HHS Public Access

Author manuscript

Invest New Drugs. Author manuscript; available in PMC 2023 October 23.

Published in final edited form as:

Invest New Drugs. 2011 April ; 29(2): 374–379. doi:10.1007/s10637-009-9365-y.

A phase II study of everolimus in combination with imatinib for previously treated advanced renal carcinoma

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Summary

Purpose: This phase II study evaluated the activity of combined treatment with the mTOR inhibitor everolimus and the PDGFR inhibitor imatinib in patients with previously-treated, advanced renal carcinoma. The primary endpoint was estimation of the 3-month progression-free rate.

Patients and methods: Eligible patients had metastatic or unresectable clear cell renal carcinoma, at least one prior systemic therapy, no prior mTOR inhibitor therapy, performance status 0–2, and measurable disease. Treatment consisted of everolimus 2.5 mg p.o. daily and imatinib 600 mg p.o. daily. The primary endpoint was the 3-month progression-free rate.

Results: The study was closed after the first 19 patients because of an insufficient number of patients who were progression-free at 3 months. The 3-month progression-free rate was 49% (95% C.I. 23%, 72%) and the median progression-free survival was 2.9 months (95% C.I. 1.9, 6.2). Toxicities with an incidence of >50% included nausea, elevated serum creatinine, edema, anemia, hypocalcemia, fatigue, diarrhea, vomiting, and dyspnea, and leukopenia.

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Conclusion: The combination of everolimus with imatinib in previously treated patients with advanced renal carcinoma did not result in a sufficient 3-month progression-free rate to warrant further investigation of this combination.

Keywords

Renal cell carcinoma; Everolimus; Imatinib; Phase II clinical trial

Introduction

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that plays a central role in the coordination of cellular response to nutritional and growth factor signals thereby regulating cell growth and cell cycle progression. In cancer, deregulation of upstream cell surface growth factor receptors can initiate signaling that converges on mTOR, thus driving cell growth and proliferation. In clear cell renal cell carcinoma (RCC), accumulation of hypoxia-inducible factor 1 (HIF-1) due to loss of the von Hippel-Lindau tumor suppressor gene may promote cancer progression and activated mTOR may further contribute to HIF-1 expression [1, 2]. Inhibition of mTOR has been validated as a therapeutic strategy in the treatment of advanced RCC [3, 4]. Temsirolimus, a pro-drug of sirolimus, improved survival in prior-untreated patients with poor prognosis disease over treatment with interferon [3]. Everolimus, an orally administered macrolide derivative of sirolimus, improved progression-free survival as compared to placebo in patients who had received prior treatment with a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) [4].

Inhibition of tyrosine kinase receptors that signal downstream through mTOR in conjunction with mTOR inhibition may provide an opportunity for increased activity. One potential target is the platelet-derived growth factor receptor (PDGFR). Platelet-derived growth factor beta (PDGF-B) is overexpressed in RCC secondary to enhanced HIF-1 activity and may play an important role in tumor-driven angiogenesis through pericyte recruitment and other mechanisms [1, 5]. Additionally, high PDGFR expression has been associated with tumor progression in RCC [6].

Imatinib mesylate is a TKI with specificity towards KIT, ABL, and PDGFR-A/B kinases [7]. In renal carcinoma, a phase II study of single-agent imatinib reported no responses among 14 patients with a median PFS of only 2.3 months [8]. Studies combining imatinib with interferon or with the combination of bevacizumab and erlotinib have also been reported; however, none have shown evidence of improved efficacy with the addition of imatinib [9, 10]. While these studies have not revealed substantial activity of imatinib in metastatic RCC, the exploitation of the agent's PDGFR inhibitory activity in combination with mTOR inhibition has not been explored. Targeting PDGFR-B expressing perivascular cells with imatinib may compliment the antivascular and antiangiogenic effects that have been described with mTOR inhibition [1, 11, 12].

We chose to study the combination of everolimus and imatinib as a strategy of dual mTOR and PDGFR inhibition. The safety of combining everolimus with imatinib was evaluated

in an earlier phase I/II trial in gastrointestinal stromal tumors [13]. We used the maximum tolerated daily dose of 2.5 mg/day everolimus and 600 mg/day imatinib reported in that trial.

