Med. J. Cairo Univ., Vol. 86, No. 3, June: 1663-1670, 2018
www.medicaljournalofcairouniversity.net

Sunitinib in Metastatic Renal Cell Carcinoma: Response Rate and Survival Outcome

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Abstract

Background: Sunitinib demonstrated robust antitumor activity in preclinical studies resulting not only in tumor growth inhibition, but tumor regression in models of colon cancer, non-small-cell lung cancer, melanoma, renal carcinoma, and squamous cell carcinoma, which were associated with inhibition of VEGFR and PDGFR phosphorylation.

Aim: The aim of this work is to evaluate the role of Sunitinib as a first line treatment in metastatic Renal Cell Carcinoma (RCC) as regard the response rate, survival outcome and toxicity.

Patients and Methods: This study was conducted at Clinical Oncology and Nuclear Medicine Departments, Tanta University Hospitals and Tanta Cancer Center. All patients with metastatic renal cell carcinoma who treated throughout the period from January 2012 to December 2015 were included. Patient data were retrospectively and personally collected.

Result: All patients were evaluated for tumor response, one (3.3%) of 30 patient had a complete response, 11 (36.7%) patients had a partial response, 6 (20%) patients had a stationary disease and only 12 (40%) had a progressive disease. Median time for treatment failure was 22 months (range 2-34 months). The progression free survival in all patient: the median time was: 22 months 95% CI: 17.5, 27.5 the correlation between PFS and histological types of kidney cancer in which the p-value is <0.001 which is statistically significant in favor of clear renal cell carcinoma. The correlation between OS and MSKCC score in which the p-value is <0.001 which is statistically significant. The correlation between OS and histological types in which the p-value is <0.001 which is statistically significant in favor of clear cell carcinoma.

Conclusion: The present study has suggested that Sunitinib was both effective as a first-line treatment and well tolerated in patients with metastatic renal cell carcinoma.

Key Words: *Sunitinib – mRCC – Response rate – Survival outcome.*

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Introduction

RENAL Cell Carcinoma (RCC) is the most common cancer of the kidney [1]. Approximately 20%-30% of patients presented with metastatic disease and 70-80% of patients presented with localized or locally advanced disease at the time of diagnosis, which is potentially curable by radical surgical resection alone [2]. Among patients who undergo radical resection for localized disease, future metastatic disease develops in 20-40% of the patient population [3].

An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomized clinical trials, have established the standard role of the orally administered vascular endothelial growth factor receptor and platelet derived growth factor receptor inhibitor Sunitinib for the treatment of advanced renal cell carcinoma [4].

Sunitinib is an oral small molecular tyrosine kinase inhibitor that was rationally designed and chosen for its high bioavailability and its nanomolar-range potency against the antiangiogenic Receptor Tyrosine Kinases (RTKs), Vascular Endothelial Growth Factor Receptor (VEGFR) and Platelet-derived Growth Factor Receptor (PDGFR) [5].

Sunitinib inhibits other tyrosine kinases including, KIT, FLT3, colony-stimulating factor 1 (CSF-1), and RET, which are involved in a number of malignancies including small-cell lung cancer, GI Stromal Tumors (GISTs), breast cancer, acute myelogenous leukemia, multiple endocrine neoplasia types 2A and 2B, and familial medullary thyroid carcinoma [5].

Clinical activity was demonstrated in neuroendocrine, colon, and breast cancers in phase II

studies, whereas definitive efficacy has been demonstrated in advanced renal cell carcinoma and in imatinib-refractory GISTs, leading to US Food and Drug Administration approval of Sunitinib for treatment of these two diseases [6].

Studies investigating Sunitinib alone in various tumors types and in combination with chemotherapy are ongoing. The clinical benchmarking of this small-molecule inhibitor of members of the split-kinase domain family of RTKs will lead to additional insights regarding the biology, potential biomarkers, and clinical utility of agents that target multiple signaling pathways in tumor, stromal, and endothelial compartments [7].

The aim of this work is to evaluate the role of Sunitinib as a first line treatment in metastatic Renal Cell Carcinoma (RCC) as regard the response rate, survival outcome and toxicity.

Patients and Methods

This study was conducted at Clinical Oncology and Nuclear Medicine Departments, Tanta University Hospitals and Tanta Cancer Center. All patients with metastatic renal cell carcinoma who treated throughout the period from January 2012 to December 2015 were included. Patient data were retrospectively and personally collected.

