Original Study

Long-Term Response to Sunitinib Treatment in Metastatic Renal Cell Carcinoma: A Pooled Analysis of Clinical Trials

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Abstract

A subset of patients with metastatic renal cell carcinoma treated with sunitinib achieved long-term response (ie, progression-free survival [PFS] > 18 months). Long-term responders had improved objective response rate, PFS, and overall survival versus others. Patient baseline characteristics predictive of long-term response to sunitinib were identified.

Background: We characterized clinical outcomes of patients with metastatic renal cell carcinoma (mRCC) treated with sunitinib who were long-term responders (LTRs), defined as patients having progression-free survival (PFS) $>$ 18 months. **Patients and Methods:** A retrospective analysis of data from 5714 patients with mRCC treated with sunitinib in 8 phase II/III clinical trials and the expanded access program. Duration on-study and objective response rate (ORR) were compared between LTRs and patients with PFS $\leq$ 18 months ("others"). PFS and overall survival (OS) were summarized using Kaplan–Meier methodology. **Results:** Overall, 898 (15.7%) patients achieved a long-term response and 4816 (84.3%) patients did not achieve long-term response. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others. ORR was 51% in LTRs versus 14% in others ($P < .0001$). Median PFS in LTRs was 32.11 months and median OS was not reached. LTRs had higher percentage of early tumor shrinkage $\geq$ 10% at the first scan (67.1% vs. 51.2%; $P = .0018$) and greater median maximum on-study tumor shrinkage from baseline (−56.9 vs. −27.1; $P < .0001$) versus others. White race, Eastern Cooperative Oncology Group performance status 0, time from diagnosis to treatment $\geq$ 1 year, clear cell histology, no liver metastasis, lactate dehydrogenase $\leq$ 1.5 upper limit of normal (ULN), corrected calcium $\leq$ 10 mg/dL, hemoglobin greater than the lower limit of normal, platelets less than or equal to ULN, body mass index $\geq$ 25 kg/m^2, and low neutrophil-to-lymphocyte ratio were associated with LTR. **Conclusion:** A subset of patients with mRCC treated with sunitinib achieved long-term response. LTRs had improved ORR, PFS, and OS.

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Introduction

Sunitinib malate (Sutent), a multitargeted tyrosine kinase inhibitor, is approved globally for the treatment of metastatic renal cell carcinoma (mRCC).[1] Sunitinib has demonstrated efficacy in many clinical trials,[2-6] and is a standard-of-care first-line treatment for patients with mRCC.[7] In the pivotal trial, the median

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progression-free survival (PFS) was significantly longer in patients with mRCC treated with sunitinib versus interferon-alfa (11 vs. 5 months, respectively).[3] Efficacy of sunitinib was confirmed by almost all subsequent trials performed in the first-line setting.[2,8-12] Median PFS with sunitinib in the first-line setting ranged between 9 and 11 months.[2,8,10-12] Median PFS with other targeted therapies in the first-line setting ranged between 8 and 11 months,[4,13,14] and in the second-line setting ranged between 4 and 8 months.[15-18]

Molina et al[19] reported a subset of patients (n = 34) with mRCC treated in clinical trials at Memorial Sloan Kettering Cancer Center (MSKCC) who achieved a long-term response with sunitinib, defined as patients achieving durable complete response or remaining progression-free for > 18 months. Of this group, 3 patients achieved complete response and 24 achieved partial response at 18 months after treatment start; the median PFS at a landmark time point of 18 months after treatment initiation was 17.4 months (95% confidence interval [CI], 7.0-29.9 months).[19] Lack of bone or lung metastases and favorable MSKCC risk status were found to be associated with long-term response.[19]

The goal of this retrospective study was to identify and characterize sunitinib long-term responders (LTRs), defined as patients with mRCC having PFS > 18 months while on sunitinib therapy. We used a large, contemporary clinical trial database of patients with mRCC who were treated with sunitinib to describe the clinical characteristics, duration of treatment, and clinical outcome of patients identified as LTRs, and to identify risk factors that may predict long-term response.

Methods

Patients and Study Design

A retrospective analysis of data in patients (n = 5714) with mRCC treated with sunitinib in 8 phase II or III clinical trials (n = 1173) and patients (n = 4543) treated in the expanded access program (EAP; Supplemental Table 1 in the online version). In 6 trials (n = 5199), sunitinib was started at 50 mg daily for 4 weeks followed by a 2-week break ("4/2 schedule")[3,5,6,10,11,20-22]; in 2 trials (n = 226), the starting dose was 37.5 mg administered on a continuous once-daily dosing (CDD) regimen[8,23]; and, in 1 trial (n = 289), the starting dose was 50 mg 4/2 schedule or 37.5 mg CDD.[9]

Phase II or III trials included patients with histologically confirmed clear cell RCC with measurable disease, metastases (except for 1 study by Motzer et al,[9] wherein patients could have locally recurrent or mRCC), adequate organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 or Karnofsky performance score > 70.[3,5,6,8,9,20,22,23] In the EAP trial, patients had histologically confirmed mRCC (of all histological subtypes) with adequate organ function.[10,11] In all trials, tumor response was assessed according to Response Evaluation Criteria in Solid Tumors criteria. A central independent review of response was conducted in 3 trials.[3,6,22] All trials were registered on ClinicalTrials.gov and were previously reported (Supplemental Table 1 in the online version).