Patients and methods

Patients were required to have metastatic or unresectable, clear cell renal carcinoma with measurable disease, ECOG performance status 0–2, and be 18 years of age or older. Patients must have received at least one prior systemic treatment for renal cell carcinoma. At least 28 days must have elapsed from any immunotherapy, chemotherapy, or investigational agents. Prior mTOR inhibitor therapy was not allowed. Previous radiotherapy to >25% of the bone marrow was not allowed and at least 2 weeks must have elapsed since major surgery. Laboratory requirements included total bilirubin <1.5 times upper limit of normal (ULN), SGOT and SGPT <2.5 times the ULN, serum creatinine <1.5 times ULN, hemoglobin >8 g/dL, and platelets $>100\times10^9$/L. Patients must not have been receiving therapeutic-dose warfarin. Concomitant use of drugs known to interact with the CYP450 isoenzymes 2D6 and 3A4 was not an exclusion criterion, but consideration was to be given to the use of alternative agents with less potential for interaction with everolimus or imatinib. Patients with a history of known brain metastases were not eligible unless previously adequately treated with radiation and/or surgery. Pregnant or nursing women were not eligible and both male and female patients of reproductive potential must have agreed to employ 2 effective methods of birth control. Patients less than 5 years free of another malignancy were ineligible unless the other primary malignancy was not currently clinically significant nor required active intervention, or if the other primary malignancy was basal cell skin cancer or cervical carcinoma in situ. Additional exclusion criteria included Grade III/IV cardiac disease as defined by the New York Heart Association Criteria, chronic liver disease, gastrointestinal disease or impaired function that might significantly alter study drug absorption, known human immunodeficiency virus infection, severe and/or uncontrolled medical illness, and any significant history of non-compliance to medical regimens. All subjects gave written, informed consent in accordance with institutional and federal guidelines.

Study design

Treatment was initiated with everolimus 2.5 mg and imatinib 600 mg p.o. daily with a cycle length defined as 6 weeks. Treatment delays and dose reductions (to everolimus 2.5 mg p.o. daily/imatinib 400 mg p.o. daily and further to everolimus 2.5 mg p.o. every other day/imatinib 400 mg p.o. daily) were undertaken for grade 3–4 toxicity and, at the investigator's discretion, grade 2 clinically-significant non-hematologic toxicity. For grade 3–4 stomatitis, the everolimus was reduced prior to imatinib dose reduction. Grade 3–4 hyperlipidemia was managed by temporarily holding everolimus and initiating lipid-lowering therapy.

Baseline evaluation included a medical history and physical examination; assessment of performance status; biochemical profile, fasting lipid panel, and complete blood count; disease assessment with scans as needed for disease measurement; and bone scan, if clinically indicated. Subjects underwent history and physical every 3 weeks during the first 5 cycles, then at the beginning of each additional 6 week cycle. Biochemical profile,

fasting lipid panel and complete blood count were monitored throughout the study. Disease assessment using scans as needed for disease measurement was performed every 6 weeks through cycle 6 and then every 12 weeks thereafter. Study treatment was continued until progressive disease, unacceptable toxicity, withdrawal of consent, or development of an intercurrent illness or situation that would affect safety or study endpoints.

Study evaluation and statistical methods

The NCI Common Terminology Criteria for Adverse Events Version 3.0 was utilized for toxicity assessment. RECIST was used for response assessment [14].

The primary objective was estimation of the fraction of patients who remained progression-free at 3-months. Secondary objectives included assessment of (1) median time to progression; (2) response rate; (3) overall reduction of tumor measurements; (4) toxicity.

Previously, a large, randomized, placebo-controlled phase III study of patients with advanced RCC reported a median progression-free survival of 2.8 months in the placebo arm [15]. Therefore, we considered a 3 month progression-free rate of less than 50% to be consistent with the natural history of the disease and suggestive of a non-effective therapy. Alternatively, a 3-month progression-free rate of 70% or more would be promising. This single arm, phase II trial was designed according to the optimal criteria of Simon's two-stage design with 5% significance level and 80% power [16]. Fifteen patients were to be accrued to the first stage; if 9 or more of these patients were progression-free at 3 months, enrollment would continue to a total of 43 patients. During the first stage, patients who were not assessable for progression-free status at 3 months due to study discontinuation for any reason except death or progression were replaced only for purposes of determining continuation to the second stage. Therefore, a total of 19 patients were enrolled in the first stage (15 evaluable patients at 3 months and 4 patients who withdrew earlier).

