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Safety and efficacy of targeted agents in metastatic kidney cancer patients with renal dysfunction

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Abstract

Background: Multiple molecularly targeted agents (MTAs) have been approved for the management of metastatic renal cell carcinoma(mRCC). Sunitinib and M-TOR inhibitors (temsirolimus, everolimus) are primarily metabolized in the liver, while the metabolism of bevacizumab is unclear. There are limited data on the toxicity profile and efficacy of these agents in patients with renal impairment(RI). This is clinically relevant especially since about one third of mRCC patients have renal dysfunction.

Methods: The primary objective was to assess the safety and efficacy of targeted agents in mRCC patients with RI. Medical records of patients with mRCC at Wayne State University started on sunitinib, temsirolimus, everolimus or bevacizumab were reviewed. Patients with a calculated creatinine clearance(CrCl) of ≤60ml/min were deemed to have RI. Data on safety and efficacy of MTA therapy were collected and analyzed with respect to renal function.

Results: RI was observed in 33% of our mRCC patients. The incidence of toxicities, responses, time to progression(TTP), and overall survival(OS) were not significantly different in patients with RI compared to patients with normal renal function. Patients with RI had larger median increases in blood pressure with sunitinib and bevacizumab, increased incidence of thyroid dysfunction with sunitinib, and increased incidence of rash and dose interruptions with m-TOR inhibitors, than did patients with normal renal function.

Conclusions: RI was commonly observed in our mRCC patients. MTAs are well tolerated and efficacy appears to be maintained in patients with RI. Vigilant monitoring of hypertension would be recommended for pts receiving sunitinib and bevacizumab.

Keywords

renal dysfunction; kidney cancer; sunitinib; temsirolimus; bevacizumab; everolimus

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CONFLICT OF INTEREST:
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INTRODUCTION:

Renal cell carcinoma(RCC) is the third most common tumor of the urinary tract and accounts for about 3.8% of all adult malignancies(1). About 58,240 new cases of RCC were diagnosed in the United States(US) in 2010, with an estimated 13,040 deaths. More than a quarter of patients present with advanced stage of disease and about one-third of patients undergoing resection for localized disease will have a recurrence(2). Previously the median survival of patients with mRCC despite immunotherapy was 12-15 months(3). The use of molecularly targeted agents(MTA) revolutionized the management of mRCC with the availability of several treatment options.

The United States Food and Drug Administration(FDA) has approved several MTAs for the treatment of mRCC. Sorafenib(Nexavar®) in a phase III trial consisting of 903 patients pretreated with immunotherapy was shown to significantly prolong progression free survival(PFS) of mRCC patients compared to placebo(4). Sunitinib(Sutent®) also improved PFS and overall survival(OS) compared to interferon-α in a 750 patient randomized, phase III trial(5). Temsirolimus(Torisel®) improved OS and PFS in poor-risk patients with mRCC compared to interferon-α(6). Everolimus(Afinitor®) was approved for treatment of patients with mRCC after failure of treatment with sunitinib or sorafenib(7). The combination of bevacizumab(Avastin®) and interferon-α was approved based on evidence from a randomized, phase III study of 649 patients, showing longer PFS in patients receiving the combination, compared to those receiving interferon-alpha alone(8). In a recent randomized, placebo-controlled trial, pazopanib monotherapy significantly prolonged PFS and tumor response in both treatment-naive and cytokine-pretreated patients with mRCC(9). In summary, since 2005 a concerted effort via clinical trials has led to the successful establishment of a number of targeted therapies in RCC management.