Eligibility criteria:

- Patients >18 years who were treatment-naïve metastatic RCC.
- Patients had clear cell type renal carcinoma and non-clear cell type renal carcinoma (papillary and undifferentiated).
- No previous chemotherapy or target therapy.
- Clinical and radiological evidence of metastasis.
- Adequate hematological picture (absolute neutrophil count of 1000/ul or more without growth factor support, platelet 75000/ul or more, and hemoglobin 80g/l or more). Total serum bilirubin less than or equal to twice the upper normal limit (normal rang 0.3mg/dl to 1.0mg/ dl), serum aminotransferase (ALT) less than five-times ULN (normal range 10 to 40U/L), serum creatinine less than or equal to twice ULN (normal range 0.6 to 1.2mg).
- Echocardiography revealing good systolic and diastolic function.

Exclusion criteria:

- Patient with acute medical or psychiatric condition that make assessment inappropriate.

The assessment of the patient was done by:

- CT chest, abdomen and pelvis.
- Bone scan.
- Brain MRI when indicated.
- PET-CT when indicated.
- ECHO.
- Serum Lactate Dehydrogenase (LDH).
- Serum calcium.
- Laboratory assessment of blood counts.
- Kidney and liver functions were carried before each cycle and as clinically indicated.
- Thyroid function test (T3, T4, TSH).

Retrospective study:

Sunitinib was administered orally with dose of 50 mgonce daily without regard to meals, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. Dose reduction or treatment interruption was allowed for the management of adverse events, depending on their type and severity. Treatment was continued until evidence of disease progression or unacceptable adverse events.

Palliative irradiation to specific site of disease was permitted in such cases as indicated, Sunitinib was interrupted during palliative irradiation. Stopping one day before and resuming treatment one day after.

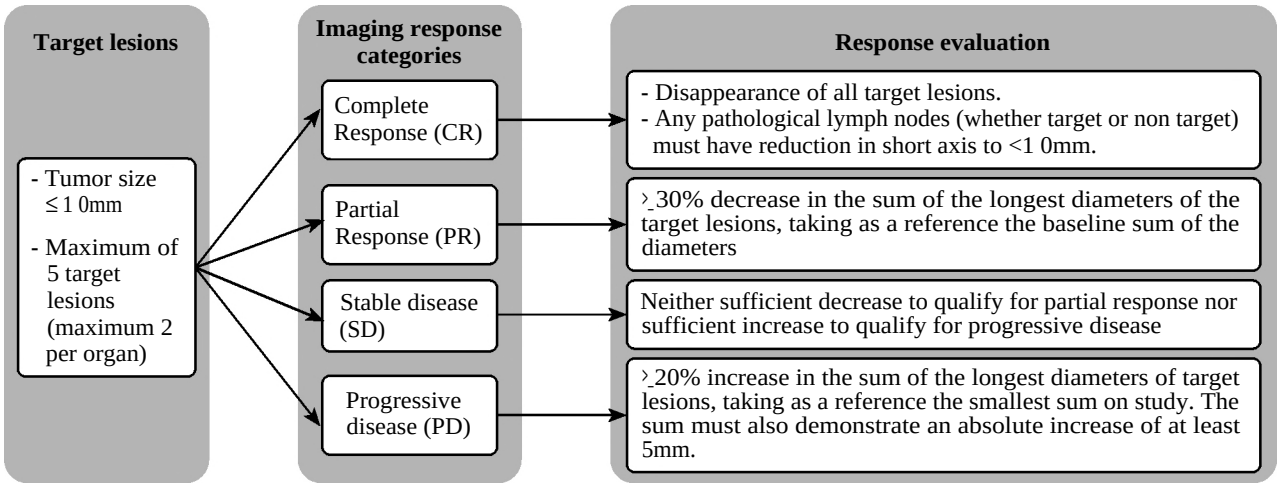
The prognosis of patient was assessed according to the memorial sloankettering cancer center (MSKCC) which include five variables: Interval from diagnosis to treatment of less than 1 year, Karnofsky performance status less than 80%, serum Lactate Dehydrogenase (LDH) greater than 1.5 times the Upper Limit of Normal (ULN) normal LDH 140-280U/L, corrected serum calcium greater than the ULN normal serum calcium 8.5-10.2mg/dl, and serum hemoglobin less than the Lower Limit of Normal (LLN) normal serum hemoglobin for men 13.5-17.5g/dl and for women 12-15.5g/dl.

Safety assessments:

Adverse events were assessed every cycle and were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC) version 3.