Results

Patient characteristics

The study was activated in February 2006 and completed accrual in December 2007. The study was closed after enrollment of 19 subjects due to an insufficient number of subjects who were progression-free at 3 months in accordance with the protocol-specified stopping rule. All enrolled subjects were evaluable for PFS and for toxicity. Baseline patient characteristics are shown in Table 1. The majority of patients (89%) were either classified as favorable or intermediate prognosis using prognostic criteria for previously-treated patients with metastatic RCC [17]. All but 2 subjects had received prior VEGF receptor TKI therapy (89%), and 21% had received 3 or more prior systemic therapies.

Treatment delivery

The median duration of protocol treatment was 2.6 months (range <1 – 21 months). All subjects are currently off study treatment. Reasons for treatment discontinuation were disease progression (12), withdrawal of consent (3), adverse events (2), physician decision (1), and subject non-compliance (1).

Of the 19 patients, 6 (32%) had their dose of imatinb reduced and 1 of these patients also required dose reduction of everolimus. Fourteen patients (74%) required a dose-interruption during protocol treatment.

Response and survival

Eighteen subjects were evaluable for response. There were no objective responses. Best response was stable disease in 12 (67%) subjects and progressive disease in 6 (33%) subjects. Five of 17 subjects who underwent at least 1 post-baseline scan demonstrated a decrease in the sum of target lesions but did not meet criteria for partial response.

The median progression-free survival was 2.9 months (95% C.I. 1.9, 6.2) and the 3− and 6−month progression-free survival rates were 49% (95% C.I. 23%, 72%) and 41% (95% C.I. 16%, 65 %), respectively. The median overall survival was 14.4 months (95% C.I. 11.3, N.R.).

Toxicity

Table 2 shows a summary of the most common and grade 3–4 treatment-related adverse events. The overall most common adverse events associated with everolimus and imatinib treatment were nausea (79% of subjects), limb edema (74%), and fatigue (68%). The most common laboratory abnormalities were elevated serum creatinine (79%), anemia (74%), hypocalcemia (63%), and leukopenia (58%). Sixty-three percent of subjects experienced a grade 3 or greater adverse event. One subject experienced everolimus-related pneumonitis. Two subjects were removed from protocol treatment due to adverse events, one each for grade 3 angioedema and grade 3 pleural effusion.

Discussion

Combination treatment strategies in advanced RCC are an area of active investigation given the availability of multiple new agents with potential synergistic effects on signaling pathways. We hypothesized that the activity of the mTOR inhibitor everolimus could be augmented by inhibition of a relevant upstream receptor tyrosine kinase. We chose to study imatinib because of its inhibition of the PDGFR, a logical target for RCC therapy given its role in angiogenesis and the overexpression of PDGF-B secondary to VHL dysregulation [1, 5]. We studied this treatment strategy in pre-treated advanced RCC patients, with all but 2 subjects (89%) having received prior treatment with sorafenib and/or sunitinib, agents that had became commercially available shortly before activation of this trial.

Concurrent with our trial, everolimus was studied in a placebo-controlled, phase III study in advanced RCC patients who had prior treatment with sorafenib or sunitinib [4]. That study found an improvement in PFS compared with placebo (H.R. 0.31, 95% C.I. 0.24–0.41; p<0·0001) and reported a median PFS of 4.6 months (95% C.I. 3.9, 5.5) in the everolimus arm using investigator assessments. While the median PFS that we found with everolimus in combination with imatinib was only 2.9 months, the 95% confidence interval overlaps with that of the phase III trial. Additionally, our 6 month PFS rate of 41% (95% C.I. 16%, 65 %) is comparable to the 6-month progression-free rate of 26% reported in that study. While comparing the results of a small, phase II study with those of a phase III trial may be

misleading, the outcome of subjects treated with everolimus 2.5 mg and imatinib is arguably no worse than those treated with everolimus 10 mg monotherapy. However, we did not find evidence that the addition of imatinib augments everolimus activity in RCC and do not recommend that the combination be further pursued in this disease.