Statistical Analysis

Dose reduction/interruptions, treatment discontinuation, and treatment-related adverse events (AEs) were summarized between LTRs and patients who had PFS ≤ 18 months ("others").

Multiple univariable logistic regression analyses were conducted to identify potential baseline characteristics associated with LTRs. Baseline characteristics assessed included age, race, sex, ECOG PS, time from diagnosis, histology, metastasis, serum lactate dehydrogenase (LDH), corrected serum calcium, hemoglobin, platelets, prior nephrectomy, prior therapy, body mass index (BMI), and neutrophil-to-lymphocyte ratio (NLR). A multivariable logistic regression analysis was further conducted for the baseline characteristics that were statistically significant ($P < .05$) in the univariable analyses to identify the independent baseline factors associated with LTRs.

A Cox proportional analysis was conducted to identify baseline and post-baseline characteristics associated with overall survival (OS).

Tumor burden was determined based on the sum of the longest diameters of the target lesions by the investigators. Median tumor burden at baseline was compared between LTRs and others. Early tumor shrinkage, defined as ≥ 10% reduction in sum of the longest diameters of target lesions at the first scan after initiation of sunitinib treatment, was calculated and compared between LTRs and others. The 10% threshold was selected based on a study showing that early tumor shrinkage ≥ 10% at first post-baseline assessment could serve as a putative early end point in patients with mRCC.[24] Patients from the EAP were excluded from the analysis of tumor burden and tumor shrinkage because tumor response assessments were not mandated and were performed at the discretion of the investigators. Because early decline in NLR is associated with favorable outcome and early increase in NLR with worse outcome,[25] these trends were compared separately.

Results

Patients

A total of 898 (15.7%) patients met the definition of LTRs. The remaining 4816 (84.3%) had PFS < 18 months that included stable disease, progressive disease, or death (ie, others). Patient demographics were similar between the LTRs and others (Supplemental Table 2 in the online version). Patient disease characteristics were mostly similar between the 2 groups, except for ECOG PS 0, time from diagnosis to treatment ≥ 1 year, and low MSKCC risk group that were more common in the LTR versus others. LTRs also had favorable laboratory findings versus others (Supplemental Table 2 in the online version).

Sunitinib Treatment and AEs

Overall, 14.9% of LTRs and 14.0% of others received sunitinib as first-line therapy, whereas 85.1% of LTRs and 86.0% of others received sunitinib as second-line therapy. Most patients (865 [96.3%] of LTRs and 4406 [91.5%] of others) received sunitinib on a 4/2 schedule; 33 (3.7%) of LTRs and 410 (8.5%) of others received sunitinib on CDD. The median (range) duration on-study was 28.6 (16.8-70.7) months in LTRs and 5.5 (0-68.8) months in others.

A similar number of patients discontinued treatment due to insufficient clinical response in the 2 groups (34.9% in LTRs and 36.1% in others). Dose reduction/interruption occurred in 58.5% of LTRs and 31.5% of others and discontinuation of treatment due to AEs occurred in 11.1% of LTRs and 16.5% of others (see

Table 1 Dose Reduction/Interruptions and Treatment Discontinuation Over the Entire Duration of Therapy

	LTRs n = 898	Others n = 4816	All Patients n = 5714
Dose Reductions/interruptions			
Yes	525 (58.5)	1518 (31.5)	2043 (35.8)
Reason for discontinuation			
Adverse event	100 (11.1)	794 (16.5)	894 (15.6)
Completed	144 (16.0)	249 (5.2)	393 (6.9)
Global deterioration of health status	0	16 (0.3)	16 (0.3)
Insufficient clinical response	313 (34.9)	1739 (36.1)	2052 (35.9)
Insufficient response	13 (1.4)	63 (1.3)	76 (1.3)
Lost to follow-up	20 (2.2)	118 (2.5)	138 (2.4)
Objective progression or relapse	10 (1.1)	197 (4.1)	207 (3.6)
Other	82 (9.1)	364 (7.6)	446 (7.8)
Protocol violation	4 (0.4)	16 (0.3)	20 (0.4)
Study terminated by sponsor	102 (11.4)	24 (0.5)	126 (2.2)
Died	48 (5.3)	879 (18.3)	927 (16.2)
No longer willing to participate in study	51 (5.7)	319 (6.6)	370 (6.5)
Refused continued treatment for reason other than adverse event	1 (0.1)	13 (0.3)	14 (0.2)
Withdrew consent	9 (1.0)	20 (0.4)	29 (0.5)
Other	0	1 (0.0)	1 (0.0)
Missing	1 (0.1)	4 (0.1)	5 (0.1)

NOTE. Values are n (%).
Abbreviation: LTR = long-term responder.

summary in Table 1). The most common grade ≥ 3 treatment-related AEs reported by LTRs were hypertension (12.8%), palmar-plantar erythrodysesthesia (12.5%), diarrhea and neutropenia (10.2% each), and fatigue (10.1%; Table 2).