Purpose of assessment:

The revised RECIST (RECIST 1.1).



- Progression Free Survival (PFS) was calculated from the date of the start of treatment to the date of local disease recurrence and/or distant metastasis.
- Overall Survival (OS) from the date of the start of treatment to the date of last follow-up or death.
- The median duration of PFS & OS was calculated using Kaplan-Meier method.

Results

During the period from January 2012 to December 2015, 38 patients with treatment naive metastatic renal cell carcinoma had been enrolled and patients are no longer being recruited.at the time of analysis, data for safety, treatment duration, tumor response, and survival were available for 30 patients who presented to Clinical Oncology and Nuclear Medicine Department, Tanta University Hospital and Tanta Cancer Center were included and followed-up in this study.

Patient characteristics:

- The clinical features and characteristics of all patients are shown in thirteen (43.3%) patients were males and 17 (56.7%) were females.
- The median age of the patients included was 57 years (range 27-78). Fourteen (46.7%) patients were less than 57 years old.
- As regard histology, 25 (83.3%) patients had clear cell RCC and only five (16.7%) had non clear cell histology undifferentiated-papillary).
- Our study is included 30 metastatic RCC, lung and liver were the most common sites of metastasis (60%).
- Median number of treatment cycles was 5 cycles with range (3-12).

Treatment modalities:

Twenty six (86.7%) patients had underwent nephrectomy and the other patients had metastatic lesion at the first presentation.

Tumor response:

All patients were evaluated for tumor response, one (3.3%) of 30 patient had a complete response, 11 (36.7%) patients had a partial response, 6 (20%) patients had a stationary disease and only 12 (40%) had a progressive disease. Table (1).

Table (1): Tumor response.

Tumor response	No.	%
Complete response	1	3.3
Partial response	11	36.7
Stationary	6	20
Progressive	12	40

Progression free survival:

Median time for treatment failure was 22 months (range 2-34 months). The one-year PFS was 66.2%.

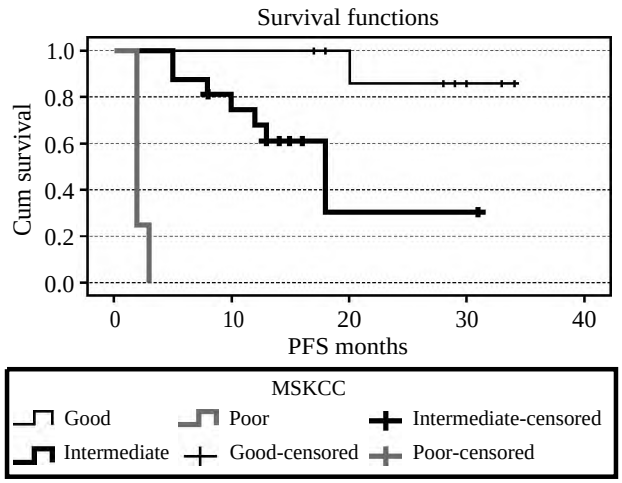


Fig. (1): Progression free survival according to MSKCC score.

Fig. (1) shows the correlation between PFS and MSKCC score in which the p-value is <0.001 which is statistically significant.

Denotes statistically significant difference at p-value <0.05.

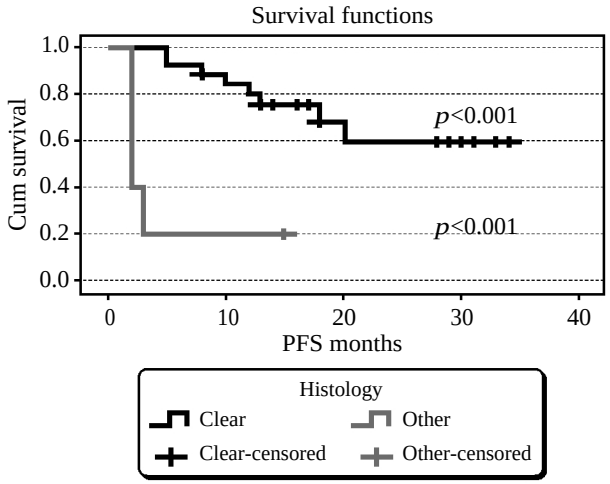


Fig. (2): Progression free survival according to histology.

Fig. (2) shows the correlation between PFS and histological types of kidney cancer in which the p-value is <0.001 which is statistically significant in favor of clear renal cell carcinoma.

