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A single arm phase 1b study of everolimus and sunitinib in patients with advanced renal cell carcinoma (RCC)

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Abstract

Background—Everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR), and sunitinib, an oral inhibitor of VEGF/PDGF receptor tyrosine kinase signaling, have both been shown to provide clinical benefit in patients with advanced RCC. We sought to determine the safety and efficacy of combination therapy with these agents in patients with advanced RCC.

Methods—We conducted a phase Ib dose escalation trial of sunitinib and everolimus in patients with advanced metastatic RCC. Prior nephrectomy was required, and prior radiation or chemotherapy other than VEGF/mTOR-based therapies was permitted. The primary endpoint was to determine the MTD/recommended phase 2 dose.

Results—A total of 4 out of a planned 30 subjects were enrolled in this study (M:F= 2:2; mean age 52 years, 50% with KPS <80). The first three patients were enrolled on a 4+2 dosing schedule of daily sunitinib 50 mg and weekly everolimus 30 mg. Mean time on drug was 99 days. One partial response was seen. Toxicities included mucositis, thrombocytopenia, anemia, fatigue, dehydration and hypoglycemia. Due to multiple grade 3–4 toxicities, the protocol was amended to 2+1 dosing of sunitinib 37.5 mg and daily everolimus 5mg. The first patient on this schedule died from multi-organ failure with septic shock after 1 cycle of treatment. Subsequently, the study was closed. Pharmacokinetics results inconclusively suggest that toxicities could be attributed to the drug exposure.

Conclusions—Combined use of everolimus and sunitinib in the treatment of mRCC was not well tolerated in this small cohort.

Keywords

VEGF TKI; mTOR inhibitor; combination; metastatic; kidney cancer

INTRODUCTION

Recently there has been a dramatic rise in the number of targeted agents effective against metastatic renal cell carcinoma (RCC). These FDA approved drugs fall into the following classes; epithelial growth factor inhibitors (anti-VEGF), monoclonal antibodies (bevacizumab), multi-targeted tyrosine kinase inhibitors (TKIs, e.g., sunitinib, sorafenib, pazopanib, axitinib)¹⁻⁴ and mammalian target of rapamycin (mTOR) inhibitors (temsirolimus, everolimus)^{5,6}. Current clinical guidelines and strategies suggest the sequential use of these agents using a risk-adapted algorithm (National Comprehensive Cancer Network guidelines)

In general, treatment with VEGF inhibitors induces partial responses or stable disease in renal cell carcinoma patients. However, progression free survival (PFS) remains less than a year with pazopanib or sunitinib in the front line metastatic RCC setting, and thus exploration of novel approaches with combination therapy is rational^{1,2}. Sunitinib malate (Sutent, Pfizer, Inc. New Yor, NY) is a small molecule, multi-targeted receptor tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinase VEGFR and PDGFR, as well as FLt-3 and c-Kit.

Everolimus (Afinitor, Novartis Pharmaceuticals, East Hanover, NJ) is an orally absorbed macrolide that functions to bind intracellular mTOR (TORC1) and its chaperone, FKBP12, in an inactive state, inhibiting its activation in a similar mechanism of action to rapamycin. In a phase III registration study, everolimus demonstrated a significant improvement in progression-free survival (PFS) over placebo in patients with metastatic RCC previously treated with VEGFR tyrosine kinase inhibitor⁶.

Signaling through the mTOR/TORC1 complex may represent an important mechanism of VEGF production by the cancer cell. Numerous connections have been identified linking PI3K/Akt/mTOR signaling, regulation of hypoxia-induced factor 1(HIF-1), and VEGF expression⁷. Preclinical models have suggested that inhibiting multiple points in the mTOR-HIF-VEGF loop may be superior to the use of single agents^{8,9}. This study evaluated the combination of an mTOR inhibitor and a VEGF TKI.

A phase 1 trial of everolimus was recently reported by the Memorial Sloan Kettering Cancer Center group in 20 patients with metastatic RCC. Although a positive response to therapy was noted, the combination was associated with significant toxicities¹⁰. During this same period, the present phase 1b trial was open and accruing subjects but evaluated a different dose/schedule of everolimus (30mg weekly) in combination with sunitinib (50mg daily).