Efficacy

Based on univariable logistic regression analyses of baseline characteristics, white race, ECOG PS 0, or 1-2 (vs. ECOG > 2), time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver or bone metastasis, serum LDH ≤ 1.5 upper limit of normal (ULN), corrected serum calcium ≤ 10 mg/dL, hemoglobin greater than lower limit of normal (LLN), platelets less than or equal to ULN, BMI ≥ 25 kg/m^2, prior nephrectomy, and low (≤ 3) NLR were associated with longer PFS (Table 3).

Using a multivariable logistic regression analysis, white race, ECOG PS 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, serum LDH ≤ 1.5 ULN, corrected serum calcium ≤ 10 mg/dL, hemoglobin greater than LLN, platelets less than or equal to ULN, BMI ≥ 25 kg/m^2, and low (≤3) NLR were associated with longer PFS (Table 4).

A Cox proportional analysis of OS demonstrated that age < 65 years, ECOG PS 0, time from diagnosis to treatment ≥ 1 year, lack of metastasis (lung, liver, bone, or other site), hemoglobin greater than LLN, platelets less than or equal to ULN, and NLR ≤ 3 were associated with longer OS (Supplemental Table 3 in the online version).

Objective response rate (ORR; complete or partial response) was 51.0% in LTRs versus 14.0% in others ($P < .0001$; Table 5). For LTRs, median PFS (95% CI) was 32.11 (30.30-33.76) months and median OS was not reached (Figure 1). For others, median PFS (95% CI) was 7.16 (6.86-7.62) months and median OS was 14.74 months.

Of the 1171 patients included in the tumor shrinkage analysis, 167 were LTRs and 1007 were others. Median tumor burden at baseline differed significantly between LTRs and others (85.0 vs. 100.5, respectively; $P = .0041$). Median tumor shrinkage at the first post-baseline scan also differed significantly between LTRs and others (change from baseline, −17.1 vs. −11.5, respectively; $P < .0001$). More patients in the LTR group had early tumor shrinkage ≥ 10% at the first scan versus others (67.1% vs. 51.2%, respectively; $P = .0018$). The median maximum on-study tumor shrinkage from baseline was −56.9 for LTRs versus −27.1 for others ($P < .0001$).

More LTRs (63.9%) had low NLR at baseline versus others (46.7%; Supplemental Table 4 in the online version). In both groups, there were significant differences in OS, PFS, and ORR in patients who had low (≤ 3) NLR both at baseline and after 6 weeks versus patients with low NLR at baseline and high (> 3) NLR (Supplemental Table 4 in the online version). NLR change from high at baseline to low at 6 weeks was also associated with better outcome versus NLR high at baseline and high after 6 weeks, although the differences were not statistically significant (Supplemental Table 4 in the online version).

LTRs Over Time

Among the 898 LTR patients who achieved PFS > 18 months, 532 (59.2%) achieved PFS > 2 years, 226 (25.2%) achieved PFS > 3 years, 98 (10.9%) achieved PFS > 4 years, and 35 (3.9%) achieved PFS > 5 years (Figure 2). The number of patients censored in the others group (ie, PFS < 18 months) over time (using the 2-, 3-, 4-, and 5-year cutoffs) is also reported (Figure 2).

Discussion

In this analysis, we identified a subset of patients with mRCC who were LTRs, defined as patients who had PFS > 18 months while on sunitinib therapy. Not surprisingly, LTRs had improved PFS and OS (median PFS, 32.11 months; median OS, not reached). Furthermore, objective response was achieved in 51.0% of LTRs compared with 19.8% in the overall population in this study and the 38.0% of patients reported previously for sunitinib-treated patients.[26]

LTRs remained on-study longer than others (median duration on-study, 28.6 vs. 5.5 months, respectively). As expected of patients treated for a longer duration, LTRs experienced more treatment-related AEs versus others. However, the safety profile of sunitinib in LTRs was similar to previous reports of short- and long-term safety of sunitinib treatment in patients with mRCC.[2,3,10,27] Previous studies have shown that hypertension and neutropenia were associated with improved clinical outcome in patients treated with sunitinib.[28,29] Indeed, hypertension and neutropenia in our analysis were found to be higher among LTRs versus others (43.8% vs.

