4612

Overall and Progression-free Survival with Everolimus, Temsirolimus or Sorafenib as Second Targeted Therapies for Metastatic Renal Cell Carcinoma: A Retrospective US Chart Review

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BACKGROUND

- Renal cell carcinoma (RCC) is a common adult malignancy in the US, with an estimated 50,000 new cases and over 10,000 deaths in the US in 2010.[1]
- About 25-30% of patients have metastatic disease at the time of RCC diagnosis[2] and face an expected 5-year survival rate of less than 20%.[3]
- Treatment of metastatic RCC (mRCC) has changed greatly with the introduction of tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin (mTOR) inhibitors. These new targeted agents can prolong overall survival (OS) and progression-free survival (PFS) in mRCC patients and have replaced cytokine therapy as the standard of care in mRCC.[4]
- TKIs are commonly used as 1st targeted therapies. However, the majority of patients develop resistance and experience disease progression within 6-11 months of starting treatment.[5-7]
- Everolimus, temsirolimus and sorafenib are commonly used as 2nd targeted treatments in the US,[8] with everolimus being the only approved agent with phase 3 clinical trial evidence for efficacy after failure of a TKI.
- Real-world evidence comparing the effectiveness of 2nd targeted therapies in mRCC is limited.

OBJECTIVE

- To compare the effectiveness of treatment with everolimus, temsirolimus and sorafenib for mRCC following initial targeted therapy with a TKI.

DATA

Data Source

- A nationally representative panel of oncologists in the US was screened during September to December 2011 for treatment of mRCC patients.
- Eligible oncologists were invited to participate in an online chart abstraction and each physician randomly selected up to 5 patient charts meeting the inclusion and exclusion criteria for the present study.
- Abstracted patient data were anonymous and non-identifiable; exemption from Institutional Review Board (IRB) review and informed consent was obtained from the New England Institutional Review Board under 45 CFR 46.

Inclusion Criteria

- Adults (age ≥18 years) diagnosed with mRCC.
- Received a TKI (sunitinib, sorafenib or pazopanib) as their 1st targeted therapy for mRCC.
- Discontinued their 1st TKI for medical reasons (e.g. progression, no response, tolerability) and subsequently initiated everolimus, temsirolimus or sorafenib as the 2nd targeted therapy.
- Initiated their 2nd targeted therapy between October 2009 and June 2010. This time window ensured that patients 1) initiated their 2nd targeted therapy at least 6 months after its FDA approval for mRCC and 2) were followed for at least 14 months after initiation.

Exclusion Criteria

- Use of high dose interleukin-2 (i.e. on average ≥600,000 U/kg per day), an mTOR inhibitor or bevacizumab prior to the 1st TKI for the treatment of mRCC.
- Participation in a clinical trial of an investigational treatment for mRCC, or use of combination therapy with ≥2 targeted agents prior to or upon initiation of 2nd targeted therapy.

STUDY MEASURES

Outcome Measures

- Overall survival (OS): Time from 2nd targeted therapy initiation to death.
- Progression-free survival (PFS): Time from 2nd targeted therapy initiation to physician-assessed disease progression or death.

Patient follow-up was censored at the last recorded office visit or phone contact.

Baseline Information

- Patient characteristics prior to initiation of 2nd targeted therapy were collected:
  - Demographics
  - Comorbidities (hypertension, diabetes, cardiovascular diseases, chronic renal disease, and others)
  - mRCC characteristics: disease duration, performance status, number and location of metastases, progression or response history
  - Treatments prior to 2nd targeted therapy