The doses of everolimus and imatinib used in our study were based upon the maximum tolerated dose that had been determined in a phase I study of the combination in gastrointestinal stromal tumor patients [13]. Pharmacokinetic analysis in that trial found imatinib to increase the bioavailability of everolimus approximately 2–3 fold with an increase in both Cmax and AUC in most patients, possibly due to competition for CYP3A4 metabolism and/or P-glycoprotein at the absorption site [13]. Interestingly, everolimus administration did not affect imatinib levels. While the dose of everolimus used in our study (2.5 mg/day) was substantially lower than the single-agent dose used in the phase III trial (10 mg/day), it is unknown whether or not this impacted the clinical activity observed.

Our phase II study closed after the first stage of accrual due to an insufficient number of subjects who remained progression-free at 3 months, per the study design. We had assumed that an ineffective therapy would be associated with a median PFS of 3 months or less. Similarly, a median PFS of 3 months was assumed for the placebo arm in the phase III everolimus study. These assumptions were reasonable given that a median PFS of 2.8 months that had been reported for the placebo arm of the phase III sorafenib study, another pre-treated population, albeit mostly with cytokine therapy [15]. No large data sets existed at the time of study design regarding the natural history of RCC after VEGF receptor TKI therapy. Subsequently, the everolimus phase III study reported a median PFS of only 1.8 months (95% C.I. 1.8, 1.9) in the placebo arm, suggesting that previous assumptions regarding the natural history in the post-TKI setting were overly optimistic. Future studies in this patient population should be cognizant of the rapid progression that characterizes the clinical course of RCC patients after TKI therapy.

Toxicity of the combination was moderate, with approximately two-thirds of subjects experiencing a grade 3 or greater adverse event. Gastrointestinal side effects and fatigue were most common, occurring in an overall frequency higher than reported for either single-agent everolimus or imatinib [4, 18]. Edema and other manifestations of fluid overload were also frequent and characteristic of imatinib. Also observed was a high incidence of increased creatinine, of unclear etiology. One possibility is that fluid shifts associated with imatinib therapy may amplify underlying effects of everolimus on renal function. Several common everolimus side effects and laboratory abnormalities were observed at a relatively low frequency including stomatitis (16%) and hypercholesterolemia (16%), possibly due to the relatively short treatment duration in most patients. Several serious everolimus-associated toxicities were noted including one case of grade 3 pneumonitis that resolved with steroids and withdrawal of study drug as well as a case of grade 3 angioedema that occurred in a subject receiving concomitant angiotensin-converting enzyme inhibitor therapy. Angioedema has been previously reported in association with everolimus in the transplant population, and non-infectious pneumonitis was reported in 8% of patients in the phase III renal carcinoma study [4, 19].

In conclusion we found no evidence that imatinib augments the activity of everolimus in renal carcinoma. Despite PDGFR being a rational target in this disease, imatinib's tyrosine kinase inhibitory profile has not shown to be clinically relevant in the treatment of RCC, as suggested by this study and several other phase II studies employing the agent [8–10]. Progression-free survival is short in patients who have received prior systemic therapy for RCC, and strategies to further improve the outcome of this population are needed.

Acknowledgments

This investigation was supported in part by funding from Novartis and NIH/NCI Cancer Center Support Grant (P30 CA069533).