Sorafenib is an orally administered, multikinase inhibitor targeting the platelet derived growth factor(PDGF), vascular endothelial growth factor(VEGF) receptors, c-KIT and Ras tyrosine kinases(10). Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism mediated by CYP3A4. Sorafenib therapy has been extensively evaluated in mild and moderate hepatic dysfunction, with no dosage reduction recommended for patients with mild-moderate(Child-Pugh A-B) hepatic impairment. Sunitinib is an oral, multitargeted tyrosine kinase inhibitor of VEGFRs, PDGFRs, and KIT(11). Sunitinib is also metabolized primarily in the liver by hepatic enzyme cytochrome P450-3A4. Renal elimination is a minor route of excretion for sunitinib (16% of the administered dose is eliminated in urine) (12). Bevacizumab is a monoclonal antibody targeted against the VEGF ligand, which inhibits the biologic activity of VEGF. The metabolism of bevacizumab is nonspecific, with tissue distribution consistent with the disposition of a general monoclonal antibody(13). Temsirolimus and everolimus are both inhibitors of mammalian target of rapamycin (mTOR), an intracellular protein implicated in multiple growth-related cellular functions. M-TOR inhibitors are metabolized primarily in the liver by hepatic cytochrome P45-3A4. Elimination is primarily via the feces and only about 5% of administered dose is detected in the urine(14).

Renal insufficiency(RI) is seen commonly in patients with RCC and has been reported to be as high as 50% of all cases by one group(15). This is explained by the observation that the median age of diagnosis of RCC is 65 years(1). With a higher incidence of diabetes and hypertension in this age group, a larger proportion of patients with RCC are likely to have underlying chronic kidney disease(10). Nephrectomy prolongs OS in patients with mRCC (16). As a result, a large proportion of mRCC patients have a nephrectomy increasing the risk of RI(10). Patients maintained on chronic dialysis are also at an increased risk of

developing malignancies, including RCC. The incidence of RCC in these chronic dialysis patients has been reported to be around 1-3%(17).

It is not clear though whether MTAs would be safe and effective in patient populations with RI. The majority of clinical trials testing these agents excluded patients with moderately impaired renal function. Exclusion criterion for the phase III trial evaluating sunitinib was serum creatinine greater than two times normal, whereas all other clinical trials evaluating bevacizumab, temsirolimus and everolimus excluded patients with serum creatinine greater than one and half times upper limit of normal. It is possible that a few patients with mildly impaired renal function and estimated creatinine clearance(CrCL) between 40-59ml/min might have been included in the large phase III trials but this patient subgroup has not been well characterized in the published studies.

There have been multiple case reports of patients with impaired renal function successfully treated with newer MTAs(18, 19). We have previously published our experience in the clinical application of sorafenib in mRCC with RI. Tolerability and comparable efficacy was noted in the patients with RI treated with sorafenib in our series(10). In the current retrospective study we attempt to evaluate the feasibility, safety, and efficacy of other MTAs including sunitinib, bevacizumab, temsirolimus and everolimus in mRCC patients with RI. This will help guide the practical management of this fairly common clinical scenario in RCC.

MATERIALS AND METHODS:

Patient characteristics

The primary objective was to assess the safety and efficacy of the four MTAs in patients with impaired renal function and contrast it with that noted in patients with normal renal function. The protocol was approved by the Human Investigation Committee of Wayne State University. Medical records of consecutive patients with mRCC treated with sunitinib, bevacizumab, temsirolimus or everolimus between July 2004–March 2010 were reviewed. According to the MDRD(Modification of Diet in Renal Disease) method for estimating glomerular filtration rate(20), patients with a calculated CrCl ≤60ml/min [chronic kidney disease stage 3, 4 or 5, per Kidney Disease Outcomes Quality Initiatives guidelines] were deemed to have RI(21). Data on patient demographics, safety, efficacy, and dosing of all the MTA therapy were collected and analyzed with respect to renal function. Toxicities were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Dose modifications and interruptions of targeted therapy administration were noted. Response was evaluated per RECIST criteria(22).

Statistical methods

Descriptive statistics were used to summarize the various patient characteristics, safety, and efficacy data. Time to progression(TTP) was measured from the day of starting MTA therapy until documented disease progression or death from mRCC. TTP was censored as of the date of last tumor assessment for patients still free of progression or if a patient died of a cause other than renal cell cancer. OS was measured from the day of starting MTA therapy until death from any cause. Patient survival data were obtained from either the patient's medical records, direct communication or from the United States Social Security Administration Death Index. OS was censored for patients still alive as of the last date of contact for vital status determination. Follow up and survival data are reported as of March 2010.

