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Phase Ib study of codrituzumab in combination with sorafenib in patients with non-curable advanced hepatocellular carcinoma (HCC)

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Abstract

Purpose—Codrituzumab, a humanized antibody against glypican-3, is highly expressed in HCC. A phase I study evaluated the combination with sorafenib in HCC.

Patients and methods—In a 3 + 3 design, codrituzumab was given intravenously in various doses with sorafenib 400 mg twice daily to patients with advanced HCC, age ≥ 18, ECOG 0–1, Child-Pugh A and B7, adequate organ functions, and no prior systemic therapy, with tumor

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Compliance with ethical standards

Conflict of interest Ghassan K. Abou-Alfa, Chia-Jui Yen, Catherine Frenette, Bert O'Neil, Steven M. Larson, Ann-Lii Cheng, and Jorge A. Carrasquillo report research funding support from Roche and Chugai to their institutions. Toshihiko Ohtomo, Takayoshi Tanaka, Hideo Morikawa, Yuko Maki, and Norihisa Ohishi report Chugai employment. Ya-Chi Chen, Tamara Agajanov, Frederic Boisserie, Laura Di Laurenzio, and Ray Lee report Roche employment.

assessment by RECIST 1.0 and safety by CTCAE 3.0. PK and pre, during, and post-therapy ^{124}I radiolabeled codrituzumab PET scan imaging were performed.

Results—41 patients were enrolled: 2.5 mg/kg weekly (qw) (12), 5 mg/kg qw (12), 10 mg/kg qw (3), 1600 mg every 2 weeks (q2w) (6), and 1600 mg qw (7). Two drug limiting toxicities occurred: grade 3 hyponatremia at 5 mg/kg and grade 3 hyponatremia and hyperglycemia at 1600 mg q2w. Adverse events occurred in 80% of patients, including at least one grade 3: ten (25%) increased AST, three (7.5%) increased ALT, and ten (25%) increased lipase. There were no responses and nine (25.7%) had stable disease. PK C_{max} and AUC_t of codrituzumab and sorafenib were comparable to single-agent data. Thirteen out of 14 patients showed ^{124}I radiolabeled codrituzumab uptake in tumor. In all three patients who underwent a post-progression PET, glypican-3 remained expressed.

Conclusion—Codrituzumab plus sorafenib were tolerated at 1600 mg q2w and 400 mg bid, respectively, with no responses. Codrituzumab exerts selective distribution to HCC cells, and GPC3 does not show any down-regulation post-progression (NCT00976170).

Introduction

Hepatocellular carcinoma (HCC) is the major type of liver cancer with limited therapeutic option in advanced stage. Sorafenib was approved in 2007 based on the SHARP Phase III study with median overall survival of 10.7 months in sorafenib group vs 7.9 months for placebo group. Until now, sorafenib remains the only approved systemic therapy for hepatocellular carcinoma [1]. The result was further confirmed by another study in Asia showing similar benefits in both hazard ratios of PFS and OS [2]. Other targeted therapies have been shown to be either less effective in direct comparison or unable to be combined with sorafenib in various clinical trials [3].

Codrituzumab (GC33 or RO5137382) is a recombinant, fully humanized monoclonal antibody that binds to human Glypican-3 (GPC3), an oncofetal protein of the glypican family that is overexpressed in over 70% of HCC [4, 5]. Once codrituzumab binds with GPC3 in tumor cell surface, it elicited antibody-dependent cellular cytotoxicity (ADCC) to control tumor growth and proliferation [6]. Prior phase 1 study in US and Japan demonstrated preliminary efficacy of the single-agent codrituzumab in treating HCC [7, 8].

The combination of codrituzumab with sorafenib was conducted in subcutaneously established human hepatoblastoma xenografts. The combination inhibited tumor growth more than codrituzumab alone or sorafenib alone [9]. This, add to the different mechanisms of action and the absence of any additive adverse events, led to this phase 1b study of the combination of codrituzumab and sorafenib for the first-line treatment of HCC.

