of sorafenib therapy was 24.1 weeks and of placebo treatment was 18.8 weeks (difference = 5.3 weeks; 95% CI = 4.77 to 5.83 weeks).

### Toxicity

All patients who were assessable for toxic effects were analyzed by age group and treatment (Table 3). The overall incidence of adverse events of any grade among younger sorafenib-treated patients was 94.2%, among older sorafenib-treated patients was 98.6%, among younger placebo-treated patients was 85.7%, and among older placebo-treated patients was 86.7%. Approximately

**Table 1.** Baseline patient characteristics by age for patients with renal cell carcinoma in the Treatment Approach in Renal Cancer Global Evaluation Trial (TARGET)\*

Characteristic	Age <70 y		Age ≥70 y		Total (n = 903)
	Sorafenib (n = 381)	Placebo (n = 407)	Sorafenib (n = 70)	Placebo (n = 45)	
Male, No. (%)	271 (71.1)	305 (74.9)	44 (62.9)	35 (77.8)	655 (72.5)
Female, No. (%)	110 (28.9)	102 (25.1)	26 (37.1)	10 (22.2)	248 (27.5)
Median age, y (range)	57 (19–69)	58 (29–69)	72 (70–86)	73 (70–84)	59 (19–86)
Disease states, No. (%)					
Anemia	28 (7)	43 (11)	10 (14)	3 (7)	84 (9)
Breathing abnormalities	33 (9)	43 (11)	11 (16)	5 (11)	92 (10)
CAD	21 (6)	21 (5)	5 (7)	7 (16)	54 (6)
DM	42 (11)	48 (12)	14 (20)	9 (20)	113 (13)
Vascular hypertens. disorder	137 (36)	138 (34)	46 (66)	27 (60)	348 (39)
MSKCC risk, No. (%)					
Low	201 (53)	200 (49)	32 (46)	28 (62)	461 (51)
Intermediate	180 (47)	206 (51)	38 (54)	17 (38)	441 (49)
Baseline ECOG performance score, No. (%)					
0	190 (50)	185 (46)	29 (41)	25 (56)	429 (49)
1	184 (49)	216 (53)	39 (56)	20 (44)	459 (49)
2	5 (2)	4 (1)	2 (3)	0	11 (1)
Baseline site of metastasis, No. (%)†					
Lung	297 (78)	309 (76)	51 (73)	39 (87)	696 (77)
Liver	93 (24)	106 (26)	23 (33)	11 (24)	233 (26)
Bone	79 (21)	86 (21)	17 (24)	11 (24)	193 (21)
Tumor sites, No. (%)					
1	52 (14)	54 (13)	10 (14)	9 (20)	125 (14)
2	112 (29)	117 (29)	19 (27)	12 (27)	260 (29)
≥3	215 (56)	235 (58)	41 (59)	24 (53)	515 (57)
Missing	2 (1)	1 (0)	0 (0)	0 (0)	3 (0)
Time since initial diagnosis‡, y (range)	1.7 (0.1–19.4)	1.8 (0.1–19.9)	1.7 (0.4–16.2)	2.2 (0.3–8.3)	1.7 (0.1–19.9)
Stage at initial diagnosis, No. (%)					
I	28 (7)	35 (9)	8 (11)	9 (20)	80 (9)
II	69 (18)	62 (15)	8 (11)	3 (7)	142 (16)
III	112 (29)	129 (32)	27 (39)	18 (40)	286 (32)
IV	164 (43)	174 (43)	25 (36)	14 (31)	377 (42)
Missing	8 (3)	7 (1)	2 (3)	1 (2)	18 (1)
Clear-cell histology,§ No. (%)	379 (99)	402 (99)	70 (100)	45 (100)	896 (99)
Prior nephrectomy, No. (%)	359 (94)	377 (93)	63 (90)	44 (98)	843 (93)
Previous IL-2/IFN,   No. (%)	321 (84)	332 (82)	53 (76)	36 (80)	742 (82)

\* CAD = ischemic coronary artery disorders; DM = diabetes mellitus; ECOG = Eastern Cooperative Oncology Group; IL-2 = interleukin-2; IFN = interferon; MSKCC = Memorial Sloan-Kettering Cancer Center; hypertens. = hypertensive.