STATISTICAL METHODS

- Baseline characteristics were compared among patients initiating their 2nd targeted therapy with everolimus, temsirolimus and sorafenib.
- Pairwise comparisons of OS and PFS were made between patients initiating 2nd targeted therapy with everolimus, temsirolimus and sorafenib, using multivariable Cox proportional hazard models adjusting for:
  - Age, sex, race (white vs. other), whether the disease was metastasized at the time of RCC diagnosis (yes/no), duration of mRCC prior to initiation of 2nd targeted therapy (<1 year vs. ≥1 year), type of 1st targeted therapy (sunitinib, sorafenib, and pazopanib), physician-assessed response to 1st targeted therapy (yes/no), duration of 1st targeted therapy (<6 months vs. ≥6 months), treatments used before 1st targeted therapy (surgery vs. other), comorbidities (yes/no), sites of metastasis (bone or central nervous system vs. other), number of metastatic sites (1, 2, and 3 or more), sarcomatoid differentiation (yes/no), non-clear cell RCC, ECOG performance status, and KPS score.
- Adjusted OS curves were generated from the multivariable Cox models using direct adjustment based on parametric survival function.[9]
- Subgroup analyses were conducted in patients who received sunitinib as 1st targeted therapy and patients who experienced disease progression during 1st targeted therapy.

RESULTS

Baseline Characteristics

- A total of 159 physicians contributed chart data. Among them, 60.4% were medical oncologists and the rest had dual practice in hematology and oncology. The majority (85.5%) practiced in community settings as opposed to academic settings.
- Charts were reviewed for 233, 178 and 123 mRCC patients receiving everolimus, temsirolimus and sorafenib as 2nd targeted therapy, respectively.
- The median age was 64 years and 70.4% were male. The majority of patients had more than 1 metastatic site. Prior to initiating the 1st targeted therapy, 16.7% of patients had surgery and the majority (80.1%) had no prior treatment for mRCC.
- Sunitinib was the most commonly used 1st targeted therapy, with 99.2%, 84.8% and 79.8% of sorafenib, temsirolimus and everolimus patients using sunitinib initially. Other first targeted therapies were sorafenib and pazopanib.
- Baseline characteristics were generally similar among patients in these three groups except for type of 1st targeted therapy, prior progression, location of metastatic sites, mRCC histology and KPS score (**Table 1**).
- Temsirolimus patients were more likely to have progression during their 1st targeted therapy (89.0% vs. 80.5%) and were more likely to have non-clear cell RCC (14.7% vs. 5.7%) and sarcomatoid differentiation (9.1% vs. 2.6%) compared to sorafenib patients. Additionally, more temsirolimus patients were able to completely care for self based on KPS score when compared with everolimus patients (KPS ≥70%: 89.2% vs. 80.7%).

Table 1. Baseline Characteristics

CHARACTERISTICS	Index Therapy (2nd Targeted Therapy) Everolimus (n = 233)		Temsirolimus (n = 178)		Sorafenib (n = 123)		Significance of *P*-value	
Age (yrs), mean (SD)	63.1	(9.0)	63.7	(8.3)	64.3	(8.2)		
Female, n (%)	69	(29.6%)	54	(30.3%)	35	(28.5%)		
Race (white) , n (%)	191	(82.0%)	133	(75.6%)	97	(79.5%)		
Treatments prior to 1st targeted therapy, n (%)								
No treatment	186	(79.8%)	140	(78.7%)	102	(82.9%)		
Systemic therapy	1	(0.4%)	1	(0.6%)	2	(1.6%)		
Surgery	40	(17.2%)	33	(18.5%)	16	(13.0%)		
Radiation therapy	9	(3.9%)	5	(2.8%)	3	(2.4%)		
First targeted therapy, n (%)								
Sunitinib	186	(79.8%)	151	(84.8%)	122	(99.2%)	†	‡
Sorafenib	32	(13.7%)	18	(10.1%)	0	(0.0%)		
Pazopanib	15	(6.4%)	9	(5.1%)	1	(0.8%)		
Responded while on 1st targeted therapy[§], n (%)	130	(58.3%)	94	(54.7%)	69	(60.0%)		
Progressed while on 1st targeted therapy[§], n (%)	197	(86.4%)	154	(89.0%)	99	(80.5%)		‡
Number of metastatic sites, median (range)	2	(1-6)	2	(1-5)	2	(1-4)		
Site of metastasis, n (%)								
Lung	154	(66.1%)	131	(73.6%)	94	(76.4%)		†
Bone	111	(47.6%)	100	(56.2%)	51	(41.5%)		‡
Liver	81	(34.8%)	45	(25.3%)	38	(30.9%)	*	
Lymph nodes	66	(28.3%)	52	(29.2%)	28	(22.8%)		
Adrenal glands	32	(13.7%)	27	(15.2%)	18	(14.6%)		
Soft tissue other than lymph nodes	20	(8.6%)	19	(10.7%)	10	(8.1%)		
Central nervous system	12	(5.2%)	2	(1.1%)	2	(1.6%)	*	
Non-clear cell RCC, n (%)	26	(11.3%)	26	(14.7%)	7	(5.7%)		‡
Sarcomatoid differentiation, n (%)	12	(5.7%)	15	(9.1%)	3	(2.6%)		‡
KPS, n (%)								
[100%, 70%]	184	(80.7%)	157	(89.2%)	98	(83.8%)	*	
(0%, 60%]	44	(19.3%)	19	(10.8%)	19	(16.2%)		
Existence of any comorbidities, n (%)	180	(77.9%)	142	(79.8%)	89	(72.4%)		
Hypertension[#]	120	(52.6%)	101	(58.4%)	63	(52.9%)		
Diabetes mellitus (type I or II)	64	(27.7%)	54	(31.0%)	41	(34.2%)		
Cardiovascular diseases	48	(21.1%)	44	(25.9%)	28	(23.1%)		
Chronic renal disease	47	(20.3%)	38	(22.0%)	29	(24.0%)		
Chronic obstructive pulmonary disease	38	(16.5%)	26	(15.4%)	15	(12.5%)		