Patients and Methods

An open label, single arm, single center, phase 1b trial of weekly everolimus and daily sunitinib was conducted in patients with metastatic RCC in the first line setting. The protocol was approved by the Duke University Health System Institutional Review Board and the trial was registered with clinicaltrials.gov (NCT00788060). Subjects were enrolled from September 2007 to January 2009.

The study population consisted of patients aged 18 years with histologically confirmed metastatic RCC who have undergone a nephrectomy, with clinical or radiographic evidence of metastatic disease and have been treated with prior radiation, cytokine therapy or chemotherapy other than VEGF/mTOR-based therapies. Inclusion criteria included: East Cooperative Oncology Group (ECOG) performance status of 0 to 2; hemoglobin 9g/dL, absolute neutrophil count 1500/uL, platelets 100,000/uL, total bilirubin 1.5× upper limit of normal (ULN); AST/ALT 2.5× ULN, creatinine 1.5×ULN, fasting cholesterol 350 mg/dL and triglycerides 300 mg/dL; and signed informed consent. Exclusion criteria included: a history of solid organ or stem cell transplantation; lack of chronic immunosuppressive therapy; active brain metastasis; history of human immunodeficiency virus (HIV) hepatitis B, or hepatitis C virus infection; severe trauma or surgery within 4 weeks prior to study entry; active infection; symptomatic congestive heart failure (New York Heart Association (NYHA) unstable angina pectoris; cardiac arrhythmia; diabetes or psychiatric illness; and impairment of gastrointestinal function or gastrointestinal disease.

Study Design—The study was initially set up on a (4 weeks on, 2 weeks off) dosing schedule of daily oral sunitinib 50 mg and weekly oral everolimus 30 mg, but was amended after the third patient. The fourth patient was enrolled to 2 weeks on, 1 week off dosing of sunitinib 37.5 mg and daily everolimus 5mg. Dose levels were planned to be escalated in successive cohorts of 3 to 6 patients following a 3+3 dose escalation design until the maximum tolerated (MTD) dose achieved. Enrollment was to continue once all 3 subjects completed cycle 1 or developed a dose limiting toxicity (DLT), which was defined as any CTC Grade 3 or greater toxicity within the first 28 days of cycle 1. If one of the 3 subjects experienced a DLT then 3 more patients would be accrued to this dose level. If 0–1/6 patients demonstrate DLT then enrolment will proceed to the next dose level. However if 2 or more patients out of the 6 demonstrated DLT at a dose level, then enrolment proceeded at the next lowest dose level. The highest dose level not resulting in greater than 1/6 DLT would be considered the MTD level. Dose expansion will then proceed at this dose level.

The initial dose level planned was sunitinib 50 mg daily for 4 weeks on followed by 2 weeks off and everolimus 30 mg once weekly. Additional planned dose levels included increases in everolimus to 40 mg, 50 mg, 60 mg and 70 mg once weekly. Based on toxicity seen at Dose level 1, a Dose level 1a was added of sunitinib 37.5 mg daily 2 weeks on followed by 1 week off and everolimus 5 mg daily.

Adverse events were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 on days 0, 14, and 28 for the 4+2 regimen and days 0, 14 and 21 for the 2+1 regimen of each cycle. Escalation decisions to the new dose cohort were based on the safety evaluation of the previous cohort. DLTs were defined as any grade 3 or greater toxicity, except for asymptomatic grade 3 hypertension, hyperlipasemia, hyperamylasemia, pancreatitis, or any grade 3 or 4 lymphopenia or hyperuricemia. Both drugs were held for DLT and restarted once resolved to grade 1 or less. Patients who had a DLT received dose adjustment to 1 or both drugs per protocol. One dose level reduction was required unless the toxicity was considered not related to that study drug. Up to two dose level reductions are allowed in the study. Patients were followed up for adverse events for at least 30 days after the last dose of the study drugs.

Treatment response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Progression free survival was assessed from the first dose of study drug until either radiologically determined disease progression or death. Those removed from study due to treatment toxicity were censored at the point of removal.

Pharmacokinetic Analysis—Plasma concentrations of sunitinib and everolimus were evaluated at hours 0, 1, 2, 5, 8 and 24 on days 1 and Day 14 of the first cycle. Plasma samples of sunitinib were analyzed by an outside contractor using a validated assay (Taylor Technology, NJ, USA) while the plasma samples of everolimus were analyzed using a validated assay by Lenexa, Kansas, USA.