† Patients may be included in more than one category.

‡ Data were not available for all patients. Data were available as follows: 377 sorafenib-treated patients <70 y, 399 placebo-treated patients <70 y, 68 sorafenib-treated patients ≥70 y, 44 placebo-treated patients ≥70 y, and 888 total patients.

§ Histology could encompass more than one category.

|| Patients who had previously received immunotherapy with interleukin-2 and/or interferon.

half of the adverse events among both younger (47.7%) and older (40.0%) sorafenib-treated patients were grades 1 and 2. Slightly more grade 3 and 4 toxic effects were reported in older sorafenib-treated patients than in younger sorafenib-treated patients (for grade 3 events, 40.0% vs 29.4%, respectively; and for grade 4 events, 5.7% vs 7.3%, respectively).

The most common adverse events that were observed in at least 10% of sorafenib-treated patients are shown in Table 4. Older patients had slightly more gastrointestinal symptoms than younger patients; younger patients had a higher incidence of sorafenib-related hypertension, sensory neuropathy, and pruritus than did older patients. More older patients than younger patients experienced fatigue.

The most frequently reported adverse events among older sorafenib-treated patients were rash or desquamation, diarrhea, alopecia, fatigue, hand-foot skin reaction, and anorexia. These events were primarily grades 1 and 2 and were medically manageable. There were no unexpected adverse events attributable to advanced age. Cardiac events, a particular concern in older patients treated with antiangiogenic agents, among older sorafenib-treated patients vs older placebo-treated patients, respectively, were as follows: grade 4 cardiac ischemia/infarction (one vs zero patients), grade 5 cardiac ischemia or infarction (two vs zero patients), and grade 3 left ventricular systolic dysfunction (one vs zero patients).

Thirty-one (8.1%) younger and 15 (21.4%) older sorafenib-treated patients permanently discontinued treatment, whereas 350

**Table 2.** Best tumor response by age group\*

Best response	Age <70 y		Age ≥70 y	
	Sorafenib (n = 381)	Placebo (n = 407)	Sorafenib (n = 70)	Placebo (n = 45)
<b>Complete response (CR)</b>				
No.	0	0	1	0
Rate, % (95% CI)	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.9)	1.4 (0.0 to 7.7)	0.0 (0.0 to 7.9)
<b>Partial response (PR)</b>				
No.	33	6	10	2
Rate, % (95% CI)	8.7 (6.0 to 11.9)	1.5 (0.5 to 3.2)	14.3 (7.1 to 24.7)	4.4 (0.5 to 15.1)
<b>Stable disease (SD)</b>				
No.	285	213	48	26
Rate, % (95% CI)	74.8 (70.1 to 79.1)	52.3 (47.4 to 57.3)	68.6 (56.4 to 79.1)	57.8 (42.2 to 72.3)
<b>Progressive disease (PD)</b>				
No.	48	152	8	15
Rate, % (95% CI)	12.6 (9.4 to 16.4)	37.3 (32.6 to 42.2)	11.4 (5.1 to 21.3)	33.3 (20.0 to 49.0)
<b>Clinical benefit (CR + PR + SD), %</b>	<b>83.5</b>	<b>53.8</b>	<b>84.3</b>	<b>62.2</b>

\* Response Evaluation Criteria in Solid Tumors criteria were used to evaluate tumor responses. The 95% confidence intervals (CIs) for the difference in response rates (ie, complete response plus partial response) were based on the Cochran–Mantel–Haenszel test. Within-treatment 95% CIs were based on the exact binomial distribution.

