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Phase I trial of sunitinib and temsirolimus in metastatic renal cell carcinoma

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Abstract

Purpose—Preclinical data suggest that anti-VEGF agents plus mTOR inhibitors yield synergistic antitumor effects. A phase I trial using a 3+3 dose escalation design of sunitinib (S) plus temsirolimus (T) was stopped after the first dose pair led to 2 of 3 patients experiencing dose-limiting toxicity (DLT).

Patients and Methods—To explore multiple potential dosing pairs of S and T a 2 stage outcome-adaptive Bayesian dose-finding method was designed. The primary objective was to find the maximum tolerated doses (MTD) of S and T in patients with advanced RCC. A 3-wk treatment cycle consisted of daily S, 2 wks on, 1 wk off, plus weekly T.

Results—Twenty patients received study drugs; median number of prior therapies 1. Number of patients (S and T doses in mg): 2 (S12.5, T6), 1 (S25, T12.5), 1 (S12.5, T8), 8 (S12.5 alt 25, T9), 2 (S25, T6), 2 (S25 alt 37.5, T6), 2 (S37.5, T6), 2 (S37.5, T8). Six patients required dose reduction, 3 due to grade 3 stomatitis, 2 due to grade 3 thrombocytopenia; mean number of cycles 6.6 ± 5.3 , mean time on study 159 ± 120 days. One patient experienced DLT in cycle 1 and was non-

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evaluable, 1 had a partial response, 16 had stable disease, and 2 had progressive disease (PD) as best response. There were 21 grade 3/4 adverse events but no treatment-related deaths.

Conclusions—The MTD of S and T were not determined because of premature trial closure. S 37.5 mg/d, 2 wks on, 1 wk off, plus T 8–10 mg weekly are close to MTD.

Keywords

Kidney; Cancer; Therapeutics; Combination; Study

INTRODUCTION

Sunitinib is a multi-tyrosine kinase inhibitor that inhibits vascular endothelial growth factor (VEGF) receptors 1–3, platelet-derived growth factor receptors alpha and beta, c-Kit, and Flt3.¹ Two phase II single-arm trials showed that sunitinib had significant antitumor activity in patients with metastatic renal cell carcinoma (mRCC) previously treated with immunotherapy, leading to accelerated approval by the U.S. Food and Drug Administration (FDA) in 2006.^{2,3} In a subsequent phase III trial comparing sunitinib to interferon alpha in mRCC, sunitinib exhibited a significant improvement in progression-free survival (PFS; 11 vs. 5.0 months) and a trend to improved overall survival (OS).^{4,5} Temsirolimus blocks G1-to-S cell cycle progression by forming a complex with FK-506 binding protein, thus inhibiting mTOR signaling, which in turn blocks crucial proteins regulating gene transcription, cell cycle progression, angiogenesis, and nutrient transport into the cell.⁶ A phase III trial comparing first-line temsirolimus with interferon alpha in patients who had mRCC with multiple poor risk prognostic features demonstrated that temsirolimus yielded improvements in both PFS and OS, leading to FDA approval.⁷ Importantly, this trial included patients with all subtypes of renal cell carcinoma.

In single-agent clinical studies of both sunitinib and temsirolimus, the majority of treated patients have not achieved a radiographic response but instead maintained stable disease, often for less than 1 year. Mechanisms of resistance can be detected quickly after initiation of therapy. Preclinical modeling has shown that concurrent administration of sunitinib and temsirolimus improves response rate and delays development of resistance.^{8–10} The only previous clinical trial combining these agents in mRCC was stopped after enrollment of 3 patients when 2 patients experienced dose-limiting toxic effects (DLT).¹¹ In that 3+3 designed phase I trial, the initial starting doses were temsirolimus 15mg IV weekly and sunitinib 25mg daily on a 4 weeks on, 2 weeks off schedule. A study evaluating the pharmacokinetics and pharmacodynamics of temsirolimus in healthy volunteers found a dose of 6.4mg IV capable of achieving adequate blood and tissue concentrations likely to achieve single agent clinical activity.¹² Using a previously described adaptive dose finding design for 2 agents, we designed a 2-stage dose-finding model to allow the testing of multiple dose pairs.¹³ Our primary objective was to determine maximum tolerated dose (MTD) of combined sunitinib and temsirolimus in mRCC. Secondary objectives were to assess the safety of the combination and preliminary response rate.