Patients and methods

Study population

The study population included patients with histologically confirmed HCC, who have measurable disease but not candidate for surgical resection or local therapy, and have not received sorafenib in the past. Patients 18 years old, with Eastern Cooperative Oncology

Group (ECOG) [10]. Performance Status (PS) of 0–1 with Child-Pugh class A was allowed on study. Child-Pugh B7 was allowed in the early version of the protocol but subsequently removed during amendment. Patients were required to have adequate organ functions, defined by AST/ALT $\leq 5 \times$ upper limit of normal (ULN), total bilirubin: ≤ 1.5 mg/dL, prothrombin time-international normalized ratio (PT-INR) ≤ 2.0 , platelets $\geq 100,000/\mu\text{L}$, absolute neutrophil count (ANC) $\geq 1,500/\mu\text{L}$, and serum creatinine: $\leq 2 \times$ ULN. Patients with known brain or other central nervous system diseases were excluded from the trial. Patients with prior liver transplantation, known positive HIV infection, lactating or pregnant women were also excluded. For the evaluation of GPC3 expression, all enrolled patients are required to provide a tumor tissue sample within 12 months prior to signing informed consent or from a fresh biopsy. The study was approved by the institutional review boards of participating centers and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study design, dose administration, randomization, and cohort assignment

The study was an open label, single arm, 3 + 3 standard dose escalation design with the dose of codrituzumab in five cohorts, starting at 2.5 mg/kg weekly (qw) intravenously and advanced to 5, 10 mg/kg qw (cohorts 1, 2, and 3). This was followed by a cohort of a fixed dose at 1600 mg every 2 weeks (q2w) (cohort 3*) and then 1600 mg qw (cohort 5). If 1600 mg qw was not a tolerable dose, dose de-escalation to 1200 mg qw (cohort 4) was planned. The dose of sorafenib was 400 mg PO twice daily (bid). Dose interruption or modification due to sorafenib-related toxicities was allowed as per the sorafenib package insert. The study was followed, and decision to escalate cohort was agreed by an independent data and safety monitoring board, which included two oncologists and one hepatologist.

Safety analysis

The primary endpoint of this study was safety and tolerability of codrituzumab in combination with sorafenib. Safety evaluations were done weekly, before each dose of codrituzumab administration. These included blood counts, serum chemistry, and liver function tests.

Dose limiting toxicity was defined as any toxicity grade ≥ 3 based on the NCI Common Terminology Criteria for Adverse Events Version 3.0, except for the following: Grade 3 acute infusion reaction; $\geq 2.5 \times$ baseline increase hepatic function parameters (ALT, AST, alkaline phosphatase, albumin, total Bilirubin, PT-INR); any liver enzyme increase that resolves within 2 weeks; grade 3 neutropenia, lymphopenia, or thrombocytopenia; grade 3 nausea, vomiting, diarrhea, anorexia, and hypertension manageable by optimal supportive care; asymptomatic increased amylase or lipase; grade 3 hypophosphatemia; skin toxicities; or any toxicity with a clear documented alternative explanation for the toxicity that does not involve the investigational drug codrituzumab. Human anti-human immunoglobulin (HAMA) development was performed in pretreatment, weeks 3, 15 and off-study visit.

Efficacy analysis

The secondary endpoints include progression free survival (PFS) based on investigator assessment and time to progression (TTP). Radiologic tumor assessment was performed at

screening, and every 8 weeks until progression using mainly triple phase contrast enhanced CT. Response evaluation was performed using the criteria of RECIST 1.0 [11]. Alpha-fetoprotein was tested similar to the imaging schedule.

GPC3 expression

Tumor expression of GPC3 was examined in biopsied specimens by immunohistochemistry (IHC) using mouse anti-human GPC3 monoclonal antibody (Charles River Laboratories). IHC scoring was performed on either formalin fixed paraffin embedded block sample within 12 month prior to informed consent or on unstained slides obtained within 3 month prior to informed consent. IHC was performed and interpreted as previously described assigning score based on positive cell rate and staining intensity (cytoplasmic or cell membrane) [7].

Pharmacokinetics

Serum for the measurement of concentration of codrituzumab was collected at pre-dose, end of the first dose and either fourth dose for Cohorts 1, 2, 3, and 5 or third dose for Cohort 3* of codrituzumab, 1, 8, 24, 48, 72, 96, 120, 144 h after the completion of infusion. Serum codrituzumab assay was performed by the Kamakura Branch, Chugai Research Institute for Medical Science, Inc. (Kanagawa, Japan).