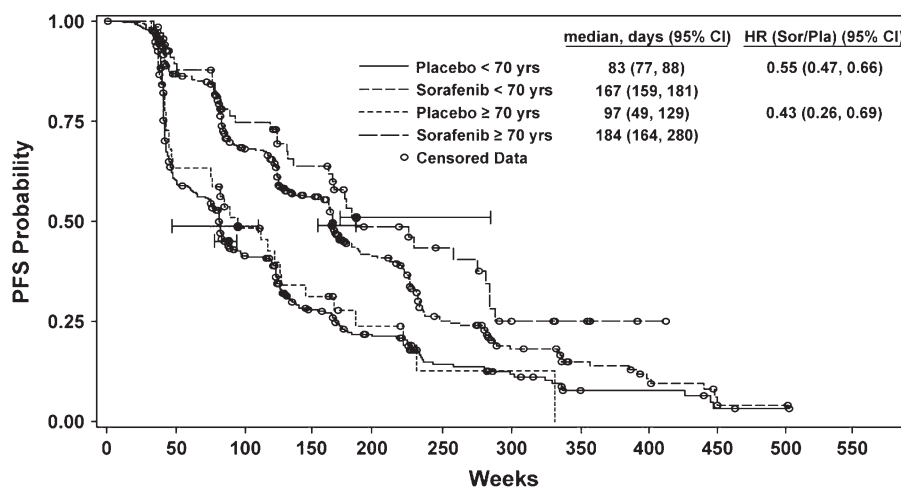
(91.8%) younger and 55 (78.6%) older patients tolerated treatment. For younger patients, discontinuation was most commonly attributed to pulmonary or upper respiratory (2.1%, or eight patients) and constitutional (1.3%, or five patients) disorders (eg, fatigue or fever), whereas older patients discontinued sorafenib mostly because of gastrointestinal (5.7%, or four patients) and dermatologic (4.3%, or three patients) issues. Additionally, dose reductions occurred in 43 (11.3%) younger and 15 (21.4%) older sorafenib-treated patients, most frequently as a result of dermatologic adverse events (6.6%, or 25 patients) of younger and (8.6%, or six patients) of older patients, most commonly hand–foot skin reaction), followed by gastrointestinal events (2.9%, or 11 patients, vs 5.7%, or four patients, most commonly diarrhea), and general cardiac issues (1.0%, or four patients, vs 4.3%, or three patients, most commonly for hypertension). Hematologic events were rare (<5%) among sorafenib-treated patients, with the only exception

being anemia in the older subgroup (11.4%, or eight patients) and in younger patients (6.8%, or 26 patients).

### Quality of Life

Among younger patients, the median number of days to health status deterioration as measured by the FKSI-15 tool was 90 days for sorafenib-treated patients and 52 days for placebo-treated patients (HR = 0.69, 95% CI = 0.59 to 0.81) (Figure 3, B). When measured by PWB, medians were 93 and 73 days (HR = 0.69, 95% CI = 0.58 to 0.81) (Figure 4, B). Among older patients, sorafenib treatment, compared with placebo treatment, also delayed the time to health status deterioration (121 vs 85 days, HR = 0.66, 95% CI = 0.43 to 1.03, when measured by the FKSI-15 tool; and 126 vs 84 days, HR = 0.65, 95% CI = 0.42 to 1.01, when measured by PWB), although neither delay was statistically significant (Figures 3, A, and 4, A).

**Figure 2.** Progression-free survival by age (<70 or ≥70 y) among patients with renal cell carcinoma who were treated with sorafenib or with placebo. The median survival and 95% confidence interval (CI) are shown as well as the hazard ratios (HRs) that compare progression in the sorafenib treatment group with that in the placebo treatment group. Sor = sorafenib; Pla = placebo.



Patients at Risk										
Placebo < 70 yrs	221	138	71	47	24	17	7	6	2	1
Sorafenib < 70 yrs	305	212	153	91	45	25	15	9	3	1
Placebo ≥ 70 yrs	27	18	11	6	2	1	0	0	0	0
Sorafenib ≥ 70 yrs	57	44	34	20	15	6	4	1	0	0

**Table 3.** Overall treatment-emergent adverse events by worst grade in each age group

Grade	Age <70 y, No. (%)			Age ≥70 y, No. (%)		
	Sorafenib (n = 381)	Placebo (n = 406*)	P value†	Sorafenib (n = 70)	Placebo (n = 45)	P value†
1	44 (11.5)	72 (17.7)	.016	5 (7.1)	11 (24.4)	.013
2	138 (36.2)	137 (33.7)	.501	23 (32.9)	17 (37.8)	.689
3	112 (29.4)	90 (22.2)	.022	28 (40.0)	8 (17.8)	.014
4	28 (7.3)	26 (6.4)	.673	4 (5.7)	1 (2.2)	.647
5	37 (9.7)	23 (5.7)	.043	9 (12.9)	2 (4.4)	.197
Total with any grade	359 (94.2)	348 (85.7)	<.001	69 (98.6)	39 (86.7)	.014

\* One of the 407 patients withdrew consent, leaving 406 patients.