PATIENTS AND METHODS

Patient Eligibility

Eligible patients were required to have mRCC of any histologic type with evaluable disease as defined by the initial RECIST criteria.¹⁴ Patients were required to be at least 18 years of age; have an ECOG performance status 1; and to have adequate organ and marrow function within 14 days before study enrollment, defined as an absolute neutrophil count 1500/ μ L, platelet count 100,000/ μ L, hemoglobin 9.0 g/dL, total bilirubin 2.0 mg/dL, albumin 2.5 g/dL, serum creatinine 2.0 mg/dL, and aspartate aminotransferase and alanine aminotransferase 2.5 times upper limit of normal without evidence of liver metastasis or 5 times upper limit of normal with evidence of liver metastasis. Patients were required to be able to swallow pills and sign informed consent; women were required to have a pregnancy test to ensure that they were not pregnant; and men and women were required to use an acceptable form of birth control while on study. Exclusion criteria included prior malignancy, with the exception of non-melanoma skin cancer, carcinoma in situ, or malignancy that had been definitively treated and monitored with no evidence of disease for at least 2 years. Other exclusion criteria included uncontrolled brain metastasis; current administration of alternative anticancer therapy, with the exception of bisphosphonates or megestrol acetate; stroke or transient ischemic attack in the previous 6 months; uncontrolled infection; myocardial infarction or unstable angina in the previous 6 months; NYHA grade II or higher congestive heart failure; serious cardiac dysrhythmia refractory to medical management; peripheral vascular disease (grade III or greater); uncontrolled hypertension defined as >140/90 mm/Hg (anti-hypertensive medications were allowed); pregnancy; immune deficiency, including HIV on HAART therapy; history of coagulopathy or serious bleeding diathesis; concomitant treatment with rifampin, St. John's wort, or cytochrome p450 enzyme-inducing drugs or CYP3A4 inhibitors; significant baseline proteinuria, defined as a urinary protein to creatinine ratio >2; major surgical procedure, including open biopsy or trauma, in the previous 28 days; core biopsy or other minor surgical procedure in the previous 7 days; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess in the previous 6 months; non-healing wound, ulcer, or bone fracture; or known hypersensitivity to sunitinib or temsirolimus.

Treatment Plan

All study participants were enrolled from a single institution, UT MD Anderson Cancer Center, and the trial was approved by the institutional review board (IRB). Doses were chosen from a 2-dimensional set in which sunitinib dose was on one axis (possible range = 12.5, 19, 25, 31, and 37.5mg/day on a schedule of 2 weeks on, 1 week off), and temsirolimus dose was on the other axis (with doses ranging from 3 to 19mg/week). The starting dose pair was sunitinib 12.5mg and temsirolimus 6mg. One cycle was defined as 3 weeks of treatment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.¹⁵ For determination of dose escalation, DLT was defined as a therapy-related toxic effect occurring within the first 3 weeks; grade 3 non-hematologic toxic effect; hematologic toxic effect, defined as grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; grade 4 neutropenia lasting

>7 days; grade 4 neutropenic fever >38.5°C; removal of patient from therapy because of toxicity attributable to treatment; or delay of treatment for >2 weeks because of toxicity.

Response Assessment

Response was assessed by the original RECIST criteria. Baseline computed tomographic (CT) scans were performed within 4 weeks before initiation of treatment and then every 6 weeks for the first 4 cycles; the schedule was changed to every 3 months in the event of response or stable disease. Complete response was defined as disappearance of all target and non-target lesions, confirmed on 2 separate evaluations at least 4 weeks apart. Partial response was defined as ≥30% reduction in sum of largest diameter of all target lesions without new lesions or progression of non-targeted lesions. Stable disease was defined as <30% reduction or >20% increase in sum of largest diameter of all target lesions, without new lesions or progression of non-targeted lesions. Progressive disease was defined as ≥20% increase in sum of largest diameter of target lesions compared to the smallest sum diameter from the initiation of treatment or the presence of one or more new lesions.