Standard 90% confidence limits for response rate were calculated with the method of Clopper and Pearson. Response and toxicity rates were compared with Fisher's exact test(2-

sided). Standard Kaplan-Meier estimates of the censored TTP and OS distributions were computed. Due to the small sample sizes, survival statistics(e.g., median) were estimated more conservatively using linear interpolation among successive event times on the Kaplan-Meier curves(23)

RESULTS:

Patient Characteristics

Fifty-one patients with mRCC treated with either sunitinib, bevacizumab, temsirolimus, or everolimus between July 2004–March 2010 were analyzed. Eleven of these patients were treated with more than one MTA given sequentially after the failure of the prior MTA therapy. Seventeen(33%) of the 51 study patients had RI, defined as CrCl ≤60 ml/min. The CrCl of the patients studied ranged from 24ml/min to 190ml/min, with a majority(16 of 23) having mildly impaired renal function, i.e. CrCl ranging between 40-59ml/min .None of the patients were dialysis dependent. Five of the 11 patients (45%) receiving more than one MTA had a notable decline in their renal function before the initiation of the next line of therapy.

Detailed demographics and tumor characteristics according to the MTA received and estimated CrCl levels are summarized in Table-1. Median age in the patients with RI was higher than in the patients with normal renal function in all MTA therapy groups, with most of the patients being male. All patients treated with sunitinib and bevacizumab had a Karnofsky performance status(KPS) of ≥80%. Twenty-five percent(6 of 24) of patients treated with M-TOR inhibitors had a KPS of 60-70. Patients with both RI and normal renal function were well matched with regards to Memorial Sloan Kettering Cancer Center(MSKCC) prognostic risk factors across all MTA therapy groups.

Toxicities

The types of toxicities observed were not significantly different in patients with RI as compared to patients with normal renal function[Tables 2-4].

Predominant toxicities noted in the patients receiving sunitinib were hypertension(81%), fatigue(89%) and hand-foot syndrome(35%), [Table-2]. A few notable differences were that patients with RI had an increased incidence of grade 3 fatigue(85% vs. 64%) and a higher incidence of thyroid dysfunction(60%) with sunitinib therapy, compared to the patients with normal renal function(25%).

The most frequent toxicities in the patients receiving bevacizumab were hypertension(85%), fatigue(54%) and proteinuria(50%), [Table-3]. Predominant toxicities noted in the patients receiving the M-TOR inhibitors were fatigue(83%), mucositis(46%), proteinuria (56%), hypercholesterolemia(57%), hypertriglyceridemia(64%) and hyperglycemia(50%) [Table-4]. Patients with RI had higher incidences of rash(45% vs. 15%) and infections(27% vs. 8%) compared to patients with normal renal function. The incidence of pulmonary toxicities(all grades) including interstitial pneumonitis was 30% for the group, with no major differences noted depending on renal function.

Hypertension

Hypertension is a class effect toxicity seen with VEGF inhibition therapy. Increase in blood pressure was commonly observed in patients receiving sunitinib or bevacizumab. Of the 26 patients receiving sunitinib, 16 patients(61 %) had baseline hypertension [systolic blood pressure(SBP)≥140 and/or diastolic blood pressure(DBP)≥90], 4 patients with RI and 12 with normal renal function. All RI patients had an increase in their SBP and DBP readings

on therapy. Median increase in both SBP and DBP was higher in the RI group compared to patients with normal kidney function [Tables 2-3].

Six patients(46%) receiving bevacizumab had hypertension at baseline; 2 with RI and 4 with normal renal function. Almost all patients(85%) had an increase in their SBP and DBP readings on therapy, irrespective of their renal function. Median elevations in SBP and DBP were higher in patients with RI. One patient with renal dysfunction was hospitalized for severe uncontrolled hypertension.