† P values were obtained from Fisher exact test that was used to monitor for adverse safety signals at a statistical significance level of .05.

In earlier treatment cycles (cycles 2 and 3), a similar proportion of patients in each treatment group were rated as improved, no change, or worsened on the basis of a 4-point change in the total FKSI-15 and PWB score from baseline, regardless of age. However, by treatment cycle 4, a higher proportion of younger sorafenib-treated patients were classified as improved or no change than of younger placebo-treated patients (for the FKSI-15 tool, 54.7% vs 31.8%; and for PWB, 56% vs 36.4%). Similarly, at cycle 4, a higher proportion of older sorafenib-treated patients were classified as either improved or no change than older placebo-treated patients (for the FKSI tool, 57.8% vs 40.7%; for PWB, 63.3% vs 42.4%). This trend in improvement or no change in FKSI and PWB scores, regardless of age, was also observed in cycle 5.

## Discussion

In this retrospective subgroup analysis of TARGET data, sorafenib treatment appeared to improve outcomes among patients with advanced renal cell carcinoma, regardless of age. Analysis of pre-crossover data indicated that for both older and younger patients,

progression-free survival in the sorafenib group was approximately double that in the placebo group. Furthermore, the increased clinical benefit rate was approximately equal for both younger and older patients. Additionally, side effects were expected, mild, and medically manageable. There was no notable difference in the frequency or severity of sorafenib-related toxicity between younger and older patients.

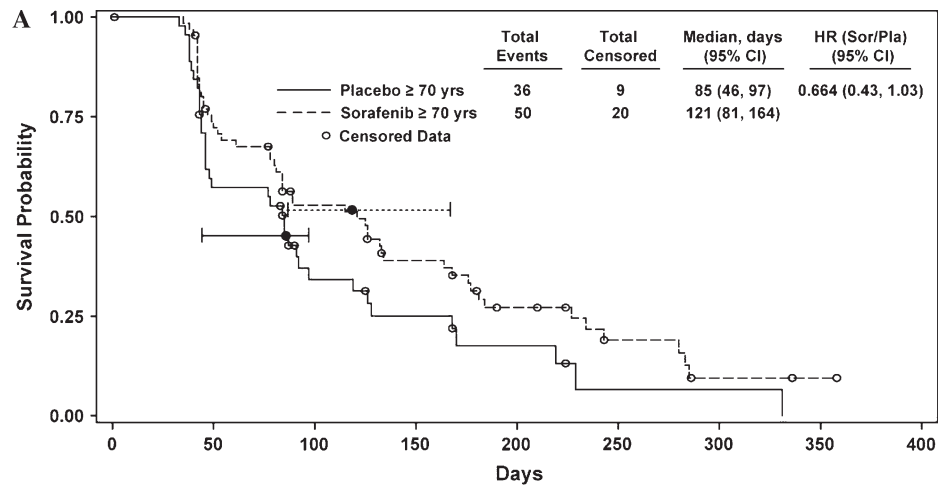
Sorafenib is a multikinase inhibitor that slows tumor growth by inhibition of intracellular signals in the Ras-Raf pathway and blocks receptor tyrosine kinases involved in tumor angiogenesis (19). TARGET is the largest randomized placebo-controlled trial among patients with renal cell carcinoma, and its results supported the approval of sorafenib as a treatment for renal cell carcinoma. Older patients (ie, 70 years or older) constituted 12.7% of the TARGET study population. This subgroup analysis of the TARGET population showed that older and younger patients treated with sorafenib benefited equally, with double the progression-free survival that was observed among placebo-treated patients. Interestingly, the magnitude of this benefit was greater in older patients (26.3 vs 13.9 weeks) than in younger patients (23.9 vs 11.9 weeks). This difference may be attributable to characteristics of the