Study Design and Statistical Considerations

A modification of the 2-stage, outcome-adaptive Bayesian dose-finding method of Thall et al. was used.^{13,16} Figure 1 is a graphical representation of this design. The first phase was planned as determining the “on-diagonal” dose, in which the percentage of single-agent MTD is the same for each component. The first stage, planned to enroll 12 patients to find acceptable dose, appears along L1, starting from 6mg temsirolimus (T) and 12.5mg of sunitinib (S) and moving toward the full dose of each agent, represented by 19mg T and 37.5mg S. The goal of stage 1 was to define the dose along L1 with average probability of DLT closest to the target of 30%. In the second stage, 20 patients were to be treated with dose pairs on the upper left and lower right portions of contour L2 (Figure 2). Descriptive statistics were calculated by both Microsoft Excel 2010 and Stata version 13 software. Kaplan-Meier progression free and overall survival plots were calculated as previously described.¹⁷

RESULTS

Population Characteristics

From May 2010 through October of 2012, 23 patients signed informed consent to participate on IRB-approved protocol 2009-0037. Table 1 provides the baseline demographic and clinical characteristics of the 23 patients. Twenty of these 23 patients received study drugs. Reasons for exclusion included proteinuria on baseline laboratory values (1 patient); multiple poor prognostic features, including declining performance status (1 patient); and declined participation because of travel requirements (1 patient).

Treatment and Adverse Events

For the 20 patients who received combination therapy, the median time on study was 107 days (range 22–464 days); all patients were off study as of September 18, 2013, when the final patient was determined to have progressive disease. A total of 132 cycles was administered, and the median was 4 (range 1–20). Table 2 shows the dose pairs with

associated DLT during the trial specifically highlighting those experienced during the first cycle, which determined selection of the subsequent dosing pair. Both patients treated with dose pair sunitinib 25mg and temsirolimus 12.5mg experienced significant mucositis requiring dose reduction. Two patients treated with dose pair sunitinib 19mg and temsirolimus 9mg experienced DLT during cycle 1, one with prolonged grade 3 neutropenia and the other with grade 2 mucositis requiring dose reduction. Figure 3 represents the scatterplot for dosing pairs and DLTs during the trial. Dose reductions were required for 6 patients on study, but no patient required a dose reduction of more than one level. Four patients required removal from the trial because of unacceptable toxicity. Of the patients removed for toxicity, one had prolonged neutropenia, one prolonged anemia despite transfusions, one persistent fatigue/weakness, and one significant proteinuria. Table 3 represents the grade 3 or 4 adverse events recorded during the trial.

Efficacy Endpoints

Based on an intention to treat analysis, of the 20 patients who received study drug, one was removed from the trial before the end of cycle 1 because of unacceptable toxicity and thus was not evaluable. Using RECIST 1.0 to assess response for the 19 evaluable patients, 1 (5%) had a partial response, 16 (80%) had stable disease, and 2 (10%) had disease progression as the best treatment response. A waterfall plot is shown in figure 4. The one patient with a partial response had clear cell histology and had previously received high dose interleukin 2 as his only systemic treatment. Of the 20 patients who received treatment on study, 14 patients had disease progression or died. The estimated median progression free survival was 10.7 months (95% CI: 5.5 months – NA). As of November 1, 2013, 7 of the 23 patients had died. The estimated 3-year OS rate was 58.5% (95% confidence interval: 38.1–89.1%). Figure 5 represents the Kaplan-Meier survival analysis per the date of censor.

Maximum Tolerated Dose

The isotoxic contour for the set of MTDs for this doublet was not determined. The sponsor elected to halt trial accrual after 23 patients were enrolled. The decision to stop trial accrual was reached internally by Pfizer. On the basis of the experience from the previous phase I trial and with our accumulated patients on both the initial and linear portions of the trial, we believe the DLT for a sunitinib dose of 37.5mg (on the 2 weeks on, 1 week off schedule) requires a temsirolimus dose of 8 to 10mg weekly.