References

1. Kaelin WG Jr (2004) The von Hippel-Lindau tumor suppressor gene and kidney cancer. Clin Cancer Res 10:6290S–6295S [PubMed: 15448019]
2. Hudson CC, Liu M, Chiang GG, Otterness DM, Loomis DC, Kaper F, Giaccia AJ, Abraham RT (2002) Regulation of hypoxia-inducible factor 1alpha expression and function by the mammalian target of rapamycin. Mol Cell Biol 22:7004–7014 [PubMed: 12242281]
3. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, Staroslawska E, Sosman J, McDermott D, Bodrogi I, Kovacevic Z, Lesovoy V, Schmidt-Wolf IG, Barbarash O, Gokmen E, O'Toole T, Lustgarten S, Moore L, Motzer RJ (2007) Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 356:2271–2281. doi:356/22/2271 [pii] 10.1056/NEJMoa066838 [PubMed: 17538086]
4. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G, Berg WJ, Kay A, Lebwohl D, Ravaud A (2008) Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 372:449–456. doi:S0140–6736(08)61039–9 [pii] 10.1016/S0140-6736(08)61039-9 [PubMed: 18653228]
5. Ostman A, Heldin CH (2007) PDGF Receptors as Targets in Tumor Treatment. Adv Cancer Res 97:247–274. doi:S0065–230X(06)97011–0 [pii] 10.1016/S0065-230X(06)97011-0 [PubMed: 17419949]
6. Sulzbacher I, Birner P, Traxler M, Marberger M, Haitel A (2003) Expression of platelet-derived growth factor-alpha alpha receptor is associated with tumor progression in clear cell renal cell carcinoma. Am J Clin Pathol 120:107–112. doi:10.1309/LQ9E-MK8Q-KE75-NGGX [PubMed: 12866380]
7. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, Lydon NB, Kantarjian H, Capdeville R, Ohno-Jones S, Sawyers CL (2001) Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. N Engl J Med 344:1031–1037 [PubMed: 11287972]
8. Vuky J, Isacson C, Fotoohi M, dela Cruz J, Otero H, Picozzi V, Malpass T, Aboulafia D, Jacobs A (2006) Phase II trial of imatinib (Gleevec) in patients with metastatic renal cell carcinoma. Invest New Drugs 24:85–88. doi:10.1007/s10637-005-4543-z [PubMed: 16380835]
9. Hainsworth JD, Spigel DR, Sosman JA, Burris HA 3rd, Farley C, Cucullu H, Yost K, Hart LL, Sylvester L, Waterhouse DM and Greco FA (2007) Treatment of advanced renal cell carcinoma with the combination bevacizumab/erlotinib/imatinib: a phase I/II trial. Clin Genitourin Cancer 5:427–432 [PubMed: 18272024]
10. Polite BN, Desai AA, Manchen B, Stadler WM (2006) Combination therapy of imatinib mesylate and interferon-alpha demonstrates minimal activity and significant toxicity in metastatic renal cell carcinoma: results of a single- institution phase II trial. Clin Genitourin Cancer 4:275–280 [PubMed: 16729911]

11. Bergers G, Song S, Meyer-Morse N, Bergsland E, Hanahan D (2003) Benefits of targeting both pericytes and endothelial cells in the tumor vasculature with kinase inhibitors. J Clin Invest 111:1287–1295. doi:10.1172/JCI17929 [PubMed: 12727920]
12. Lane HA, Wood JM, McSheehy PM, Allegrini PR, Boulay A, Brueggen J, Littlewood-Evans A, Maira SM, Martiny-Baron G, Schnell CR, Sini P, O'Reilly T (2009) mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. Clin Cancer Res 15:1612–1622. doi:1078–0432.CCR-08–2057 [pii] 10.1158/1078-0432.CCR-08-2057 [PubMed: 19223496]
13. van oosterom A, Reichardt P, Blay J-Y, Dumez H, Fletcher J, Debiec-Rychter M, Shand N, Drimitrijevic S, Yap A, Demetri g (2005) A phase I/II trial of the oral mTOR-inhibitor everolimus (E) and imatinib mesylate (IM) in patients (pts) with gastro-intestinalstromal tumor (GIST) refractory to IM: Study update. J Clin Oncol 23:9033
14. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216 [PubMed: 10655437]
15. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, Negrier S, Chevreau C, Solska E, Desai AA, Rolland F, Demkow T, Hutson TE, Gore M, Freeman S, Schwartz B, Shan M, Simantov R, Bukowski RM (2007) Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. N Engl J Med 356:125–134 [PubMed: 17215530]
16. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10. doi:0197–2456(89)90015–9 [pii] [PubMed: 2702835]
17. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, Mazumdar M (2004) Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 22:454–463 [PubMed: 14752067]
18. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, Heinrich MC, Tuveson DA, Singer S, Janicek M, Fletcher JA, Silverman SG, Silberman SL, Capdeville R, Kiese B, Peng B, Dimitrijevic S, Druker BJ, Corless C, Fletcher CD, Joensuu H (2002) Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 347:472–480. doi:10.1056/NEJMoa020461 347/7/472 [pii] [PubMed: 12181401]
19. Fuchs U, Zittermann A, Berthold HK, Tenderich G, Deyerling KW, Minami K, Koerfer R (2005) Immunosuppressive therapy with everolimus can be associated with potentially life-threatening lingual angioedema. Transplantation 79:981–983. doi:00007890–200504270-00020 [pii] [PubMed: 15849555]