Table 2 Treatment-Related Adverse Events Occurring in >20% of Patients in Any Group

MedDRA Preferred Term	LTRs n = 898		Others n = 4816		All Patients n = 5714	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhea	683 (76.1)	92 (10.2)	2161 (44.9)	238 (4.9)	2844 (49.8)	330 (5.8)
Fatigue	519 (57.8)	91 (10.1)	1972 (41.0)	446 (9.3)	2491 (43.6)	537 (9.4)
Nausea	413 (46.0)	26 (2.9)	1804 (37.5)	127 (2.6)	2217 (38.8)	153 (2.7)
Decreased appetite	344 (38.3)	12 (1.3)	1448 (30.1)	113 (2.4)	1792 (31.4)	125 (2.2)
Stomatitis	328 (36.5)	32 (3.6)	1320 (27.4)	130 (2.7)	1648 (28.8)	162 (2.8)
Mucosal inflammation	337 (37.5)	30 (3.3)	1296 (26.9)	132 (2.7)	1633 (28.6)	162 (2.8)
Dysgeusia	340 (37.9)	3 (0.3)	1291 (26.8)	27 (0.6)	1631 (28.5)	30 (0.5)
PPE	454 (50.6)	112 (12.5)	1163 (24.2)	317 (6.6)	1617 (28.3)	429 (7.5)
Vomiting	259 (28.8)	23 (2.6)	1354 (28.1)	154 (3.2)	1613 (28.2)	177 (3.1)
Hypertension	393 (43.8)	115 (12.8)	1072 (22.3)	266 (5.5)	1465 (25.6)	381 (6.7)
Thrombocytopenia	253 (28.2)	64 (7.1)	973 (20.2)	395 (8.2)	1226 (21.5)	459 (8.0)
Asthenia	222 (24.7)	54 (6.0)	979 (20.3)	307 (6.4)	1201 (21.0)	361 (6.3)
Dyspepsia	317 (35.3)	12 (1.3)	881 (18.3)	18 (0.4)	1198 (21.0)	30 (0.5)
Rash	266 (29.6)	15 (1.7)	801 (16.6)	35 (0.7)	1067 (18.7)	50 (0.9)
Anemia	197 (21.9)	45 (5.0)	760 (15.8)	206 (4.3)	957 (16.8)	251 (4.4)
Neutropenia	232 (25.8)	92 (10.2)	667 (13.9)	283 (5.9)	899 (15.7)	375 (6.6)
Epistaxis	198 (22.1)	6 (0.7)	634 (13.2)	33 (0.7)	832 (14.6)	39 (0.7)
Hypothyroidism	321 (35.8)	17 (1.9)	362 (7.5)	21 (0.4)	683 (12.0)	38 (0.7)
Pain in extremity	218 (24.3)	16 (1.8)	416 (8.6)	43 (0.9)	634 (11.1)	59 (1.0)

NOTE. Values are n (%).
Abbreviations: LTR = long-term responder; MedDRA = Medical Dictionary for Regulatory Activities coding dictionary; PPE = palmar-plantar erythrodysesthesia syndrome.

22.3%, and 25.8% vs. 13.9%, respectively).[28,29] Furthermore, LTRs had a numerically higher rate of dose reductions/interruptions and a numerically lower rate of treatment discontinuations due to AEs versus others; this higher incidence of AEs is in line with the known relation between toxicity and efficacy. The lower rate of treatment discontinuation in LTRs might be due to better AE management in patients who had better efficacy, and better baseline ECOG PS in the LTRs group.

Retrospective analyses showed early tumor shrinkage ≥ 10% at first scan after baseline may have predictive and prognostic value for PFS and OS in patients with mRCC.[24,30,31] In our analysis, although early tumor shrinkage ≥ 10% was significantly more common in LTRs (67%) versus others (51%), it occurred in most patients in both groups. A study by Grünwald and colleagues[32] showed that the magnitude of tumor shrinkage correlated with a better survival rate in patients with mRCC. The current analysis found the median maximum on-study tumor shrinkage was significantly greater in LTRs versus others, potentially contributing to improved PFS and OS in LTRs.

An elevated baseline NLR has been shown to be associated with a poor prognosis in patients with mRCC.[33,34] Our results showed that a decrease in NLR from baseline to week 6 was associated with better ORR, PFS, and OS, whereas an increase in NLR was associated with worse outcome. These findings are consistent with a previous study that showed early decline of NLR in response to targeted therapy was associated with favorable outcomes, and an increase in NLR was associated with the opposite effect.[25]

In the current study, risk factors associated with long-term response included white race, ECOG PS 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, serum LDH ≤ 1.5 ULN, corrected serum calcium ≤ 10 mg/dL, BMI ≥ 25 kg/m^2, and favorable hematology values. These baseline characteristics associated with long-term response are consistent with previously reported predictors for survival in patients with mRCC treated with sunitinib[2,26,35] and with other inhibitors of the vascular endothelial growth factor pathway.[36] Four of the risk factors identified in this study (ie, hemoglobin < 1.5 ULN, corrected calcium, LDH > 1.5 ULN, and time from initial RCC diagnosis) constitute the 5-factor MSKCC model that is the most commonly used prognostic model.[37] Because of the variations in patient characteristics, identifying early predictors of LTRs may help guide the treatment selection for particular patients with specific baseline characteristics. Tailoring treatment to the patient characteristics may improve outcome in patients with mRCC.