DISCUSSION

In our study, we were not able to define the isotoxic contour for these 2 agents on the schedules explored because of observed toxicity and premature trial closure. On balance, the experience suggests that the most attractive portion of the isotoxic contour corresponds to higher doses (relative to the single-agent MTDs) of S with lower doses of T. Our final 8 patients enrolled did not experience a pre-defined DLT.

The most problematic non-hematologic DLT was mucositis. The overall incidence for all grades of mucositis was 45%. Four of the 10 (40%) patients receiving a temsirolimus dose greater than or equal to 9mg experienced a DLT related to mucositis. As such, exploration of

the dosing curve with higher doses of temsirolimus paired with lower doses of sunitinib was believed likely to result in significant toxicity with questionable benefit and was not pursued.

For this heavily pretreated study cohort sample, the combination of sunitinib and temsirolimus yielded disease stability in 73.9%. Unfortunately, the duration of benefit was modest, with a median time on trial of 3.6 months. The response rate of 4.3% was disappointing. While 59% of patients on study were alive at 3 years, the rapid influx of multiple targeted therapies allowing for subsequent treatment, the presence of patients with previously untreated disease, and the likelihood of at least several patients on trial having a more indolent disease course made this finding challenging to interpret. The doses on the initial dosing curve are much lower than the FDA-approved doses for the individual drugs. Even at 50% of the FDA-approved doses of sunitinib (25mg) and temsirolimus (12.5mg), significant mucositis was encountered, requiring dose reduction. Moving to lower dosing pairs likely reduced efficacy, while patients continued to experience toxic effects well known for both of these classes of agents. While avoiding direct comparison, objective response rates (ORR) have been prospectively established for both single-agent temsirolimus and sunitinib after progression on a first-line VEGF-targeting agent. In a phase II trial of second-line sunitinib after progression on front-line bevacizumab, the ORR was 23%.¹⁸ In a recently published phase III trial comparing sorafenib with temsirolimus after progression on front-line sunitinib, the ORR of temsirolimus was 8%.¹⁹ The number of targeted agents received as previous treatment in our study cohort ranged from 0 to 5. Response rates after multiple lines of previous therapy have not been defined for sunitinib and temsirolimus as single agents but are anticipated to be lower than in the front-line or second-line setting.

Trials of combinations of other targeted agents have been published recently. A phase I trial of everolimus and sunitinib enrolled 20 patients with progressive mRCC enrolling both clear cell and non-clear cell histologies.²⁰ Daily everolimus with sunitinib 4 weeks on and two weeks off was associated with significant toxicity leading to the trial being halted and revised after the first two cohorts were enrolled. The revision changed the everolimus to weekly dosing with sunitinib 4 weeks and 2 weeks off finding the MTD to be 30mg of everolimus and 37.5mg of sunitinib. The ORR was 25% (0 CR, 5PR), interestingly 3 out of 7 (43%) patients with non-clear cell histologies experienced a partial response. As witnessed in our trial, a high proportion of patients experienced both acute and chronic toxicity. A phase II trial testing the combination of bevacizumab with everolimus enrolled 30 patients who had previously received a targeted agent and found a response rate of 23%.²¹ The PFS duration was modest in this group, 7.1 months. A phase III trial comparing the combination of bevacizumab and interferon alpha with the combination of bevacizumab and temsirolimus in untreated patients yielded ORRs of 27.8% and 27.0%, respectively. The differences in PFS and OS did not meet statistical significance.²² Therefore, despite the strong preclinical rationale for combining VEGF- and mTOR-targeting agents, this has not translated to significant benefit in the clinical setting. The combination of sunitinib and temsirolimus should likely not be pursued further as a rational treatment for mRCC.

CONCLUSION

For dose pairs emphasizing S, the MTD is close to sunitinib 37.5mg/day on a 2 weeks on and 1 week off schedule and temsirolimus 8 to 10mg IV weekly. The toxicity profile for the combination was similar to those observed previously with single-agent sunitinib or temsirolimus, though mucositis was a more severe problem with the combination. We were unable to find a way of combining these agents that improved the therapeutic index of the components, and it appears that this combination is not of interest for further development.