Dose interruptions and dose adjustments

All patients were started on the FDA approved starting doses of sunitinib, bevacizumab, temsirolimus, everolimus and these MTAs seemed to be well tolerated in RI patients as well as in patients with normal renal function. There were no observed increases in the number of dose interruptions or dose adjustments in the RI group compared to the renally sufficient group receiving either sunitinib or bevacizumab [Table 2,3]. Patients with RI receiving the M-TOR inhibitors had a higher incidence of dose interruptions(64%) than the patients with normal renal function(38%), although the number of patients requiring dose reductions was similar in both groups [Table-4].

Response and survival

RI patients receiving either sunitinib, bevacizumab, temsirolimus, or everolimus demonstrated comparable response rates, TTP, and OS as noted in their counterparts with normal renal function [Tables 5]. Clinical benefit rates (CBR=PR+SD) were 57% vs. 47% with sunitinib, 80% vs. 63% with bevacizumab, and 70% vs. 53% with M-TOR inhibitors in patients with RI versus normal renal function, respectively.

Median TTP was 2.7months vs. 2.8months with sunitinib, 6.2months vs. 3.7months with bevacizumab and 8.3months vs. 2.3months with M-TOR inhibitors in patients with RI versus normal renal function, respectively. Median OS was 13.2months vs. 8months with sunitinib, 28.8months vs. 11.4months with bevacizumab and 12.5months vs. 6.2months with M-TOR inhibitors in patients with RI versus normal renal function, respectively.

DISCUSSION:

In our study, RI defined as CrCl ≤ 60ml/min was seen in 37% of renal cell carcinoma patients, consistent with rates previously reported in the literature(15). The CrCl of the RI patients ranged from 24ml/min to 59ml/min and a majority of our RI patients(16 of 23) had mildly impaired renal function, with none of the patients being dialysis dependent. As would be expected, the RI patients were older than the patients with normal renal function. Chronic kidney disease is frequent in this group possibly because of underlying age-related medical problems like diabetes or hypertension besides the history of prior nephrectomies.

Multiple targeted therapies have now been FDA approved for use in mRCC. Although the large randomized clinical trials evaluating these drugs might have included a few patients with mildly impaired CrCl, the outcomes of this subgroup of patients have not been well characterized. There are minimal data regarding safety and efficacy of the use of MTAs in mRCC patients with RI compared to patients with normal renal function. There have been multiple case reports in the literature of patients with Rl being successfully treated with these newer agents (18, 19). Most of these case reports do not report on the toxicities peculiar to these MTAs in great detail. Our group recently reported on safety and efficacy of using sorafenib in patients with RI(10). Such patients had a higher incidence of diarrhea, hand-foot syndrome and dose reductions/interruptions than patients with normal renal function, with no noted difference in response rates, PFS, or OS.

There are reports in the literature describing clinical experience with sunitinib in patients with renal dysfunction. Khosravan et al reported on the pharmacokinetics(PK) of a single dose of 50mg of sunitinib in subjects with severe RI or end-stage renal disease(ESRD)(24). The PK of sunitinib in subjects with severe RI appeared to be similar to those with normal renal function. Plasma exposure to sunitinib and its metabolites appeared lower in subjects with ESRD compared to subjects with normal or severe RI. Since this tested only a single dose of sunitinib, no definite conclusions on cumulative toxicities, clinical outcomes, and acute toxicities can be drawn to help guide clinical decisions in practice. Josephs et. al. reported on 21 patients from five institutions with CrCl <30ml/min or ESRD treated with sunitinib(25). Their experience suggested that patients treated with sunitinib with severe RI or ESRD on hemodialysis have PFS comparable to patients with normal renal function. In addition sunitinib appeared to be reasonably well tolerated in this group of patients without any excess toxicities.