Pharmacokinetics (PK) samples for sorafenib were collected on Day 22 (Cohorts 1, 2, 3, and 5) or Day 29 (Cohort 3*) prior to dosing and at 30 min, 1, 2, 4, and 8 h postsorafenib dose, and at the end of the exit visit. Plasma sorafenib assay was performed by Covance Bioanalytical Services, LLC. All pharmacokinetic parameters were calculated using non-compartmental analysis method (NCA) by Phoenix WinNonlin version 6.3 (Pharsight Co., Mountain View, CA, USA).

Imaging analysis of the distribution of codrituzumab

A positron emission tomography (PET) imaging study was performed in 14 patients in Cohorts 1 and 2 at Memorial Sloan Kettering Cancer Center, to explore the distribution of codrituzumab in HCC patients. ^{124}I -codrituzumab radiolabeling and dose preparation were performed at the MSK Radiochemistry and Molecular Imaging Probe Core Facility. In brief, 10 mg of codrituzumab were radiolabeled with 10 mCi (370 MBq) of ^{124}I , using the iodogen method in accordance with an FDA approved investigational drug application. For each patient doses, 5 mCi (185 MBq) were withdrawn into a syringe, and the total mass of codrituzumab was adjusted to ~10 mg with cold codrituzumab. Three infusions of a nominal 5 mCi (185 MBq) of ^{124}I -codrituzumab (10 mg) were planned during the study period. Patients received a baseline ^{124}I -codrituzumab injection at least 1 week prior to the first codrituzumab infusion (Imaging Day 1). Patients underwent PK blood sampling and PET-CT imaging on four occasions during the ensuing 7 days (on imaging Day 1 post-infusion 1–4 h and on imaging Day 2, Day 3–4, and Day 5–7). Patients started their codrituzumab infusions and sorafenib dosing at least 1 week after their first ^{124}I -codrituzumab injection. Patients received a weekly codrituzumab infusion and twice-daily sorafenib administration from Day 2. During their fourth codrituzumab infusion (Day 22), patients received a second ^{124}I -codrituzumab injection in conjunction with the non-labeled codrituzumab (i.e., co-infused during the last ~10 min of the codrituzumab therapeutic injection) and imaging,

and PK blood sampling was performed same as for their baseline injection. At progression of disease, 4–6 weeks after final injection of codrituzumab, patients received a third ^{124}I -codrituzumab injection and imaging was performed at 1–4 h post-infusion and on Day 3–7.

Statistical design

All patients enrolled were included in the intent-to-treat population (ITT). All patients who received at least one dose of codrituzumab and/or sorafenib were included in the safety population. Only patients who completed cycle 1 of codrituzumab and/or sorafenib with 35 days follow-up were counted as evaluable for DLT.

Statistical analysis of the nuclear imaging results was done using descriptive statistics, including median or mean and standard deviation and Spearman correlation coefficient. Comparison between groups was performed with either paired t test or ANOVA using the Sigma Stat 3.5 (Systat Software Inc, Point Richmond, CA).

Results

Enrollment and disposition

Forty two patients enrolled between 2009 and 2013 and 40 patients received at least one dose of codrituzumab and sorafenib, and were distributed among the five cohorts as follows: 12 patients each in Cohort 1 (2.5 mg/kg qw codrituzumab) and Cohort 2 (5 mg/kg qw) and 3, 6, and 7 patients in Cohorts 3 (10 mg/kg qw), 3* (1600 mg q2w), and 5 (1600 mg qw), respectively (Fig. 1). The demographics of the 40 patients in the safety population are shown in Table 1. The average dose intensities of codrituzumab and sorafenib received by patients in each cohort are shown in supplemental tables 1 and 4. The mean relative dose intensity for codrituzumab was 81.7% of the total planned dose; whereas that of sorafenib was 64.8% of the scheduled dose, and patients in the cohort 5, received 50.4% of the planned dose of sorafenib.

Safety profile

The DLT evaluable population included 26 patients (Fig. 1). Two of the 26 patients (7.7%) who completed first cycle experienced DLTs. One patient in Cohort 2 had grade 3 hyponatremia, due to SIADH, and 1 patient in Cohort 3* had grade 3 hyponatremia and hyperglycemia. An additional patient in cohort 2 who had Child-Pugh B7 cirrhosis at baseline experienced a DLT of elevated LFTs (grade 4) but was excluded from the DLT evaluable population based on an amendment of the study that excluded Child-Pugh B patients. With the amendment in place, tolerability was reassessed in Cohort 2 (codrituzumab 5 mg/kg qw and sorafenib 400 mg bid), Cohort 3 (codrituzumab 10 mg/kg qw and sorafenib 400 mg bid), and Cohort 3* (codrituzumab 1600 mg q2w and sorafenib 400 mg bid). However, Cohort 5 (codrituzumab 1600 mg qw and sorafenib 400 mg bid) had 2/7 subjects with sorafenib-related toxicities even though not fulfilling DLT criteria.