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References

1. Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol.* 2007; 25(7):884–896. [PubMed: 17327610]
2. Motzer RJ, Michaelson MD, Redman BG, et al. Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2006; 24:16–24. [PubMed: 16330672]
3. Motzer RJ, Rini BI, Bukowski RM, et al. Sunitinib in patients with metastatic renal cell carcinoma. *JAMA.* 2006; 295:2516–2524. [PubMed: 16757724]
4. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal cell carcinoma. *N Engl J Med.* 2007; 356:115–124. [PubMed: 17215529]
5. Motzer RH, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2009; 27(22):3584–3590. [PubMed: 19487381]
6. Rini B. Temsirolimus, an inhibitor of mammalian target of rapamycin. *Clin Cancer Res.* 2008; 14:1286–1290. [PubMed: 18316545]
7. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal cell carcinoma. *N Engl J Med.* 2007; 356(22):2271–2281. [PubMed: 17538086]
8. Falcon BL, Barr S, Gokhale PC, et al. Reduced VEGF production, angiogenesis, and vascular regrowth contribute to the antitumor properties of dual mTORC1/mTORC2 inhibitors. *Cancer Res.* 2011; 71(5):1573–1583. [PubMed: 21363918]
9. Hammer, H.; Paesante, S.; Shen, L., et al. Combination of the VEGF receptor tyrosine kinase sunitinib and the mTOR inhibitor rapamycin leads to tumor regression in the RENCA model. AACR Annual Meeting Abstract 1104; 2008;
10. Fueeder T, Jaeger-Lansky A, Hoeflmaier D, et al. mTOR inhibition by everolimus counteracts VEGF induction by sunitinib and improves anti-tumor activity against gastric cancer in vivo. *Cancer Lett.* 2010; 296(2):249–256. [PubMed: 20471160]
11. Patel PH, Senico PL, Curiel RE, et al. Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma. *Clin Genitourin Cancer.* 2009; 7(1):24–27. [PubMed: 19213664]
12. Boni J, Burns J, Hug B, Sonnichsen D. mTOR inhibition following a single intravenous infusion of temsirolimus in healthy individuals. *Mol Cancer Ther.* 2007; 6:3573S.
13. Thall PM, Millikan RE, Mueller P, et al. Dose-finding with two agents in Phase I oncology trials. *Biometrics.* 2003; 59(3):487–496. [PubMed: 14601749]
14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst.* 2000; 92(3):205–216. [PubMed: 10655437]

15. Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.0. DCTD, NCI, NIH, DHHS; Mar 31. 2003 (<http://ctep.cancer.gov>), Publish Date: August 9, 2006
16. Thall, PF. A two-stage design for dose-finding with two cytotoxic agents in phase I trials. In: Chevret, S., editor. Statistical Methods for Dose Finding Experiments. New York: John Wiley and Sons; 2006. p. 259-274.
17. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Amer Stat Assoc. 1958; 53(282):457–481.
18. Rini B, Michaelson MD, Rosenberg JE, et al. Antitumor activity and biomarker analysis of sunitinib in patients with bevacizumab-refractory metastatic renal cell carcinoma. J Clin Oncol. 2008; 26(22):3743–3748. [PubMed: 18669461]
19. Hutson TE, Escudier B, Esteban E, et al. Randomized phase III trial of temsirolimus versus sorafenib as second line therapy after sunitinib in patients with metastatic renal cell carcinoma. J Clin Oncol. 2014; 32(8):760–767. [PubMed: 24297950]
20. Molina AM, Feldman DR, Voss MH, et al. Phase I trial of everolimus plus sunitinib in patients with metastatic renal cell carcinoma. Cancer. 2012; 118(7):1868–1876. [PubMed: 21898375]
21. Hainsworth JD, Spigel DR, Burris HA 3rd, et al. Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma. J Clin Oncol. 2010; 28(13):2131–2136. [PubMed: 20368560]
22. Rini BI, Bellmunt J, Clancy J, et al. Randomized phase III trial of temsirolimus and bevacizumab versus interferon alfa and bevacizumab in metastatic renal cell carcinoma: INTORACT trial. J Clin Oncol. 2014; 32(8):752–759. [PubMed: 24297945]

Figure 1.
Adaptive 2-stage design model: The x and y axis reflect minimum and maximum dose of each pair. L_1 represents the initial linear phase, while L_2 represents the contour phase.