Overall the frequency of toxicities noted in our patient population treated with sunitinib was comparable to the range reported in the literature, with the exception of a higher incidence of therapy induced hypertension(26). In addition our study found that RI patients had increased incidence of higher grade fatigue, increased thyroid dysfunction and higher median rises in both SBP and DBP on therapy than patients with normal renal function.

There is very limited literature on the use of bevacizumab in patients with renal impairment. Since bevacizumab was approved for use much earlier in metastatic colorectal cancer than in mRCC, isolated case reports in the literature relate to the safety of bevacizumab in metastatic colorectal cancer patients with RI(27). Garnier-Viougeat et al. recently reported on the PK of bevacizumab in a patient with mRCC on hemodialysis(28). They treated their patient with a reduced dose of 5mg/kg every two weeks compared to the standard 10mg/kg every two weeks. Bevacizumab PK data obtained on the off-dialysis day were similar to the reference values at steady state in patients with normal renal function treated at the standard dose. Although the bevacizumab area under the curve for the hemodialysed patient was half of the reference normal values, the bevacizumab concentrations were above the reference bevacizumab IC_{50} during the first 10 days following infusion. Bevacizumab did not seem to be dialysable and could be administered anytime before or after hemodialysis. Because of these findings, they recommended a dose of 5mg/kg to be used in hemodialysis dependent patients. Toxicities or efficacy of bevacizumab was not reported. The patients in our study received the standard dose of bevacizumab at 10mg/kg every 2 weeks, although none of them were dialysis dependent. Despite being treated at standard dose, only 1 patient of the 5(20%) with RI required a dose reduction compared to 3 patients of 8(37%) with normal renal function. There were no significant differences in the toxicities on therapy with bevacizumab noted between the RI group and those with normal renal function, with the exception of higher median rises in both SBP and DBP in the RI group.

The successful use of M-TOR inhibitors such as everolimus and sirolimus as immunosuppressants in cardiac, kidney, and liver transplant patients with RI has been described, although these reports do not include toxicities(29, 30). Overall the incidences of toxicities seen in our study patients with M-TOR inhibitors are consistent with those reported in the literature(26). Patients with RI had higher incidences of rash, infections, and dose interruptions than the patients with normal renal function, with no significant difference noted in the incidence of other toxicities.

Our RI patients receiving any of the MTAs seem to have comparable response rates, but favorable TTP and OS, than patients with normal renal function. It is unclear if this difference is related to longer plasma exposure of the MTAs or its metabolites in RI patients. Khosravan et al. showed that plasma exposure to sunitinib and its metabolites appeared

lower in subjects with ESRD compared to subjects with normal or severely impaired renal function(24). The PK of a single dose of sunitinib have been reported to be no different in renally impaired patients, however it is possible that kinetics of sunitinib and its metabolites may change with chronic administration. Garnier-Viougeat et al. also reported that the bevacizumab PK data in a hemodialysis patient were similar to the reference values at steady state in patients with normal renal function, despite the patient being treated at a lower dose than the standard doses received by patients in our study.

In conclusion, RI is seen in about one-third of our patients with mRCC. The study conclusions are limited by the fact that a majority of the RI patients had mildly impaired renal function(CrCl = 40-59ml/min). Also the study is a retrospective analysis of a group of highly selected patients treated at a single institution and the results should be interpreted in that light. However, it still reasonably demonstrates that the newer MTAs like sunitinib, bevacizumab, temsirolimus, and everolimus are well tolerated at standard doses and efficacy is maintained in patients with mild to moderate RI. Patients with RI have greater magnitude of increases in blood pressure with sunitinib and bevacizumab, and higher incidence of thyroid dysfunction with sunitinib. Close monitoring for these specific toxicities is recommended. Our study should help guide the clinical management of mRCC patients with renal impairment, on targeted therapies.