The single-dose pharmacokinetic (PK) parameters for everolimus were computed from the drug concentration-time data after the first oral dose of everolimus using non-compartmental methods within WinNonLin Phoenix Version 6.3 (Pharsight Corporation). It was assumed that everolimus concentrations were zero at the time of the first dose. The peak drug concentration ($C_{\max}$), time of peak concentration ($T_{\max}$), and concentration at 24 hours (C_{24}) were obtained directly from the observed data, with time zero being the time of oral administration. The disposition rate constant (λ_z) was determined as the slope of a log-linear least squares of at least 2 concentration-time points judged, by visual inspection, to be in the apparent terminal elimination phase. Half-life was calculated as $t_{1/2} = \ln 2 / \lambda_z$. Partial area under the drug concentration curve (AUC_{24}) was calculated from 0–24 hours using the linear trapezoidal method. The area under the plasma drug concentration versus time curve from zero to infinity (AUC_{inf}) was obtained from $AUC_{0-\text{last}} + C_t / \lambda_z$ where $AUC_{0-\text{last}}$ is the partial AUC from time 0 to the time of the last measured concentration and C_t is the last measurable concentration. The AUC_{inf} % extrapolated was obtained from $[(AUC_{\text{inf}} - AUC_{24}) / AUC_{\text{inf}}] * 100$. Apparent oral clearance (CL/F) was calculated as $CL/F = \text{dose} / AUC_{\text{inf}}$ and then normalized per kg by dividing CL/F by patient weight.

The multiple dose PK parameters for everolimus and sunitinib were computed from the drug concentration-time data after the 14th dose of both drugs using non-compartmental methods within WinNonLin Phoenix Version 6.3 (Pharsight Corporation). Both drugs were assumed to be at steady state by dose 14. The $C_{\max}$, $T_{\max}$, C_{24} , λ_z , and $t_{1/2}$ were obtained using the same methods as for single dose PK. The minimum drug concentration ($C_{\min}$) and time of minimum concentration ($T_{\min}$) were obtained directly from the observed data. AUC for the dosing interval (AUC_{tau}) was calculated differently for everolimus and sunitinib. Sunitinib was dosed once every 24 hours so AUC_{tau} was calculated using observed data via the linear trapezoidal method. Everolimus was dosed once weekly. PK sampling was only done for the first 24 hours after administration of the dose. However, because steady state was assumed for the multiple-dose analysis, the 0 hour drug concentration measurement for dose 14 was used as the input for the 168 hour time point to be able to calculate AUC_{tau} and CL/F for everolimus. CL/F was calculated by dividing the dose by AUC_{tau} and normalized per kg by dividing CL/F by patient weight.

Statistical analysis—The primary objective was to determine the maximum tolerated dose (MTD) of sunitinib and weekly everolimus based on the rates of dose limiting toxicities and to provide a recommended phase 2 dose and schedule. The secondary

objectives of the study were to describe the non-dose limiting toxicities, pharmacokinetics, objective response rates, overall survival and time to disease progression associated with combination therapy. PK studies of both drugs were analyzed using graphical methods (estimating area under curve).

RESULTS

Four patients were enrolled into this study, which was then prematurely terminated due to severe DLTs. As the number of patients accrued in this study was small, the details of each patient and their toxicities will be described individually.

The first 3 patients were enrolled on a 4+2 dosing schedule of daily sunitinib 50 mg and weekly everolimus 30 mg. Within this initial dosing cohort, 2 of the 3 patients suffered DLTs and all 3 patients experienced grade II or greater decreases in neutropenia, and thrombocytopenia which were associated with sunitinib. Therefore the protocol was amended to create a (-1) dose level evaluating a 2+1 dosing schedule of daily sunitinib 37.5 mg and daily everolimus 5mg. The change in everolimus regimen was predicated on new information from the sponsor that everolimus would be developed on a daily dosing regimen for future phase III testing in kidney cancer. However, due to a grade 5 SAE in the 4th patient enrolled, the trial was closed due to an excess of severe dose limiting toxicities. During the study, fatigue, mucositis and thrombocytopenia occurred in all four patients; while anemia, diarrhea, and neutropenia occurred in 3 patients; and hand foot syndrome occurred in 2 patients. All adverse events were felt to be related to study drug administration and this was supported by the PK studies reported below. Treatment related adverse events are recorded in Table 1.