Figure 2.

Example of 2-stage method with temsirolimus and sunitinib: The X axis represents doses of sunitinib and the Y axis represents the dose of temsirolimus. The straight line reflects the first stage while the circles reflect dose pair combinations during the second stage.

Figure 3.

Dosing pairs and DLT experienced on trial: The black diamonds reflect dose pairs where no DLT was experienced, while the red diamond reflect DLTs encountered during the entirety of the study.

Figure 4. Waterfall plot showing best response for evaluable patients as measured using RECIST 1.0. Patients in blue had clear cell histology, those in red had non-clear cell histology. The black line drawn at -30% indicates those who achieved a partial response. S refers to sunitinib dose and T refers to temsirolimus dose.

Figure 5.
Kaplan-Meier curve showing overall survival: The black line reflects the overall survival experienced on the trial, while the dotted lines represent the 95% CI.

Table 1

Baseline demographic and clinical factors for study patients

Median (Range)	Total Population	Clear-cell histology N=18	Non-clear cell histology N=5
Sex			
Male	16 (69.5%)		
Female	7 (30.5%)		
Age, years	62 (22–75)		
Tumor histology			
ccRCC	18 (78.2%)		
nccRCC	5 (21.8%)		
Papillary			1 (4.3%)
Collecting Duct			1 (4.3%)
Chromophobe			1 (4.3%)
Unknown			2 (8.7%)
ECOG score			
0	9 (39.1%)		
1	12 (52.2%)		
2	1 (4.3%)		
MSKCC score			
0	1 (4.3%)	1	0
1–2	18 (78.2%)	15	3
3	4 (17.4%)	2	2
IMDC score			
0	1 (4.3%)	1	0
1–2	19 (82.6%)	15	4
3 or more	3 (13.0%)	2	1
Prior systemic therapy			
None	8 (34.7%)	6	2
Cytokine	4 (17.4%)	4	0
Targeted	14 (60.9%)	11	3
No. of treatment lines	1.96 ± 2.01 (0–6)		
No. of targeted agents	1.65 ± 1.77 (0–5)		

ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; MSKCC, Memorial Sloan Kettering Cancer Center. IMDC, International Metastatic renal cell carcinoma Database Consortium

Dose limiting toxicity (DLT) experienced in cycle 1 (C1 denotes cycle 1). Stage 1 refers to linear stage of dose pair finding and stage II refers to exploration along contour.

Table 2

Stage	Cohort No.	No. of patients	Sunitinib (mg)	Temsirolimus (mg)	DLT	DLT experienced
1	1	2	12.5	6.0	0	
	2	2	25.0	12.5	2	Mucositis ×2 (C1)
	3–6	8	19	9	2	Mucositis (C1)
						Neutropenia (C1)
2	7	2	25	6	0	Mucositis
						Anemia
						Thrombocytopenia
	8	2	31	6	0	Fatigue
	9	2	37.5	6	0	
	10	2	37.5	8	0	

Table 3

Grade 3 or 4 toxic effects experienced on trial

Grade 3 or 4 Toxic Effect	No. of Patients (%)
Abdominal pain	3 (15%)
Mucositis	3 (15%)
Thrombocytopenia	2 (10%)
Hypertriglyceridemia	2 (10%)
Deep vein thrombosis	1 (5.9%)
Fatigue	1 (5.9%)
Diarrhea	1 (5.9%)
Hypophosphatemia	1 (5.9%)
Neutropenia	1 (5.9%)
Hand-foot syndrome	1 (5.9%)
Chest pain	1 (5.9%)
Speech impairment	1(5.9%)