**Table 4.** Overall treatment-emergent adverse events with an incidence of 10% or higher by age

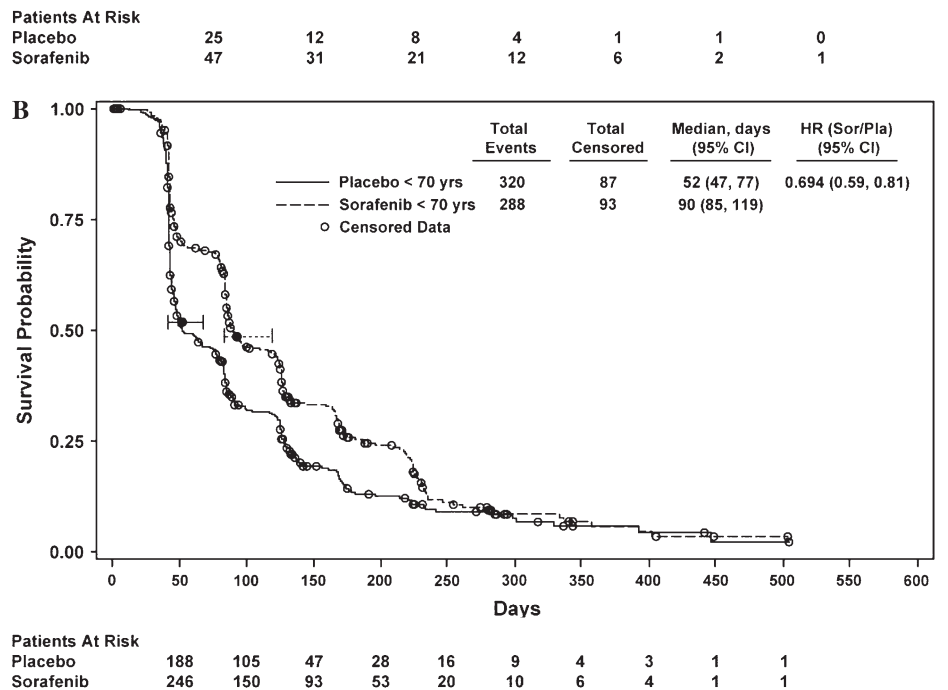
Adverse event	Age <70 y, No. (%)			Age ≥70 y, No. (%)		
	Sorafenib (n = 381)	Placebo (n = 406*)	P value†	Sorafenib (n = 70)	Placebo (n = 45)	P value†
<b>Constitutional</b>						
Fatigue	138 (36.2)	109 (26.8)	.006	27 (38.6)	16 (35.6)	.844
Weight loss	39 (10.2)	25 (6.2)	.038	7 (10.0)	0 (0)	.041
<b>Dermatologic</b>						
Alopecia	101 (26.5)	11 (2.7)	<.001	21 (30.0)	4 (8.9)	.010
Dry skin	42 (11.0)	17 (4.2)	<.001	8 (11.4)	1 (2.2)	.088
Hand-foot skin reaction	118 (31.0)	26 (6.4)	<.001	16 (22.9)	4 (8.9)	.077
Pruritus	77 (20.2)	25 (6.2)	<.001	8 (11.4)	4 (8.9)	.763
Rash/desquamation	149 (39.1)	62 (15.3)	<.001	31 (44.3)	8 (17.8)	.005
<b>Gastrointestinal</b>						
Anorexia	54 (14.2)	49 (12.1)	.399	19 (27.1)	8 (17.8)	.270
Constipation	54 (14.2)	43 (10.6)	.130	14 (20.0)	6 (13.3)	.453
Diarrhea	165 (43.3)	51 (12.6)	<.001	30 (42.9)	7 (15.6)	.002
Nausea	84 (22.0)	78 (19.2)	.333	18 (25.7)	9 (20.0)	.509
<b>Other</b>						
Hypertension	69 (18.1)	8 (2.0)	<.001	7 (10.0)	0 (0.0)	.041
Sensory neuropathy	57 (15.0)	26 (6.4)	<.001	2 (2.9)	3 (6.7)	.378

\* One of the 407 patients withdrew consent, leaving 406 patients.

† P values were obtained from Fisher exact test that was used to monitor for an adverse safety signal at a statistical significance level of .05.