Patient 1 was a 58 year old female diagnosed in June 2000 with early stage clear cell renal carcinoma status post nephrectomy. She subsequently relapsed with a pathological fracture in June 2007. She was MSKCC intermediate risk with a score of 1 due to anemia. She began treatment with everolimus and sunitinib in October 2007. On cycle 2 day 1, she presented with grade 3 anemia, along with grade 2 neutropenia and grade 2 thrombocytopenia. Treatment was held for 1 week, but no dose reduction was deemed necessary. She managed the combination therapy for another 2 cycles, and had a partial response (PR) by RECIST with decreases in the kidney, hepatic, and adrenal lesions. However, prior to the cycle 4 visit, the patient was hospitalized for a grade 3 left knee hematoma possibly related to thrombocytopenia (platelets 40,000) secondary to her treatment. She was dose reduced to sunitinib 37.5mg daily and everolimus 20mg weekly. Other than a brief episode (<1 day) of grade 2 diarrhea, the patient tolerated the reduced dose well, but on cycle 5 she presented with an enlarging hepatic mass indicating progressive disease and was subsequently removed from the study.

Patient 2 was a 49 year old male diagnosed in November 2006 with clear cell renal carcinoma who underwent nephrectomy; subsequent imaging in October 2007 showed metastatic disease to the bone and lung. He was MSKCC good risk. He was enrolled into the trial with no prior systemic therapy for metastatic RCC. On day 28, the patient experienced grade 3 thrombocytopenia (platelet count 49,000/uL) and the study drugs were withheld. For

cycle 2, the patient was dose reduced to everolimus 20mg weekly and sunitinib 37.5mg daily for 28 days. Like patient 1, patient 2 tolerated the reduced dose for several cycles. However, during cycle 5, the patient experienced grade 3 hypophosphatemia and grade 3 neutropenia which required holding both drugs. The patient was then removed from the trial two weeks later due to grade 3 hand foot syndrome, grade 1 fatigue and anemia.

Patient 3 was a 65 year old male diagnosed in October 2007 with poorly differentiated urothelial carcinoma of the renal pelvis, liver metastasis and retroperitoneal adenopathy and had undergone nephrectomy. He began treatment on the trial in December 2007 without prior systemic therapy. Within 2 weeks of starting study treatment, the patient experienced grade 1 nausea, hypertension, and mouth sores. After 22 days of study treatment, the patient developed grade 4 hypoglycemia, grade 3 fatigue and grade 2 mucositis which would later escalate to grade 3 mucositis, consistent with dose limiting toxicity. Treatment was discontinued in early January 2008. However 7 days after discontinuation, which was 35 days after beginning study treatment, the patient was hospitalized for grade 3 dehydration and grade 4 thrombocytopenia (platelet count, 14,000/uL). The patient was discharged after 7 days, at which point his platelets had climbed to 118,000/uL (grade 1), and the mucositis, and dehydration had resolved. The hospitalization for dehydration and discontinuation of treatment constituted an additional DLT.

After amending the study to develop a lower dose level for study, the trial was reopened to accrual. Patient 4 was a 35 year old female diagnosed in September 2008 with metastatic renal cell carcinoma to the bone, and indeterminate nodule in the lung. She was MSKCC intermediate risk due to anemia. Prior to undergoing a nephrectomy, which demonstrated both spindle and clear cell histology, the patient received external beam radiation to the sacrum and shoulder to alleviate pain. She was enrolled in November 2008 (no prior systemic therapy) and received the modified dosing schedule of 37.5mg sunitinib on a 2 weeks on, 1 week off schedule and 5mg daily oral everolimus. The patient completed the first cycle of treatment with grade 2 thrombocytopenia and bruising (related to study treatment) and grade 3 pain (considered unrelated to study drug) which required hospitalization. The pain was controlled with narcotics and the patient was allowed to continue on study medication. The patient developed grade 2 functional mucositis, fatigue, pressure ulcers and clinical mucositis shortly after beginning cycle 2. In December 2008, 37 days after starting treatment, the patient reported to the emergency department (ED) with diarrhea and fever. She was found to be hypotensive. She was admitted to her local hospital for acute renal failure and presumed sepsis. She was then found to have profound ischemic cardiomyopathy and severe thrombocytopenia. Despite aggressive resuscitative measures, the patient died shortly after admission from multisystem organ failure with septic shock. Subsequently, given this severe adverse event and DLT, the study was terminated.