Adverse events reported at CTCAE Grade 3 or higher in over 10% patients included elevated lipase (ten patients, 25%) and increased AST (ten patients, 25%), palmarplantar erythrodysesthesia (6 patients, 15%), as shown in Table 2.

Efficacy analysis

At their last assessment, 28 patients were still alive (80%) and 7 patients had died (20%). The median PFS for all study patients was 2.7 months (95% CI 2.0, 4.2) (Fig. 2a). The overall median time to death was 8.7 months (95% CI 8.2, 17.8) (Fig. 2b). Among the evaluable patients, there were no patients with documented CR or PR based on RECIST criteria 1.0. Nine patients (25.7%) who exhibited SD for at least 4 months.

GPC 3 expression

An exploratory analysis of GPC3 and PFS showed a patients with GPC3 score ≥ 7 by IHC to have median PFS of 2.1 months (13 patients) and those with GPC3 score < 7 (14 patients), a median PFS of 4 months (Supplemental Fig. 1). Eight patients had no GPC3 score available.

PK analysis

The mean codrituzumab serum concentration plots for all patients by dose group showed an increase in the trough concentrations of codrituzumab after repeated infusions and seemed to reach a steady state after at least six doses (Supplemental Fig. 2A). The PK parameters of codrituzumab following combination sorafenib therapy shown in supplemental tables 2 and 3 were comparable to those of historical data when codrituzumab was administered alone [7, 8]. Following the administration of codrituzumab and sorafenib, the mean $C_{\max}$ of sorafenib ranged from 3.63 to 7.64 $\mu\text{g/mL}$ and the mean AUC_{last} ranged from 17.3 to 34.5 h $\mu\text{g/mL}$ for 400 mg bid, respectively. These findings are consistent with prior reports of $C_{\max}$ of 4.9 $\mu\text{g/mL}$ and $\text{AUC}_{(0-8\text{h})}$ of 25.4 h $\mu\text{g/mL}$ ($n = 14$) at 400 mg bid in Child-Pugh A patients [12]. The parameters determined for sorafenib in the present study were in the same range, suggesting no drug–drug interaction between sorafenib and codrituzumab.

Serum concentration of co-administered ^{124}I -codrituzumab and cold codrituzumab showed a biphasic radioactivity decrease and similar clearance curves (Supplemental Fig. 2B).

We also explored the biodistribution of low-dose ^{124}I -codrituzumab, pharmacokinetics, and the effect of large therapeutic amounts of codrituzumab on ^{124}I -codrituzumab biodistribution.

Imaging analysis with ^{124}I -codrituzumab

Fourteen patients underwent a baseline scan with ^{124}I -codrituzumab, of whom 13 had positive scan findings and 1 had no uptake above normal liver background. Six patients had prominent uptake by HCC ($\text{SUV}_{\max}$ 10–31) and seven with moderate uptake in HCC above liver background ($\text{SUV}_{\max}$ 7–9). High tumor uptake is seen in a representative patient (Fig. 3). Heterogeneity in tumor visualization was frequently observed in PET-CT imaging.

Repeat imaging with ^{124}I -codrituzumab plus therapeutic amount of cold codrituzumab following day 22 of cold codrituzumab therapy was performed in seven patients and showed quantitative decrease in the tumor uptake in only two patients both of which had high initial tumor $\text{SUV}_{\max}$ on baseline ^{124}I -codrituzumab imaging. Representative baseline and co-infusion images are shown in supplemental Fig. 3A. No changes in $\text{SUV}_{\max}$ in other organ and tissue were seen. Only three patients (#7, 9, and 14) had the third scan performed after

disease progression. In all three patients, tumor uptake was noted, suggesting that GPC3 was still expressed in tumors after HCC progressed on codrituzumab therapy (Supplemental Fig. 3B).