Acknowledgments

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Table 1

Patient characteristics according to the molecularly targeted agent received and estimated creatinine clearance

CHARACTERISTICS	SUNITINIB		BEVACIZUMAB		M-TOR INHIBITORS	
	CrCl ≤ 60 ml/min N=7	**CrCl > 60 ml/min N=19**	**CrCl ≤ 60 ml/min N=5**	**CrCl > 60 ml/min N=8**	**CrCl ≤ 60 ml/min N=11**	**CrCl > 60 ml/min N=13**
Median Age (yrs)	67	54	70	60	61	55
Sex Male Female	 4 3	 16 3	 2 3	 5 3	 9 2	 9 4
Race Caucasian African-American Others	 6 1 -	 18 - 1	 3 2 -	 8 - -	 6 2 3	 13 0 0
Prior nephrectomy	6 (86%)	18 (95%)	5 (100%)	7 (88%)	10 (91%)	13 (100%)
KPS ≥ 80 60-70	 7 (100%) -	 19 (100%) -	 5 (100%) -	 8 (100%) -	 7 (64%) 4 (36%)	 11 (85%) 2 (15%)
MSKCC score 0-1 2 3	 7 (100%) - -	 16 (84%) 3 (16%) -	 4 (80%) - -	 8 (100%) - -	 7 (64%) 3 (27%) 1 ((%)	 10 (77%) 3 (23%) -
Histology Clear cell Papillary Chromophobe Others	 6 (86%) - - 1 (14%)	 18 (95%) 1 (5%) - -	 5 (100%) - - -	 5 (100%) - - -	 11 (100%) - - -	 10 (77%) 1 (8%) 2 (15%) -
Median CrCl ml/min (range)	47 (37 – 55)	91 (66 – 190)	55 (24 - 56)	91 (76 – 100)	42 (19-59)	71 (63 – 120)

KPS- Karnofsky performance status; MSKCC- Memorial Sloan Kettering Cancer Center score

Table 2

Toxicity and efficacy data of patients treated with Sunitinib according to creatinine clearance

CHARACTERISTICS	SUNITINIB	
	CrCl ≤ 60 ml/min N=7	**CrCl > 60 ml/min N=19**
Skin Rash (mild – moderate) (Incl.Hand-foot syndrome)	2 (29%)	7 (37%)
Diarrhea (Grade 1- 2)	1 (14%)	7 (37%)
Infections	0	8 (42%)
Fatigue Mild Moderate Severe	0 5 (71%) 1 (14%)	5 (26%) 10 (53%) 2 (11%)
Drop in Ejection Fraction >15%	1/ 3* (33%)	3/15* (20%)
Decrease in CrCl Median drop in CrCl (ml/min)	1 (14%) 5	6 (32%) 15
Bleeding	1(14%)	2(11%)
Thyroid Dysfunction	3/5* (60%)	2/8* (25%)
Proteinuria	0/5*	6/13* (46%)
Median Systolic Blood Pressure prior to starting therapy (mm Hg) Median Diastolic Blood Pressure prior to starting therapy (mm Hg)	146 (99-153) 77 (50-88)	143 (114-180) 82 (61-100)
Median rise in Systolic BP during therapy Median rise in Diastolic BP during therapy	30mm 15mm	18mm 5mm
Dose interruption(s)	1 (14%)	6 (32%)
Dose reduction(s)	0	3 (16%)

* Denominator indicates the number of patients tested if less than the total number

Table 3

Toxicity and efficacy data of patients treated with Bevacizumab according to creatinine clearance

CHARACTERISTICS	BEVACIZUMAB	
	CrCl ≤ 60 ml/min N=5	**CrCl > 60 ml/min N=8**
Skin Rash (mild – moderate)	1(20%)	1 (12%)
Diarrhea (Grade 1- 2)	0	1 (13%)
Infections	1 (20%)	5 (63%)
Fatigue Mild Moderate Severe	0 2 (40%) 1 (20%)	4 (50%) 3 (38%) 1 (13%)
Proteinuria	2 (40%)	4 (50%)
Bleeding	1(20%)	2(25%)
Gastrointestinal perforations	0	0
Arterial or Venous Thrombotic events	0	1(12%)
Median Systolic BP prior to starting therapy (mm Hg) Median Diastolic BP prior to starting therapy (mm Hg)	131 (103–143) 64 (50-80)	144 (106-183) 83 (60-90)
Median rise in Systolic BP during therapy Median rise in Diastolic BP during therapy	42mm 18mm	21mm 12mm
Dose interruption(s)	3 (60%)	5 (63%)
Dose reduction(s)	1 (20%)	3 (37%)