Pharmacokinetic (PK) Results

PK studies were done on 3 out of the 4 subjects in the study. Single dose and multiple dose PK data were collected for both everolimus and sunitinib. The 4th subject who passed away did not have PK studies analysed as the study was closed.

Everolimus Single-dose PK—A total of 2 subjects with 9 concentrations were used for the analysis of the single-dose everolimus data. Two subjects were excluded from the analysis because of lack of drug concentration data. Concentration-time profiles are presented in Figure 1 and PK parameters are shown in Table 2.

The apparent terminal elimination $t_{1/2}$ and T_{max} of oral everolimus are comparable to values reported in the literature for steady state dosing in patients with solid tumors.^{10,11} The AUC_{inf} % extrapolated was high at 48.7% and 35.2% for subjects 1002 and 1003, respectively. This raises concerns about the accuracy of the AUC_{inf} estimate and the need to sample subjects beyond 24 hours to get an accurate estimate. However, the mean AUC_{inf} in the current study is comparable to the steady state AUC_{tau} (1798 h*ng/mL, StdDev 827) reported for the same dose of 30 mg/day,¹¹ indicating good agreement in exposure between these studies.

Everolimus Multiple-dose PK—A total of 3 subjects (1001, 1002, and 1003) with 16 concentrations were used for the analysis of the multiple-dose everolimus data. For subject 1001 there were no concentrations reported at times 0 or 24 hours. Concentration-time profiles are presented in Figure 2 and PK parameters are shown in Table 3.

Sunitinib Multiple-dose PK—A total of 3 subjects (1001, 1002, and 1003) with 18 concentrations were used for the analysis of the multiple-dose sunitinib data. For subject 1001 no apparent terminal elimination slope was identified preventing calculation of λ_z , and $t_{1/2}$. Concentration-time profiles are presented in Figure 3 and PK parameters are shown in Table 4.

DISCUSSION

The results of this phase 1 study shows that combination therapy of sunitinib and everolimus in a treatment naïve population of previously healthy metastatic RCC patients was poorly tolerated. An excess of DLTs were observed, including severe thrombocytopenia, anemia, fatigue, mucositis, cardiomyopathy and multi-organ failure. The final patient enrolled in this trial received an attenuated 2 weeks on 1 week off combination of sunitinib 37.5mg and everolimus 5 mg daily, and in spite of lower doses died secondary to septic shock thought to be related to the regimen.

A number of different groups have studied the effects of combining a VEGF TKI with an mTOR inhibitor, with most of them terminating prematurely due to significant toxicity. These trials include combinations using sunitinib plus temsirolimus¹², sorafenib and temsirolimus[7], sorafenib and everolimus[8] and sunitinib with everolimus¹⁰. Adverse effects seen were similar; including thrombocytopenia, infection, haemorrhage and gastrointestinal toxicity. It is unclear if the toxicity is due to the VEGF TKI, mTOR inhibitor, or the combination.

A recent meta-analysis by Houck, et al¹³ suggests that higher sunitinib exposure, as measured by AUC, is linked to increased efficacy and higher rates of toxicity. This is consistent with studies of other tyrosine kinase inhibitors that have shown toxicity is

associated with elevated exposure to the drug.^{14,15} The AUC_{tau} and toxicity in the current study were substantially higher than those reported by Faivre, et al¹⁶ in a Phase I study evaluating the same dose of sunitinib (50 mg/d) as monotherapy. The reason for the differences in exposure between these two trials is unclear. When standardized by dose, the sunitinib AUC observed in this study was comparable to that seen in another Phase I study using a combination of sunitinib and everolimus¹⁰. In retrospect, a lower starting dose of sunitinib may have limited toxicity in the current study. However, the wide range of sunitinib exposure for the same dose limits the ability to determine this a priori.