Discussion

This phase 1b study examined the combination of codrituzumab and sorafenib in HCC patients who have not been treated with sorafenib in the past. Since sorafenib was first approved in 2007 [1], there has been no other agent demonstrated to be superior or equivalent to sorafenib in HCC [3]. Agents that intended to build on sorafenib as a combination turned out to be futile as well [12]. Codrituzumab, a monoclonal antibody targeting an HCC cell surface protein GPC3, is generally well tolerated [7, 8]. The mechanism of therapeutic effect of codrituzumab is mediated through antibody-dependent cytotoxicity (ADCC), which is different from that of sorafenib; hence, little overlapping toxicity would be anticipated. After the amendment that excluded patients with Child-Pugh B, the dose escalation of codrituzumab in this study was able to advance to the highest proposed dose of 1600 mg QW, which aimed to achieve a mean target saturation over 90% based on the Target Mediated Drug Disposition (TMDD) model [13]. The lack of DLT in the highest dose cohort may suggest that the MTD was not reached. However, no further enrollment was performed in the cohort due to the observation that more patients required either holding or dose modification of sorafenib as shown by the mean relative dose intensity down to around 50%.

The efficacy of the codrituzumab–sorafenib combination was difficult to assess in this study due to the small sample size of the phase 1 trial. It nonetheless did not show any added benefit over sorafenib single agent.

Preclinical data of codrituzumab suggested that the higher the tumor expression of GPC3, the more likely tumor would benefit from codrituzumab treatment [6]. We found the contrary with a trend of longer PFS associated with low expression of GPC3. This was consistent with the previous reports that HCC with high expression of GPC3 has been reported to be a poor prognostic marker [5, 14]. However, due to the small sample size and potential selection bias, definitive conclusion cannot be made. This also may have to wait until we develop further understanding of the correlation between GPC-3 expression and efficacy of codrituzumab, within the context of circulating immune cells, as we previously reported [15]. Further role of GC33 and targeting GPC3 in enhancing anti-tumor immune therapy will await the planned study of the combination of codrituzumab with anti PD-L1 atezolizumab.

The imaging result using ^{124}I -codrituzumab provided a confirmation of the specificity of codrituzumab. In 13 of 14 patients tested with this radiolabeled antibody, tumor visualization was seen on PET-CT scans. The normal organ, including spleen and the reticuloendothelial system, had proportional activity to the blood pool, suggesting that codrituzumab accumulation was not due to cross reactivity with GPC3 in these organs (data not shown). Tumor distribution of ^{124}I -codrituzumab in patients with high tumor uptake on a baseline scans decreased with the co-administration of therapeutic dose of codrituzumab and a small

dose of ^{124}I -codrituzumab. This also suggests that the ^{124}I -codrituzumab has specific uptake in tumor and not other organs. Whether codrituzumab could elicit ADCC activity as anticipated, however, remains to be determined. In addition, the finding that patients who have progressed after codrituzumab and sorafenib still have relative accumulation of radiolabeled codrituzumab suggests that GPC3 in tumor cell surface remains present even after completion of codrituzumab therapy. This would have important implication if an antibody-drug conjugate approach would be considered in the future.

In conclusion, this phase 1b study of the combination of codrituzumab and sorafenib achieved the highest planned dose of codrituzumab with the standard dose sorafenib without DLT among Child-Pugh A patients. Although target engagement has been confirmed by ^{124}I -conjugate, more studies will be necessary to examine the efficacy of this combination.

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Fig. 1.
Consort diagram of enrollment into various cohorts and patients evaluable for DLT

Fig. 2.
a PFS Kaplan–Meier curve for the evaluable patients enrolled in various cohorts of the study. **b** OS Kaplan–Meier curve

Fig. 3.

a Whole body PET scan images of a representative patient #7 (*upper panel*). Patient underwent serial imaging with ^{124}I -codrituzumab 5 mCi alone before codrituzumab treatment. After patient was treated with sorafenib and 5 mg/kg cold codrituzumab for 4 weeks, patient was imaged again with the same study. Targeting to the right lobe of liver tumor is shown in upper panel in contrast to the blood pool, but uptake was blocked after administration of the cold antibody (*lower panel*). **b** PET-CT cross-sectional images of the same representative patient. CT images before and after treatment were shown at right with heterogeneity pattern. SUV_{max} in PET-CT imaging and the calculated tumor volume before and after treatment are shown