* Denominator indicates the number of patients tested if less than the total number

Table 4

Toxicity and efficacy data of patients treated with M-TOR inhibitors (temsirolimus and/or everolimus) according to creatinine clearance

CHARACTERISTICS	M-TOR INHIIBITORS	
	CrCl ≤ 60 ml/min N=11	**CrCl > 60 ml/min N=13**
Skin Rash (mild – moderate)	5 (45%)	2 (15%)
Diarrhea (Grade 1- 2)	1 (9%)	2 (15%)
Infections	3 (27%)	1 (8%)
Fatigue Mild Moderate Severe	6 (55%) 3 (27%) 0	9 (69%) 2 (15%) 0
Proteinuria	7 (64%)	6/12* (50%)
Mucositis	4 (36%)	7 (54%)
Pulmonary Toxicity	4 (36%)	3 (23%)
Hypercholesterolemia Grade 1 Grade2 Hypertriglyceridemia Grade 1 Grade2 Grade 3 Hypercholesterolemia/Hypertriglyceridemia requiring treatment	 1/7* (14%) 2/7* (29%) 1/7* (14%) 2/7* (29%) 1/7* (14%) 3/9* (33%)	 2/7* (29%) 3/7* (43%) 3/7* (43%) 1/7* (14%) 1/7* (14%) 3/12* (57%)
Hyperglycemia Grade 1 Grade2 Hyperglycemia requiring treatment	3/7* (43%) 1/7* (14%) 3/9* (33%)	1/7* (14%) 2/7* (29%) 1/12* (57%)
Dose interruption(s)	7 (64%)	5 (38%)
Dose reduction(s)	3 (27%)	3 (23%)

*Denominator indicates the number of patients tested if less than the total number.

TABLE 5

Response rates, time to progression and overall survival according to the molecularly targeted agent received and the estimated creatinine clearance

CHARACTERISTICS	SUNITINIB		BEVACIZUMAB		M-TOR INHIBITORS	
	CrCl ≤ 60 ml/min N=7	**CrCl > 60 ml/min N=19**	**CrCl ≤ 60 ml/min N=5**	**CrCl > 60 ml/min N=8**	**CrCl ≤ 60 ml/min N=11**	**CrCl > 60 ml/min N=13**
RECIST Response*	0	-	0	0	0	0
CR	0	4 (21%)	0	0	3 (30%)	2 (15%)
PR	4 (57%)	5 (26%)	4 (80%)	5 (63%)	4 (40%)	5 (38%)
SD	1 (14%)	8 (42%)	0	3 (37%)	1 (10%)	4 (31%)
PD						
Median Time to Progression (months) (90% CI)	2.7 mo (1.6 – 9.6)	2.8 mo (2.4 – 4.3)	6.2 mo (2.4 – 16.4)#	3.7 mo (0.0 – 6.4)#	8.3 mo (0.0 – 9.0)	2.3 mo (1.6 – 3.9)
Median Overall Survival (months) (90% CI)	13.2 mo (1.1 – 27.4)	8.0 mo (4.4 – 16.3)	28.8 mo (0.3 – 29.5)	11.4 mo (5.1 – 24.2)	12.5 mo (7.4 – 21.0)	6.2 mo (3.1 – 8.7)

CR= complete response; PR= partial response; SD= stable disease; PD=progressive disease; CI = confidence interval.

* = Patient responses may not add up to 100% because of few patients that are too early for evaluation.

An 80% CI, due to the very small number of patients treated with bevacizumab.