Everolimus toxicity has not been linked to any specific PK parameters (e.g., AUC, trough concentration). Participants in the current trial experienced more frequent and severe toxicity than those subjects enrolled in the other trial evaluating the sunitinib-everolimus combination¹⁰. The AUC_{24} of everolimus after dose 14 in the current study was proportionally higher compared to the other trial due to the higher starting dose in the current study (30mg weekly). However the difference noted with that of the other trial is not large (~1 standard deviation), and hence it is unlikely that the elevated AUC was the cause for excessive toxicities observed.

C_{max} was also evaluated as a possible indicator of everolimus toxicity. While median values after dose 14 were comparable to those reported by Molina¹⁰, all three subjects in the current study exhibited wide inter-individual variability in C_{max} . Subject 1002 had the highest everolimus C_{max} but did not exhibit excessive toxicity compared to subjects 1001 and 1003 who had much lower concentrations. In the small cohort of the present study, C_{max} does not appear to correlate with toxicity. It is possible that subjects also experienced high intra-individual differences in everolimus concentrations and exposure. The single-dose AUC_{inf} should be equal to AUC_{tau} at steady state if the drug is dosed at a fixed dose and interval. The AUC_{tau} for subjects 1002 and 1003 is almost double their respective AUC_{inf} after the first dose. This may be evidence of accumulation of the dosing regimen used, potential drug interactions resulting in different exposure from dose to dose, or inaccurate estimates of AUC with the sampling scheme used. Everolimus has low bioavailability (16%),¹⁷ so differences in its absorption can have a large impact on C_{max} . Other potential sources of variability include fasting state^{18,19} and hepatic impairment.²⁰ Because everolimus is metabolized primarily in the liver and gut via cytochrome P450 (CYP) 3A4, 3A5, and 2C8 and eliminated almost entirely in bile (98%)²¹ renal dysfunction does not significantly impact elimination and should not be a source of variability. The other possible explanation for the difference in AUC_{inf} and AUC_{tau} could simply be that the estimate of AUC_{inf} was biased by lack of sufficient PK sampling (e.g., high % extrapolation of AUC_{inf}).

Because sunitinib and everolimus are better tolerated as sequential monotherapy, the increased toxicity is likely related to the combination. Other than an increase in sunitinib exposure seen with combination therapy, there are no conclusive changes in PK that can explain this increase in toxicity. The comparison with other trials is limited by the extremely small patient numbers and high interpatient variation observed in the current study.

Combination therapies using a bevacizumab and mTOR inhibition appear to hold more promise with several ongoing phase 2 and 3 trials. Nevertheless an initially promising phase

1/2 trial with a bevacizumab and temsirolimus combination did not provide a positive outcome in a randomized phase 2 setting, illustrating the importance of tolerability of long term combination therapies in order to achieve and maintain efficacy [9]. On top of higher toxicities noted, there was also no improvement in efficacy seen with this combination [9]. Thus, at this time, the current paradigm of sequential use of VEGF TKI and mTOR therapies is suggested outside of a clinical trial. The use of everolimus with and without bevacizumab, however, appears to be better tolerated in the second line setting, and is currently being evaluated in a randomized phase 3 trial (CALGB 90802-[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01198158) identifier: NCT01198158).

In conclusion, although hypothetically, a combination regimen consisting of a VEGF TKI and another mTOR inhibitor should have a synergistic effect, we found the toxicity of this regimen overwhelming and not amenable to long term therapy. This supports the findings of a larger single centre study using a similar dosing schedule that was closed for the same reason¹⁰. It is also essential that future trials incorporate extensive pharmacokinetic analysis to better evaluate and understand the risk for toxicities. Future efforts should also focus on other combination approaches and rational sequencing of the many new active agents in RCC.

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Disclosure

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Clinical Practice Points

- Everolimus is an orally absorbed macrolide that functions to bind intracellular mTOR (TORC1) and its chaperone, FKBP12, in an inactive state, inhibiting its activation in a similar mechanism of action to rapamycin. In a phase III registration study, everolimus demonstrated a significant improvement in progression-free survival (PFS) over placebo in patients with metastatic RCC previously treated with TKI-VEGFR.
- Sunitinib malate is a small molecule, multi-targeted receptor tyrosine kinase inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinase VEGFR and PDGFR, as well as FLt-3, c-Kit.
- The increased toxicity when combining both the drugs at the doses we used could be related to pharmacokinetic interactions although with such small patient numbers it is impossible to draw strong conclusions on this.
- Although a combination regimen consisting of a VEGF TKI and an mTOR inhibitor should have a synergistic effect, we found the toxicity of this regimen overwhelming and not amenable to long term therapy. This supports the findings of a larger single centre study using a similar dosing schedule that was closed for the same reason as well.