Table 1

Baseline disease characteristics—safety population

	Cohort 1 (N = 12)	Cohort 2 (N = 12)	Cohort 3 (N = 3)	Cohort 3* (N = 6)	Cohort 5 (N = 7)	Overall (N = 40)
Age (years): mean (range)	56.8 (37–81)	63.8 (45–82)	57.7 (49–64)	64.5 (45–78)	57.9 (36–70)	60.3 (36–82)
Gender						
Male (%)	10 (83.3%)	10 (83.3%)	3 (100%)	5 (83.3%)	7 (100%)	35 (87.5%)
Race						
Asian (%)	25%	50%	100%	66.7%	85.7%	55%
Non-Asian	75%	50%	–	33.3%	14.3%	45%
Weight (kg)						
Mean (range)	80.8 (49–127)	74.6 (55–106)	68 (61–76)	79.8 (62–118)	67.7 (55–93)	75.5 (49–127)
Child-Pugh scores of:						
5	8 (66.7%)	6 (50.0%)	3 (100%)	5 (83.3%)	3 (42.9%)	25 (62.5%)
6	3 (25.0%)	4 (33.3%)	–	1 (16.7%)	4 (57.1%)	12 (30.0%)
7	–	2 (16.7%)	–	–	–	2 (5.0%)
8 and above	1 (8.3%)	–	–	–	–	1 (2.5%)
TNM staging						
I–III	5 (41.7%)	7 (58.3%)	2 (66.7%)	2 (33.3%)	5 (71.4%)	21 (52.5%)
IV	5 (41.7%)	4 (33.3%)	1 (33.3%)	3 (50.0%)	2 (28.6%)	15 (37.5%)
ECOG						
0	3 (25%)	7 (58.3%)	3 (100%)	1 (16.7%)	5 (71.4%)	19 (47.5%)
I	9 (75%)	5 (41.7%)	–	5 (83.3%)	2 (28.6%)	21 (52.5%)
Hepatitis						
B	5 (41.7%)	4 (33.3%)	3 (100%)	5 (83.3%)	2 (28.6%)	19 (47.5%)
C	4 (33.3%)	3 (25.0%)	–	–	2 (28.6%)	9 (22.5%)
Cirrhosis	8 (66.7%)	6 (50.0%)	2 (66.7%)	3 (50%)	4 (57.1%)	23 (57.5%)
Mean diameter of target lesions (mm) and range	57.0 (16–166)	71.2 (14–159)	30.5 (17–39)	55.5 (40–68)	85.6 (13–180)	64.0 (13–180)
IHC GPC3						
7 total score	3 (25.0%)	5 (41.7%)	1 (33.3%)	3 (50.0%)	3 (42.9%)	15 (37.5%)
<7 total score	4 (33.3%)	4 (33.3%)	1 (33.3%)	2 (33.3%)	4 (57.1%)	15 (37.5%)
Not evaluable	5 (41.7%)	3 (25.0%)	1 (33.3%)	1 (16.7%)	–	10 (25.0%)

ECOG PS Eastern Cooperative Oncology Group Performance Status; TNM tumors, nodes, metastasis; IHC immunohistochemical; GPC3 Glypican-3;

Table 2

Incidences of selected adverse events with grade 3 or higher in safety population

AE terms	Cohort 1 (N = 12) Patients ^a	Cohort 2 (N = 12) Patients ^a	Cohort 3 (N = 3) Patients ^a	Cohort 3* (N = 6) Patients ^a	Cohort 5 (N = 7) Patients ^a	Overall (N = 40) Patients ^a
Lipase increased	4 (33.4%)	3 (25%)	1 (33.3%)	2 (33.3%)	2 (28.6%)	12 (30.0%)
Aspartate aminotransferase increased	2 (16.7%)	3 (25%)	1 (33.3%)	0 (0.0%)	4 (57.1%)	10 (25.0%)
Palmar-plantar erythrodysesthesia syndrome	1 (8.3%)	1 (8.3%)	3 (100%)	0 (0.0%)	1 (14.3%)	6 (15.0%)
Alanine aminotransferase increased	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	2 (28.6%)	3 (7.5%)
Fatigue	2 (16.7%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (7.5%)
Amylase increased	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	2 (5.0%)
Hyperglycemia	2 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
Hyponatremia	1 (8.3%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	2 (5.0%)
Hypertension	1 (8.3%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.0%)
Blood bilirubin abnormal	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)
Diarrhea	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (2.5%)

^aMore than one AE by preferred term is counted only once in each category