Table (2): Univariate analysis of prognostic factors according to overall survival.

Factors	1-year OS	p-value
Age:		
<_57	40	0.146
>57	56.4	
Sex:		
Male	38.2	0.167
Female	61	
PS (karnofsky):		
70%-90%	24	0.001
50%-70%	80	
30%-50%	66.7	
Site:		
Left kidney	5.9	0.351
Right kidney	72.9	
Histology:		
Clear RCC	87.1	<0.001
Non-clear RCC (undifferentiated-papillary)	0	
MSKCC score:		
Good	100	<0.001
Intermediate	70.9	
Poor	0	
Surgery:		
Yes	83.4	0.013
No	0	

Denotes statistically significant difference at p-value <0.05.

Progression free survival according to surgery:

The correlation between PFS and surgery in which the p-value is <0.038 which is statistically significant in favor of patients underwent nephrectomy.

Denotes statistically significant difference at p-value <0.05.

Overall survival:

All patients were followed-up for a median of 20 months (range 5-49), and the median time for overall survival was 33 months.

One year overall survival is 87.8% showed the prognostic factors affecting OS.

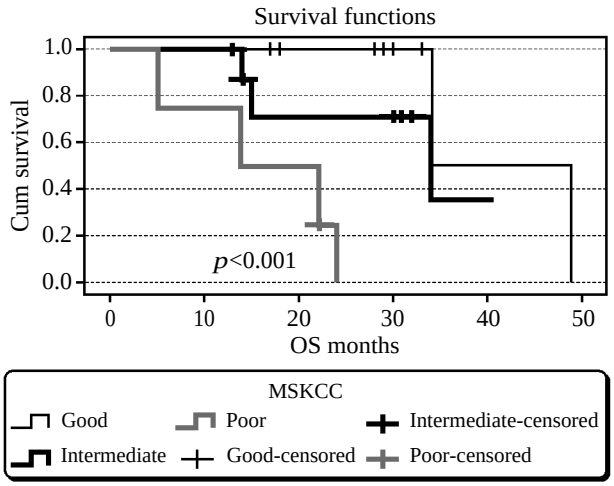


Fig. (3): Overall survival according to MSKCC.

Fig. (3) shows the correlation between OS and MSKCC score in which the p-value is <0.001 which is statistically significant.

Denotes statistically significant difference at p-value <0.05.

Overall survival according to histology:

The correlation between OS and histological types in which the p-value is <0.001 which is statistically significant in favor of clear cell carcinoma.

Denotes statistically significant difference at p-value <0.05.

Overall survival according to surgery:

The correlation between OS and surgery in which the p-value is=0.013 which is statistically significant in favor of patients underwent nephrectomy.

Denotes statistically significant difference at p-value <0.05.

Non haematological adverse events:

The most commonly reported treat-related non-hematological adverse events were diarrhea, fatigue, nausea, and mucosal inflammation, most of which were of grade 1-2 severity. The most common grade 3-4 treatment-related non-hematological adverse events were rash, constipation, and hand foot syndrome. 12 patient (40%) complain from diarrhea grade 1-2, 9 patient (30%) complain from fatigue and nausea grade 1-2, while 8 (26.5%) patient complain from mucosal inflammation, while 6 patient (20%) complain from hand foot syndrome, and 4 patient (13%) complain from constipation.

Haematological adverse events:

CBC showed thrombocytopenia in 4 patients, anemia in 3 patients, and neutropenia in 2 patients grade 1-2. The grade 3-4 treatment-related hematological adverse events were thrombocytopenia (23%), anemia (13%) and neutropenia (6.5%).

Sunitinib doses were reduced from 50mg/day to 37.5mg/day in 16 patients of 30 patients (53%) with further reduction to 25mg/day in only 1 patient (3.3%). Dose modification was according patient tolerability and safety such sever hematological adverse effect, diarrhea and cardiac effect. All patients began treatment on schedule 4-2, andsunitinib was interrupted in most of patients.

Discussion

Sunitinib (Sutent) is a multikinase inhibitor approved by the FDA for the treatment of metastatic renal cell carcinoma that has progressed after a trial of immunotherapy. The receptor tyrosine kinases inhibited by Sunitinib include vascular endothelial growth factor receptors 1,2, and 3 (VEGFR 1-3), platelet-derived growth factor receptor alpha (PDGFR-alpha), and PDGFR-beta. Approval of Sunitinib was based on the high response rate (40% partial responses), a median time to progression of 8.7 months, and an overall survival of 16.4 months [8].