**Figure 3.** Time to self-reported health status deterioration by age according to treatment (sorafenib vs placebo) as measured by the Functional Assessment of Cancer Therapy–Kidney Cancer Symptom Index (FKSI). **A)** Patients aged  $\geq 70$  y. **B)** Patients aged  $< 70$  y. The median time to self-reported health status deterioration and 95% confidence interval (CI) is shown as well as the hazard ratios (HRs) that compare self-reported health status deterioration in the sorafenib treatment group with that in the placebo treatment group. Sor = sorafenib; Pla = placebo.



vasculature in the elderly population that make them more susceptible to inhibition by agents targeting receptor tyrosine kinases. Preclinical evidence indicates that tumor vasculature in older animals is different from that in younger animals, with the vasculature in older animals having more and smaller vessels (20). In addition, angiogenesis inhibitors have shown more pronounced antitumor effects and have resulted in a greater increase in survival among older xenograft mice than among younger xenograft mice (21).

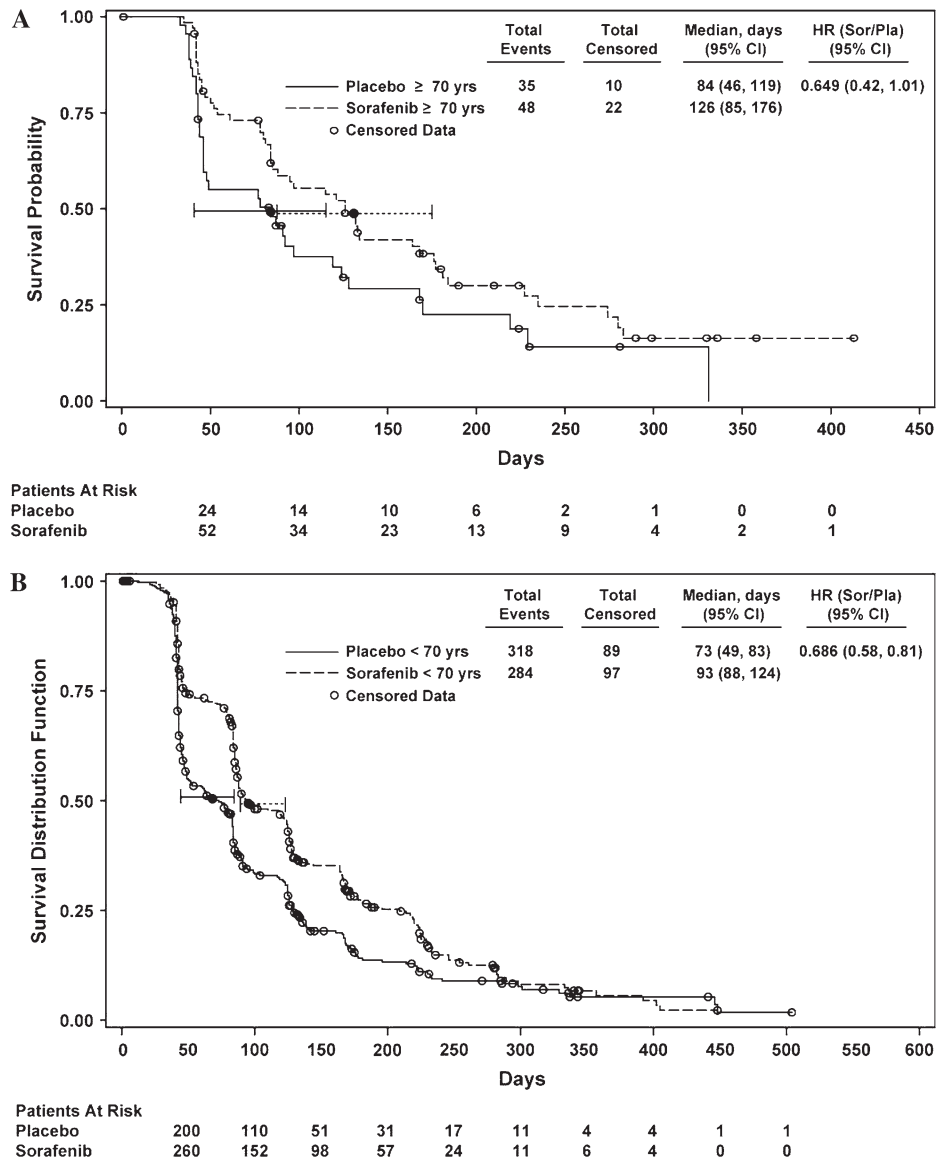
Before sorafenib approval for renal cell carcinoma, immunotherapy with interleukin-2 and/or interferon- $\alpha$  was the most frequently used systemic treatment option. Individuals aged 65 years or older who received immunotherapy performed better than those aged 60–64 years, with longer progression-free survival (8 vs 4 months) and overall survival (23 vs 20 months) (13). Although older patients with renal cell carcinoma perform better on immunotherapy than younger patients, the limited disease control rate and the severe toxicity profile render immunotherapy less attractive to use than the emerging targeted treatments, such as sorafenib