a. Concentration-time Profiles for Everolimus Single Dose by subject **b. Mean concentration-time Profiles for Everolimus Single Dose**

Error bars represent standard deviation

Figure 1.

a. Concentration-time Profiles for Everolimus Multiple Dose by Subject **b. Mean Concentration-time Profiles for Everolimus Multiple Dose**

Error bars represent standard deviation

Figure 2.

a. Concentration-time Profiles for Sunitinib Multiple Dose by Subject **b. Mean concentration-time Profiles for Sunitinib Multiple Dose**

Error bars represent standard deviation

Figure 3.

Table 1

Treatment related adverse events

Toxicity	Grade1	Grade2	Grade3	Grade4	All Grades	%
Fatigue		3	1		4	100
Mucositis	1	1	2		4	100
Diarrhoea	2		1		3	75
Haemorrhage	3	1			4	100
Rash	2	1			3	75
Pain	2	1	1		4	100
Hypertension	2				2	50
Hand-foot reaction	1		1		2	50
Nausea	3				3	75
Constipation	2				2	50
Infection				1	1	25
Fever		1			1	25
Vomiting	3				3	75
Weight loss	3				3	75
Dry skin	3				3	75
Diaphoresis	1				1	25
Pulmonary embolism				1	1	25
Febrile neutropenia	1				1	25
Neuropathy	2				2	50
Gastrointestinal,other		1			1	25
Dysgeusia	4				4	100
Anemia	1	11	1		3	75
Neutropenia		1111			4	100
Leukopenia		1	1		2	50
Thrombocytopenia		111		1	4	100
Hypoglycemia				1	1	25

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Toxicity	Grade1	Grade2	Grade3	Grade4	All Grades	%
Hypertiglyceridemia	1	1			2	50

Table 2

Pharmacokinetic Parameters for Everolimus Single Dose

Subject	t _{1/2} (h)	T _{max} (h)	C _{max} (ng/mL)	AUC _{inf} (h*ng/mL)	CL/F (mL/kg/h)
1002	25.7	2	82.3	1555	200.5
1003	17.2	2	120.6	1752	252.6

t_{1/2}: half-life, T_{max}: time to maximum concentration, C_{max}: maximum concentration, AUC_{inf}: AUC from 0 to infinity, CL/F: apparent oral clearance, StDev: standard deviation

Table 3

Pharmacokinetic Parameters for Everolimus Multiple Dose

Subject	t _{1/2} (h)	T _{min} (h)	C _{min} (ng/mL)	T _{max} (h)	C _{max} (ng/mL)	AUC _{tau} (h*ng/mL)	AUC ₂₄ (h*ng/mL)	CL/F mL/kg/h
1001	-	-	-	1	92.9	-	-	-
1002	32.4	0	1.1	1	285.3	3020	1248	103.3
1003	34.7	0	1.8	5	66.4	3611	1179	122.5

t_{1/2} half-life, T_{min} time to minimum concentration, C_{min} minimum concentration, T_{max} time to maximum concentration, C_{max} maximum concentration, AUC_{tau} AUC for the dosing interval (168 hours), AUC₂₄ AUC for the first 24 hours after the dose. CL/F: apparent oral clearance, StDev: standard deviation

Table 4

Pharmacokinetic Parameters for Sunitinib Multiple Dose

Subject	t _{1/2} (h)	T _{min} (h)	C _{min} (ng/mL)	T _{max} (h)	C _{max} (ng/mL)	AUC _{tau} (h*ng/mL)	CL/F mL/kg/h
1001	-	2	59.4	8	83.1	1865	427.6
1002	33.0	0	80.3	5	142.0	2773	187.4
1003	85.5	1	77.0	8	106.0	2302	320.4

t_{1/2} half-life, T_{min} time to minimum concentration, C_{min} minimum concentration, T_{max} time to maximum concentration, C_{max} maximum concentration, AUC_{tau} AUC for the dosing interval (24 hours), CL/F: apparent oral clearance, StDev: standard deviation