This retrospective study was conducted at Clinical Oncology and Nuclear Medicine Department, Tanta University Hospitals and Tanta Cancer Center. All patients with metastatic renal cell carcinoma treated throughout the period from January 2012 to December 2015 were included.

Several studies have demonstrated that first-line Sunitinib is associated with a marked activity in terms of both overall disease control rate and time to tumor progression in mRCC treatment-naïve patients. Specifically the efficacy of Sunitinib was demonstrated in a randomized phase III trial in all Memorial Sloan-Kettering Cancer Center prognostic groups (Motzer et al., 2007), and also in a retrospective analysis of an unselected population of patients treated in a clinical practice setting (Gore et al., 2009).

As regard histology, 25 (83.3%) patients had clear cell RCC and only five patients (16.7%) had non clear cell histology. This result coincide with that reported by Capitanio et al., where clear cell (cRCC) represented 80-90%, papillary (pRCC) represented 5-15% and chromophobe (chRCC) reported 2-5% [9].

In our study, the commonest metastatic sites include lung (40%) and liver (20%). This coincide with Chow et al., which reported that the incidence of lung metastasis was (45-60%) and the incidence of liver metastasis was (20%) in patient with renal cell carcinoma [10].

In our study the incidence of bone, lymph nodes, and brain metastasis was (6.6%, 30% and 3.3%) respectively. This is inconsistent with that reported by Chow WH et al., which reported a high incidence of bone metastasis (30%), lung (45-60%), bone lymph nodes (22%), liver (20%), and brain (8%) this difference may be due to the small number of patients in our study (30) patients compared to study by Chow et al., was (1640) [10].

As regard response of our patients to Sunitinib, according to RECIST criteria complete response was (3.3%) partial response was (36.7%) stationary disease was (20%) and progressive disease was (40%) this is consistent with that reported by Motzer et al., [11] that reported partial response in (40%) of all patients stationary disease in (27%) of all patients and progressive disease in (33%) of all patients.

Median time for treatment failure was 22 months (range 2-34 months) this is inconsistent with that reported by Keizman et al, which reported that the median PFS was 10-11 months [12].

In agreement with our result, a study was done by Buda-Nowak A, Kucharz et al., 27 patients treated at the Department of Oncology, University Hospital in Krakow. The inclusion criteria were as follows: Diagnosis of stage IV clear cell mRCC, application of Sunitinib as first-line treatment for the mRCC, prior nephrectomy (total or nephron sparing surgery) and good or intermediate Memorial Sloane Kettering Cancer Centre (MSKCC) risk

prognosis. All patients received Sunitinib on a standard schedule (initial dose 50mg/day, 4 weeks on, 2 weeks off). The median progression-free survival was 28.3 months [95% (CI) 20.4-36.2 months] **[13]**.

In our study the median overall survival was 33 months and this is inconsistent with what reported by Keizman et al., that reported the median overall survival was 23 months **[14]**.

In agreement with our result, a study was done by Rini et al., reported that Median overall survival was 33.17 months **[15]**.

Overall survival differed according to MSKCC risk groups (favorable >intermediate >poor risk), p-value <0.001. This suggests that underlying tumor biology remains an important factor in determining patient survival, even in the setting of treatment with a highly active agent such as sunitinib **[16]**.

It might seem that there was a discrepancy between the relatively low incidence of grade 3-4 adverse events in this trial and the apparently high percentage of dose reductions **[17]**.

In our study, Sunitinib doses were reduced from 50mg/day to 37.5mg/day in about 16 patients of 30 patients (6.6%) with further reduction to 25 mg/day in only 1 patient (3.3 %). Dose modification or interruption was according patient tolerability and safety such sever hematological adverse effect, diarrhea and cardiac effect. All patients began treatment on schedule 4-2, and Sunitinib was interrupted in most of patient.

Within the analysis reported here, the total incidence of grade 3 or higher treatment-related cardiac disorders was only 1% (1 of 30). These data are similar to those included in the approved labeling for Sunitinib **[18]**.

Routine monitoring is recommended for patients with cardiac risk factors and baseline evaluation of ejection fraction is recommended for consideration in patients without risk factors **[16]**.