(22). That concept was confirmed in this subanalysis, because patients older than 70 years with advanced renal cell carcinoma benefited from sorafenib treatment.

The most frequently reported adverse events in older sorafenib-treated patients were rash or desquamation, diarrhea, alopecia, fatigue, hand-foot skin reaction, and anorexia. These events were mostly grades 1 and 2 and were medically manageable. No unexpected adverse events attributable to advanced age were observed. Cardiac ischemia or infarction and left ventricular dysfunction events are of particular concern in older patients treated with anti-angiogenic and certain cytotoxic agents. Although not common, cardiac ischemia or infarction was reported in 10 (2.6%) younger sorafenib-treated patients but in only three (4.3%) older patients, and left ventricular dysfunction was observed in three younger patients but in only one older patient.

Although there is a reasonable concern that older patients may not tolerate cytotoxic or immunotherapy as well as younger patients, in the current subset analysis approximately 79% of older





**Figure 4.** Time to self-reported health status deterioration by age according to treatment (sorafenib vs placebo) as measured by the Physical Well-Being (PWB) domain of Functional Assessment of Cancer Therapy–General. **A)** Patients aged  $\geq 70$  y. **B)** Patients aged  $< 70$  y. The median time to self-reported health status deterioration and 95% confidence interval (CI) is shown as well as the hazard ratios (HRs) that compare self-reported health status deterioration in the sorafenib treatment group with that in the placebo treatment group. Sor = sorafenib; Pla = placebo.

patients tolerated treatment with sorafenib. The mean duration of therapy was approximately 25 weeks, regardless of age. The most common adverse events among these patients were gastrointestinal (primarily diarrhea and nausea) and dermatologic (primarily rash, hand-foot syndrome, and alopecia). However, few of these events were grade 3 and/or 4. This result indicates that prophylactic and/or maintenance treatment to control gastrointestinal and dermatologic symptoms may increase the proportion of older patients who can tolerate sorafenib to approach the level observed among younger patients (92%). In addition, cardiac events, a particular concern in older patients treated with antiangiogenic agents, were infrequent.

The quality of life (as measured by FKSI and FACT-G) of placebo-treated patients deteriorated more quickly than that of sorafenib-treated patients, regardless of age. In addition, sorafenib-treated patients maintained or improved their quality of life at a later stage in therapy than placebo-treated patients. Thus, by accepted quality of life measures, sorafenib therapy resulted in maintained or improved quality of life.

This study had several limitations. The subgroup analyses in this study were conducted in a post hoc exploratory fashion, and interpretation of the results is subject to the following limitations of the data. This study was not designed to test for statistically significant differences between treatment effects in the older and younger age subgroups. Other caveats that may influence interpretation of results include a limited sample size and an imbalance in treatment assignment for the elderly subgroup. As with any subgroup analysis, the limited sample size and imbalance in the treatment assignment influence the strength of the observations, yet the data that we presented provide some important trends between treatment groups for key study data across the older and younger subgroups in TARGET. These analyses provide valuable informative results that will help clinicians to offer targeted therapy appropriately and that also provide some guidance in the design of trials involving targeted therapies.

Although exploratory in nature, this subgroup analysis of the pivotal TARGET trial demonstrated that sorafenib conferred a statistically significant increase in progression-free survival and

increased clinical benefit without compromising the quality of life of both older and younger patients with advanced renal cell carcinoma. The efficacy of sorafenib was maintained in patients who were 70 years or older. This result, combined with an acceptable toxicity profile in both younger and older patients, supports the use of sorafenib as a treatment for advanced renal cell carcinoma in all age groups.

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## Notes

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