Although this study is based on a large, contemporary clinical trial database of patients with mRCC treated with sunitinib, it has limitations. In addition to the inherent issues associated with a retrospective analysis, the patient population was heterogeneous and included treatment-naïve patients, as well as previously treated patients who received different dosing regimens. Most patients were excluded from the tumor shrinkage analysis because tumor assessment was not mandated in the EAP study. Another potential limitation of this study is the selection of the 18-month cutoff to define LTRs. However, a cut point of 18 months is 64% longer than the median PFS observed in the sunitinib pivotal study, and is longer than the median PFS observed in the first-line setting with other targeted therapies (range, 64%-125%).[12-14] Finally, > 85% of patients in this study received sunitinib as second-line therapy, before

Table 3 Univariable Logistic Regression of Baseline Characteristics Predictive of LTRs Versus Others

Parameter	Odds Ratio	95% CI	*P*
Age, y (<65 vs. ≥65)	1.014	0.871-1.180	.8602
Sex (female vs. male)	0.895	0.760-1.054	.1853
Race			
Asian vs. white	0.753	0.568-0.998	.0481
Black vs. white	0.315	0.098-1.013	.0526
Not applicable vs. white	0.414	0.191-0.897	.0255
Other vs. white	0.971	0.751-1.253	.8186
ECOG PS			
0 vs. 1-2	2.078	1.793-2.409	<.0001
>2 vs. 1-2	0.277	0.087-0.881	.0297
Time from diagnosis to treatment (≥1 vs. <1 y)	1.709	1.458-2.003	<.0001
Histology			
Non–clear cell histology vs. clear cell	0.677	0.524-0.875	.0029
Not reported vs. clear cell	<0.001	<0.001->999.999	.9519
Metastasis (no vs. yes)			
Liver	1.458	1.226-1.735	<.0001
Lung	1.171	0.991-1.384	.0631
Bone	1.466	1.248-1.722	<.0001
Other site	1.073	0.927-1.241	.3471
LDH (>1.5 vs. ≤1.5 ULN)	0.401	0.296-0.544	<.0001
Corrected calcium (>10 vs. ≤10 mg/dL)	0.414	0.330-0.520	<.0001
Hemoglobin (>LLN vs. ≤LLN)	2.375	2.050-2.753	<.0001
Platelets (≤ULN vs. >ULN)	2.975	2.329-3.802	<.0001
Prior nephrectomy (no vs. yes)	0.567	0.433-0.742	<.0001
Prior therapy (no vs. yes)	1.030	0.875-1.213	.7193
BMI (<25 vs. ≥25 kg/m^2)	0.565	0.482-0.662	<.0001
NLR (low [≤3] vs. high [>3])	2.366	2.037-2.748	<.0001
Baseline tumor burden (<median vs. ≥median)	0.990	0.711-1.379	.9517

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; LTR = long-term responder; NLR = neutrophil-to-lymphocyte ratio; PFS = progression-free survival; ULN = upper limit of normal.

Table 4 Multivariable Logistic Regression Comparison of Baseline Characteristics Predictive of LTRs Versus Others

Parameter	Odds Ratio	95% CI	*P*
Race			
Asian vs. white	0.711	0.515-0.981	.0380
Black vs. white	0.584	0.172-1.985	.3891
Not applicable vs. white	0.107	0.026-0.443	.0020
Other vs. white	0.980	0.716-1.341	.8977
ECOG PS			
0 vs. 1-2	1.583	1.317-1.902	<.0001
>2 vs. 1-2	0.393	0.094-1.643	.2009
Time from diagnosis to treatment (≥1 vs. <1 y)	1.337	1.097-1.629	.0040
Histology			
Non–clear cell histology vs. clear cell	0.666	0.483-0.918	.0132
Not reported vs. clear cell	<0.001	<0.001->999.999	.9819
Metastasis (no vs. yes)			
Liver	1.240	1.003-1.531	.0463
Bone	1.132	0.926-1.384	.2252
LDH (>1.5 vs. ≤1.5 ULN)	0.663	0.475-0.926	.0158
Corrected calcium (>10 vs. ≤10 mg/dL)	0.572	0.438-0.748	<.0001
Hemoglobin (>LLN vs. ≤LLN)	1.353	1.121-1.633	.0016
Platelets (≤ULN vs. >ULN)	1.793	1.325-2.425	.0002
Prior nephrectomy (no vs. yes)	0.889	0.631-1.253	.5017
BMI (<25 vs. ≥25 kg/m^2)	0.801	0.662-0.969	.0226
NLR (low [≤3] vs. high [>3])	1.514	1.262-1.816	<.0001

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; LTR = long-term responder; NLR = neutrophil-to-lymphocyte ratio; PFS = progression-free survival; ULN = upper limit of normal.

sunitinib becoming the standard of care in many countries, so it is likely that patients with poorer prognosis at diagnosis were not able to survive long enough to receive sunitinib. Therefore, the results from this study are probably different from what might now be expected with sunitinib.