As regard to a study was done by Rini et al., hypothyroidism has been associated with Sunitinib treatment the incidence of laboratory evidence of thyroid dysfunction was 60 to 70%. Treatment of hypothyroidism was required in 15% of the patients. While in our study treatment adverse events was in13% patients. Routine monitoring of thyroid function tests was part of this study. Over the course of its conduct, frequent abnormalities of thyroid function tests associated with Sunitinib treatment were reported. Routine monitoring of thyroid function is recommended with replacement therapy as appropriate **[19]**.

In our study the most common adverse events included hypertension (17.6%), fatigue (36.5%), diarrhea (46.5), and hand-foot syndrome (20%).

This is inconsistent with that reported by Motzer et al., where the most commonly reported Sunitinib-related grade 3 adverse events included hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). None of these adverse events occurred with grade 4 severity **[20]**.

In our study, hematologic adverse events were evaluated at day 28 and day 42. Although recovery from Sunitinib toxicity was observed with respect to thrombocytopenia and neutropenia, anemia was more severe at day 42 than at day 28. Previous cross-sectional and longitudinal studies have shown a significant correlation between anemia and fatigue in patients with cancer, such that lower hemoglobin levels are associated with worse fatigue **[21,22]**.

In agreement with this results Motzer et al., **[23]** the median age of the patients included was 57 (range 27-78). Fourteen (46.7%) patients were less than 57 years old.

In our study 13 (43.3%) patients were males and 17 (56.7%) were females. This is not consistent with that reported by Motzer et al., **[23]** which reported that there is a 1.5:1 predominance in men over women.

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السو نيتينيب فى سرطان الكلى ذو ثانويات: معدل الإستجابة ونتائج العلاج

المقدمة: سرطان الخلايا الكلوية هو من أكثر أنواع السرطان شيوعا وما يقرب من ٢٠ إلى ٣٠٪ من المرضى يعانون من وجود ثانويات، بينما ٧٠ إلى ٨٠٪ من المرضى يقتصر إنتشار المرض على الكلى فقط ويكتفى فى تلك الحالات بالإستئصال الجراحى الجزرى. فهم أسباب سرطان الكلى على المستوى الجزيئ ومن خلال التجارب العشوائية كان له دور هام فى إستخدام السينوتنيب فى علاج سرطان الكلى المتقدم. السينوتنيب هو صغير فى التكوين الجزيئ وهو مثبط للتيروزين كيينيز وهو له نشاط فعال ضد الورم.

الهدف من البحث: الهدف من البحث هو تقييم دور السينوتنيب كخط علاج أول فى سرطان الكلى ذو ثانويات من حيث معدل الإستجابة ونتائج العلاج.

المرضى وطرق الدراسة: ستجرى هذه الدراسة بأثر رجعى فى قسم علاج الأورام والطب النووى بمستشفيات جامعة طنطا ومعهد أورام طنطا خلال الفترة من يناير ٢٠١٢ وحتى ديسمبر ٢٠١٥ ويتضمن البحث مرضى سرطان الكلى ذو ثانويات الذين يزيد أعمارهم عن ١٨ سنة وقد ثبت من تحليل الأنسجة وجود سرطان بالكلى مع سلامة تحاليل الدم ووظائف الكلى والكبد والغدة الدرقية والقلب.

يستخدم عن طريق الفم بجرعة ٥٠مجم لمدة ٤ أسابيع ثم راحة أسبوعين يتم تعديل الجرعة على حسب إستجابة المريض والآثار الجانبية للعقار. حيث تقلل الجرعة إلى ٣٧.٥مجم لمدة ٤ أسابيع ثم راحة أسبوعين أو ٢٥مجم لمدة ٤ أسابيع ثم راحة أسبوعين. تم تعديل الجرعة فى ١٦ حالة من ٣٠ حالة إلى ٣٧.٥مجم وذلك لوجود آثار جانبية من العقار من إسهال وآثار جانبية على القلب وتقرح فى جلد باطن اليدين والقدم. من أشهر الآثار الجانبية التى عانى منها المريض خلال فترة العلاج هى إسهال، إعياء، إلتهابات بالفم ميل للقئ، إمساك وتقرحات بجلد باطن القدم واليدين. كما وجد أيضا نقص فى عدد الصفائح الدموية وكرات الدم البيضاء بدرجة عالية.

النتائج: متوسط النجاه بشكل عام ٣٣ شهر فى حين أن المدة التى عاشها المرض دون تطور فالحالة المرضية تعد فالتوسط ٢٢ شهر.

ملخص هذه الدراسة العلمية يوضح مدى كفاءة السونتنيب كخط أول فى علاج أورام الكلى ذو الثانويات.