* $P < 0.05$ for everolimus vs. temsirolimus.
† $P < 0.05$ for everolimus vs. sorafenib.
‡ $P < 0.05$ for temsirolimus vs. sorafenib.
§Response and progression relied on physicians' judgment, which were based on radiographic evidence, physical exams, or improved or worsening cancer-related symptoms, not based on RECIST.
#Only the 5 most prevalent comorbidities are presented in the table.

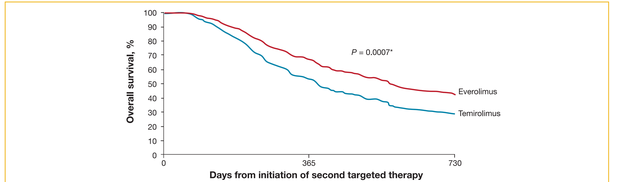
Description of Outcomes

- Patients using sorafenib as 2nd targeted therapy were more likely to have dose adjustment than those using temsirolimus and everolimus (23.6% vs. 10.7% vs. 9.0%). The most commonly observed dose adjustment was dose reduction.
- The median follow-up time, from the initiation of 2nd targeted therapy initiation to last follow-up or death, was 12.9 months for everolimus, 9.9 months for temsirolimus and 12.1 months for sorafenib.
- During the study period, 100 (42.9%), 85 (47.8%) and 48 (39.0%) patients who used everolimus, temsirolimus and sorafenib as 2nd therapy died, respectively.
- During the study period, disease progression occurred for 138 (59.2%) everolimus patients, 111 (62.4%) temsirolimus and 70 (56.9%) sorafenib patients.
- Of all reported progression events, 285 (89.3%) were based on radiographic evidence and 34 (10.7%) were based on physical exam evidence or cancer-related symptoms alone.
- Among 368 patients who discontinued 2nd targeted therapy or progressed while on 2nd targeted therapy, only a small proportion of patients (77, 20.9%) initiated a 3rd targeted therapy during the study period.

Adjusted Comparisons of OS and PFS: Everolimus vs. Temsirolimus as Second Therapy

- After adjusting for baseline characteristics, everolimus was associated with significantly prolonged OS (hazard ratio [HR] 0.56; 95% CI 0.40-0.78; $P < 0.001$) and PFS (HR 0.73; 95% CI 0.55-0.96; $P = 0.025$) compared to temsirolimus.
- Adjusted median OS was 19.0 months vs. 12.7 months for everolimus and temsirolimus, respectively (**Figure 1**).