Conclusions

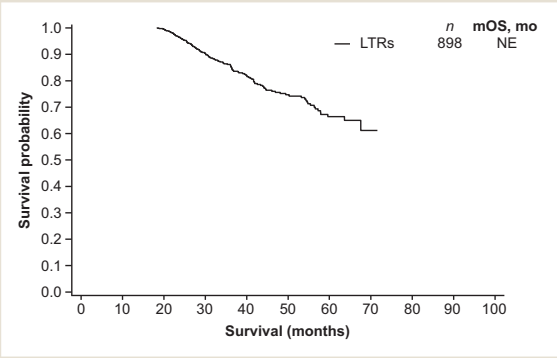
A subset of patients with mRCC treated with sunitinib in multiple clinical trials were LTRs; 15.7% achieved PFS > 18 months, and 3.9% achieved PFS > 5 years. Long-term treatment with sunitinib was associated with a numerically higher rate of dose reductions/interruptions but a numerically lower rate of treatment discontinuations due to AEs. LTRs had improved ORR, PFS, and OS. Moreover, LTRs had a higher percentage of early tumor shrinkage ≥ 10% at the first scan and greater median maximum on-study tumor shrinkage from baseline versus others. Patient baseline characteristics predicting for LTR include white race, ECOG PS 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, serum LDH ≤ 1.5 ULN, corrected serum calcium ≤ 10 mg/dL, hemoglobin greater than LLN, platelets less than or equal to ULN, BMI ≥ 25 kg/m^2, and low (≤3) NLR.

Table 5 Best Observed Objective Response

	LTRs n = 898	Others n = 4816	All Patients n = 5714
Complete response	55 (6.1)	23 (0.5)	78 (1.4)
Partial response	403 (44.9)	652 (13.5)	1055 (18.5)
Stable disease	437 (48.7)	2422 (50.3)	2859 (50.0)
Progressive disease	3 (0.3)	710 (14.7)	713 (12.5)
Other[a]	0	1009 (21.0)	1009 (17.7)
ORR	458 (51.0)	675 (14.0)	1133 (19.8)

NOTE. Values are n (%).
Abbreviations: LTR = long-term responder; ORR = objective response rate.
[a]Includes early death, indeterminate, no post-baseline tumor assessment, not assessed, not evaluable, symptomatic deterioration, and missing response.

Figure 1 Kaplan–Meier Estimates of Overall Survival in LTRs

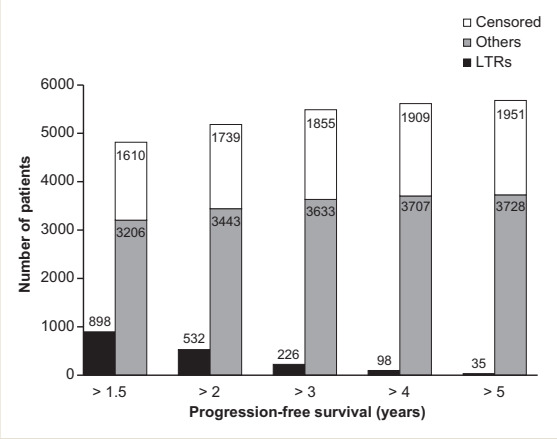


Abbreviations: LTR = long-term responder; mOS = median overall survival; NE = not estimable.

Clinical Practice Points

- Sunitinib, a multitargeted tyrosine kinase inhibitor, has demonstrated efficacy in many clinical trials, and is a standard-of-care first-line treatment for patients with mRCC.
- Of the 5714 patients with mRCC treated with sunitinib in 8 phase II/III clinical trials and in the EAP, 898 (15.7%) patients achieved a long-term response, defined as patients having PFS > 18 months while on sunitinib therapy.
- LTRs had improved ORR, PFS, and OS. The median maximum on-study tumor shrinkage was significantly greater in LTRs versus others, potentially contributing to improved PFS and OS in LTRs.
- The safety profile of sunitinib in LTRs was similar to previous reports of short- and long-term safety of sunitinib treatment in patients with mRCC.
- White race, ECOG PS 0, time from diagnosis to treatment ≥ 1 year, clear cell histology, no liver metastasis, serum LDH ≤ 1.5 ULN, corrected serum calcium ≤ 10 mg/dL, hemoglobin greater than LLN, platelets less than or equal to ULN, BMI ≥ 25 kg/m^2, and low (≤ 3) NLR were associated with long-term response.

Figure 2 LTRs and Others Over Time



Abbreviation: LTR = long-term responder.

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Disclosure

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Supplemental Data

Supplemental tables accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clgc.2017.06.005.