Table 1

Baseline patient characteristics (*N*=19)

Median age (range)	65 (50–79)
Gender	
Male	16 (84%)
Female	3 (16%)
Performance status	
0	8 (42%)
1	10 (53%)
2	1 (5%)
MSKCC risk factors for previously treated patients[17]	
Favorable	8 (42%)
Intermediate	9 (47%)
Poor	2 (11%)
Number of prior systemic therapies	
1	9 (47%)
2	6 (32%)
3+	4 (21%)
Prior systemic therapies	
Sunitinib	6 (32%)
Sorafenib	14 (74%)
Both sunitinib and sorafenib	3 (16%)
Neither sunitinib/sorafenib	2 (11%)
Interferon	7 (37%)
Interleukin-2	3 (16%)
Other	5 (26%)
Prior radiation	7 (37%)
Number of metastatic sites	
1	7 (37%)
2	8 (42%)
3+	4 (21%)
Common metastatic sites	
Lymph Nodes	14 (74%)
Lung	10 (53%)
Liver	4 (21%)
Kidney	3 (16%)

Table 2

Treatment-related adverse events and laboratory abnormalities reported in >20% of subjects or Grade 3 and higher

	Grade 1		Grade 2		Grade 3		Grade 4		Any Grade	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Adverse Events										
Nausea	10	53%	5	26%	0	–	0	–	15	79%
Edema: limb	9	47%	3	16%	2	11%	0	–	14	74%
Fatigue	3	16%	7	37%	3	16%	0	–	13	68%
Diarrhea	7	37%	3	16%	1	5%	0	–	11	58%
Vomiting	8	42%	3	16%	0	–	0	–	11	58%
Dyspnea	4	21%	6	32%	1	5%	0	–	11	58%
Periorbital edema	6	32%	2	11%	2	11%	0	–	10	53%
Anorexia	3	16%	6	32%	0	–	0	–	9	47%
Abdominal pain	7	37%	0	–	2	11%	0	–	9	47%
Cough	5	26%	2	11%	0	–	0	–	7	37%
Dyspepsia	3	16%	3	16%	0	–	0	–	6	32%
Dysgeusia	2	11%	4	21%	0	–	0	–	6	32%
Rash	3	16%	2	11%	0	–	0	–	5	26%
Myalgias	3	16%	1	5%	0	–	0	–	4	21%
Pleural effusion	0	–	1	5%	3	16%	0	–	4	21%
Fever	4	21%	0	–	0	–	0	–	4	21%
Hypotension	2	11%	0	–	0	–	1	5%	3	16%
Dehydration	1	5%	0	–	1	5%	0	–	2	11%
Angioedema	0	–	0	–	1	5%	0	–	1	5%
Rash: Hand-foot	0	–	0	–	1	5%	0	–	1	5%
Pneumonitis	0	–	0	–	1	5%	0	–	1	5%
Laboratory Abnormalities										
Elevated creatinine	7	37%	6	32%	2	11%	0	–	15	79%
Hemoglobin	7	37%	7	37%	0	–	0	–	14	74%
Hypocalcemia	10	53%	2	11%	0	–	0	–	12	63%
Leukopenia	4	21%	7	37%	0	–	0	–	11	58%
Elevated AST	9	47%	0	–	0	–	0	–	9	47%
Thrombocytopenia	5	26%	3	16%	1	5%	0	–	9	47%
Hypertriglyceridemia	3	16%	6	32%	0	–	0	–	9	47%
Hypoalbuminemia	4	21%	1	5%	0	–	0	–	5	26%
Elevated ALT	4	21%	0	–	0	–	0	–	4	21%
Hyponatremia	3	16%	0	–	1	5%	0	–	4	21%