Figure 1. Adjusted Overall Survival Curves of Everolimus vs. Temsirolimus

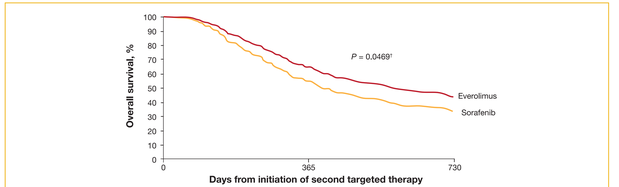


Note: Adjusted overall survival curves were generated from the Cox-proportional hazard model, including all patients receiving everolimus and temsirolimus as 2nd treatment. Prior TKI therapy that these patients received included sunitinib, sorafenib and pazopanib. *$P < 0.05$

Adjusted Comparisons of OS and PFS: Everolimus vs. Sorafenib as Second Therapy

- Everolimus was also associated with significantly longer OS compared to sorafenib (HR 0.65; 95% CI 0.42-0.99; $P = 0.047$). Although the difference was not statistically significant, everolimus was associated with a numerically longer PFS compared to sorafenib (HR 0.75; 95% CI 0.53-1.07; $P = 0.110$).
- Adjusted median OS was 18.6 months vs. 13.1 months for everolimus and sorafenib, respectively (**Figure 2**).

Figure 2. Adjusted Overall Survival Curves of Everolimus vs. Sorafenib

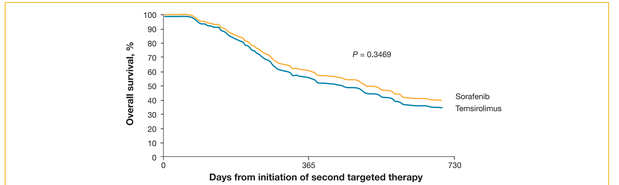


Note: Adjusted overall survival curves were generated from the Cox-proportional hazard model, including all patients receiving everolimus and sorafenib as 2nd treatment who did not use sorafenib as prior therapy. †$P < 0.05$

Adjusted Comparisons of OS and PFS: Temsirolimus vs. Sorafenib as Second Therapy

- Patients who received sorafenib as 2nd targeted therapy had prolonged OS (HR 1.23; 95% CI 0.80-1.87; $P = 0.347$) and PFS (HR 1.18; 95% CI 0.82-1.69; $P = 0.363$) compared to those with temsirolimus, although the difference was not statistically significant.
- Adjusted median OS was 14.9 months vs. 16.7 months for temsirolimus and sorafenib, respectively (**Figure 3**).

Figure 3. Adjusted Overall Survival Curves of Temirolimus vs. Sorafenib



Note: Adjusted overall survival curves were generated from the Cox-proportional hazard model, including all patients receiving temsirolimus and sorafenib as 2nd treatment who did not use sorafenib as prior therapy.

Subgroup Analysis

- Similar results were observed in subgroups of patients who used sunitinib as 1st targeted treatment and patients who had disease progression during 1st targeted therapy.

DISCUSSION

- To our knowledge, this is the first study to assess the real-world comparative effectiveness of everolimus, temsirolimus and sorafenib, at individual drug level, in mRCC patients with a prior TKI treatment.
- Results comparing everolimus and sorafenib in the present study are consistent with an indirect comparison of randomized trial data[10] and retrospective analyses of claims data.[8]
- Longer OS and PFS observed with everolimus compared to temsirolimus indicate that within-class differences should be taken into account when considering the 2nd targeted treatment options for mRCC.
- The trend of longer OS observed with sorafenib compared to temsirolimus (though not statistically significant) is consistent with the newly released results of the Phase 3 INTORSECT study (NCT00474786).[11]
- Limitations:
  - Comparisons between treatment groups were adjusted for a large number of patient characteristics collected from the chart review. However, as this was a real-world non-randomized study, these comparisons may be confounded by unobserved patient characteristics.
  - Progression in the present study was defined by physicians based on radiographic evidence, physical exams or changes in cancer-related symptoms, rather than consistent use of RECIST for all patients (as in mRCC clinical trials).
  - Further studies are needed to confirm the relative efficacy of 2nd targeted therapies in mRCC and to define the optimal treatment sequence.

CONCLUSIONS

- **Among mRCC patients receiving a 2nd targeted therapy after an initial TKI, treatment with everolimus was associated with significantly prolonged OS and PFS compared to temsirolimus and significantly prolonged OS compared to sorafenib. No significant differences of OS or PFS were found between temsirolimus and sorafenib.**

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