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Supplemental Table 1 Clinical Studies Included in the Analysis

ClinicalTrials.gov ID	Treatment Setting	Dosing	Publication
NCT00054886	Cytokine-refractory mRCC (phase II)	50 mg/d, Schedule 4/2	5
NCT00077974	Cytokine-refractory mRCC (phase II)	50 mg/d, Schedule 4/2	6
NCT00083889	Treatment-naïve mRCC (Pivotal phase III trial)	50 mg/d Schedule 4/2	3
NCT00130897	Treatment-naïve and cytokine-refractory mRCC (EAP)	50 mg/d, Schedule 4/2	10,11
NCT00089648	Bevacizumab-refractory mRCC (phase II)	50 mg/d, Schedule 4/2	20
NCT00137423	Cytokine-refractory mRCC (phase II)	37.5 mg/d, CDD (morning or evening)	23
NCT00267748	Treatment-naïve mRCC (Renal EFFECT, phase II)	50 mg/d, Schedule 4/2 or 37.5 CDD	9
NCT00254540	Treatment-naïve and cytokine-refractory mRCC (phase II)	50 mg/d, Schedule 4/2	21,22
NCT00338884	Treatment-naïve mRCC (phase II)	37.5 mg/d CDD	8

Abbreviations: CDD = continuous once-daily dosing; EAP = Expanded Access Program; ID = identifier; mRCC = metastatic renal cell carcinoma; Schedule 4/2 = 4 weeks on treatment followed by 2 weeks off treatment.

Supplemental Table 2 Patient Demographics and Baseline Characteristics

Characteristics	LTRs n = 898	Others n = 4816	All Patients n = 5714
Patient Demographics			
Age, y			
Median (range)	60 (23-89)	59 (19-88)	60 (19-89)
<65	602 (67.0)	3214 (66.7)	3816 (66.8)
≥65	296 (33.0)	1602 (33.3)	1898 (33.2)
Sex			
Male	672 (74.8)	3501 (72.7)	4173 (73.0)
Female	226 (25.2)	1315 (27.3)	1541 (27.0)
Race			
White	751 (83.6)	3862 (80.2)	4613 (80.7)
Black	3 (0.3)	49 (1.0)	52 (0.9)
Asian	60 (6.7)	410 (8.5)	470 (8.2)
Other	77 (8.6)	408 (8.5)	485 (8.5)
Region			
United States	162 (18.0)	896 (18.6)	1058 (18.5)
Non-United States	734 (81.7)	3914 (81.3)	4648 (81.3)
Missing	2 (0.2)	6 (0.1)	8 (0.1)
Disease characteristics			
ECOG PS			
0	544 (60.6)	2030 (42.2)	2574 (45.0)
1	303 (33.7)	2091 (43.4)	2394 (41.9)
≥2	36 (4.0)	603 (12.5)	639 (11.2)
Missing	15 (1.7)	92 (1.9)	107 (1.9)
Time from diagnosis to treatment, y			
<1	242 (26.9)	1841 (38.2)	2083 (36.5)
≥1	653 (72.7)	2907 (60.4)	3560 (62.3)
Missing	3 (0.3)	68 (1.4)	71 (1.2)
Prior nephrectomy			
Yes	834 (92.9)	4242 (88.1)	5076 (88.8)
No	64 (7.1)	574 (11.9)	638 (11.2)
Site of metastases			
Bone	231 (25.7)	1622 (33.7)	1853 (32.4)
Lung	663 (73.8)	3666 (76.1)	4329 (75.8)
Liver	186 (20.7)	1318 (27.4)	1504 (26.3)
Brain	24 (2.7)	316 (6.6)	340 (6.0)
Other	489 (54.5)	2665 (55.3)	3154 (55.2)
No. of metastatic sites[a]			
1	36 (21.95)	182 (18.07)	218 (18.62)
2	56 (34.15)	292 (29.00)	348 (29.72)
3	41 (25.00)	255 (25.32)	296 (25.28)
>3	31 (18.90)	211 (20.95)	242 (20.67)
Missing	0	67 (6.65)	67 (5.72)
MSKCC risk groups			
Low (0)	80 (48.78)	287 (28.50)	367 (31.34)
Intermediate (1-2)	79 (48.17)	578 (57.40)	657 (56.11)
Poor (≥3)	4 (2.44)	126 (12.51)	130 (11.10)
Missing	1 (0.61)	16 (1.59)	17 (1.45)

Supplemental Table 2 Continued

Characteristics	LTRs n = 898	Others n = 4816	All Patients n = 5714
Laboratory assessments			
Hemoglobin			
>LLN	551 (61.4)	1935 (40.2)	2486 (43.5)
≤LLN	336 (37.4)	2803 (58.2)	3139 (54.9)
Missing	11 (1.2)	78 (1.6)	89 (1.6)
Corrected calcium, mg/dL			
>10	93 (10.4)	1030 (21.4)	1123 (19.7)
≤10	710 (79.1)	3257 (67.6)	3967 (69.4)
Missing	95 (10.6)	529 (11.0)	624 (10.9)
LDH			
>1.5 ULN	48 (5.3)	579 (12.0)	627 (11.0)
≤1.5 ULN	757 (84.3)	3662 (76.0)	4419 (77.3)
Missing	93 (10.4)	575 (11.9)	668 (11.7)
Platelets			
>ULN	76 (8.5)	1032 (21.4)	1108 (19.4)
≤ULN	811 (90.3)	3700 (76.8)	4511 (78.9)
Missing	11 (1.2)	84 (1.7)	95 (1.7)
Body mass index, kg/m^2			
≥25	580 (64.6)	2510 (52.1)	3090 (54.1)
18.5-25	248 (27.6)	1804 (37.5)	2052 (35.9)
<18.5	9 (1.0)	164 (3.4)	173 (3.0)
Missing	61 (6.8)	338 (7.0)	399 (7.0)
NLR			
≤3	559 (62.2)	1988 (41.3)	2547 (44.6)
>3	316 (35.2)	2659 (55.2)	2975 (52.1)
Missing	23 (2.6)	169 (3.5)	192 (3.4)

NOTE. Values are n (%) unless otherwise stated.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; LTR = long-term responder; MSKCC = Memorial Sloan Kettering Cancer Center; NLR = neutrophil-to-lymphocyte ratio; ULN = upper limit of normal.
[a]For some studies the actual sites were not mapped to the integrated database and could not be reported.

Supplemental Table 3 Cox Proportional Analysis of Overall Survival for LTRs Versus Others

Parameter	Overall Survival		
	Hazard Ratio	95% CI	*P*
Age (<65 vs. ≥65 y)	0.86	0.79-0.95	.0018
Sex (female vs. male)	0.98	0.89-1.08	.6824
Race			
Asian vs. white	1.02	0.89-1.18	.7495
Black vs. white	1.22	0.77-1.95	.3998
Not applicable vs. white	0.98	0.73-1.31	.8800
Other vs. white	1.10	0.94-1.28	.2480
ECOG PS			
0 vs. 1-2	0.66	0.60-0.72	<.0001
>2 vs. 1-2	2.55	1.93-3.37	<.0001
Time from diagnosis to treatment (≥1 vs. <1 y)	0.74	0.67-0.82	<.0001
Clear cell histology (no vs. yes)	1.41	1.25-1.61	<.0001
Metastasis (no vs. yes)			
Liver	0.89	0.81-0.97	.0114
Lung	0.72	0.65-0.80	<.0001
Bone	0.84	0.76-0.91	<.0001
Other site	0.84	0.76-0.91	<.0001
LDH (>1.5 vs. ≤1.5 ULN)	1.61	1.43-1.81	<.0001
Corrected calcium (>10 vs. ≤10 mg/dL)	1.31	1.19-1.45	<.0001
Hemoglobin (>LLN vs. <LLN)	0.72	0.65-0.80	<.0001
Platelets (≤ULN vs. >ULN)	0.75	0.67-0.83	<.0001
Prior nephrectomy (no vs. yes)	1.10	0.96-1.25	.1642
Prior therapy (no vs. yes)	0.94	0.85-1.04	.2317
BMI (<25 kg/m^2 vs. >25 kg/m^2)	1.17	1.07-1.27	.0008
NLR (≤3 vs. >3)	0.62	0.56-0.68	<.0001

Abbreviations: BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; LTR = long-term responder; NLR = neutrophil-to-lymphocyte ratio; ULN = upper limit of normal.

Supplemental Table 4 **Change in Neutrophil-to-Lymphocyte Ratio (NLR) From Baseline to Week 6, Low (NLR ≤3) Versus High (NLR >3)**

	LTRs				Others			
	High to Low n = 196	High to High n = 120	Low to Low n = 502	Low to High n = 57	High to Low n = 1057	High to High n = 990	Low to Low n = 1528	Low to High n = 266
Overall survival								
Median, mo	NR	67.52	NR	57.79	16.55	10.29	23.57	15.00
Hazard ratio		0.730[a]		0.439[b]		0.612[a]		0.490[b]
P		.2204[a]		.0035[b]		<.0001[a]		<.0001[b]
Hazard ratio 95% CI		0.4417-1.2074		0.2529-0.7624		0.5505-0.68		0.4173-0.5762
Progression-free survival								
Median, mo	32.04	27.60	33.36	25.06	7.98	5.87	9.76	7.55
Hazard ratio		0.864[a]		0.545[b]		0.755[a]		0.692[b]
P		.3229[a]		.0002[b]		<.0001[a]		<.0001[b]
Hazard ratio 95% CI		0.6473-1.154		0.3963-0.7501		0.6811-0.8367		0.5938-0.807
Objective response rate								
n (%)	112 (57.14)	47 (39.16)	269 (53.58)	18 (31.57)	168 (15.89)	96 (9.70)	346 (22.64)	39 (14.66)
P		.0021[a]		.0021[b]		<.0001[a]		.0037[b]
Odds ratio		2.0709[a]		2.5009[b]		1.7598[a]		1.7038[b]
Odds ratio 95% CI		1.3034-3.2904		1.3927-4.4907		1.3469-2.2993		1.1884-2.4427

Abbreviations: CI = confidence interval; LTR = long-term responder; NR = not reached.
[a]High to low versus high to high.
[b]Low to low versus low to high.