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Clinical Trial Results

Electrocardiographic Characterization of Ramucirumab on the Corrected QT Interval in a Phase II Study of Patients With Advanced Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01017731
- **Sponsor:** Eli Lilly and Company
- **Principal Investigator:** Anthony J. Olszanski
- **IRB Approved:** Yes

Lessons Learned

- Cardiotoxicity can be a serious complication of anticancer therapies. To enable earlier identification of drug-related cardiac effects, the International Conference on Harmonization (ICH) adopted the ICH E14 Guidelines for evaluating the potential for QT/corrected QT (QTc) interval prolongation and proarrhythmic potential for nonantiarrhythmic drugs.
- The results of the evaluation of ramucirumab on the QT/QTc interval show a lack of effect on QTc prolongation in patients with advanced cancer.

Abstract

Background. Ramucirumab is a human immunoglobulin G1 monoclonal antibody that specifically blocks vascular endothelial growth factor receptor-2 and is approved for the treatment of advanced gastric, non-small cell lung, and colorectal cancers. This phase II study was conducted to determine if treatment with ramucirumab causes prolongation of the corrected QT interval using Fridericia's formula (QTcF) in patients with advanced cancer.

Methods. Patients received intravenous ramucirumab (10 mg/kg) every 21 days for 3 cycles. The first 16 patients received moxifloxacin (400 mg orally), an antibiotic associated with mild QT prolongation as a positive control. During cycle 3, determination of QTcF prolongation was made with triplicate electrocardiograms at multiple time points to compare with baseline.

Results. Sixty-six patients received therapy; 51 patients completed 9 or more weeks of therapy for the complete QTcF evaluation period. The upper limit of the 90% two-sided confidence intervals for the least square means of change in QTcF from baseline at each time point was less than 10 milliseconds. Concentration-QTcF analysis showed a visible, but not significant, negative association between ramucirumab concentration and QTcF change from baseline.

Conclusion. Ramucirumab at a dose of 10 mg/kg administered every 21 days for 3 cycles did not produce a statistically or clinically significant prolongation of QTcF. ***The Oncologist*** 2016;21:402–403f

Discussion

QTcF correction change from baseline was the primary endpoint for this study. Fifty-one patients received at least 9 weeks of ramucirumab (10 mg/kg) plus diphenhydramine treatment (the complete corrected QT [QTc] evaluation period). Using the time-matched QTcF values from day −1 as the baseline, repeated-measures analysis of covariance showed that the upper limit of the two-sided 90% confidence intervals of the least square means of change from baseline for QTcF values was less than 10 milliseconds at all study time points in cycle 3 (Fig. 1). The first 16 patients received treatment with moxifloxacin (400 mg orally), an antibiotic associated with mild QTc prolongation, which demonstrated assay sensitivity.

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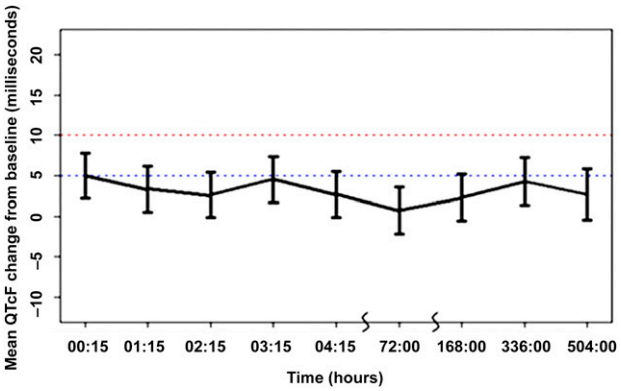

Figure 1. Graph showing 90% confidence interval of change from baseline at cycle 3 for QTcF after ramucirumab plus diphenhydramine treatment. Red dotted line and blue dotted line indicate 10- and 5-millisecond time points, respectively. The scale of the *x*-axis (time) is non-uniform.

Abbreviation: QTcF, QT corrected by Fridericia's formula.

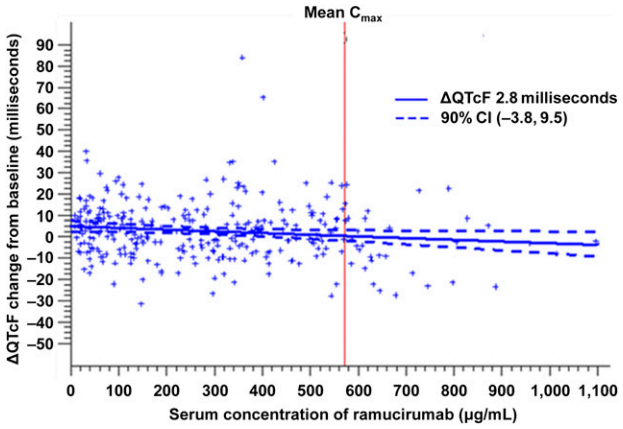

Figure 2. QTcF changes from baseline versus total drug concentrations at cycle 3 for the evaluable population. Mean C_{max} = 571 μg/mL. Mean change in QTcF at mean C_{max} = 2.8 milliseconds (90% CI: −3.8 to 9.5).

Abbreviations: CI, confidence interval; QTcF, QT corrected by Fridericia's formula.

The relationship between ramucirumab concentrations and change in QTcF was assessed using data from time points at which both the electrocardiogram data and the concentration data were available; the time-matched mean change from baseline QTcF was analyzed for correlation with the serum concentration of ramucirumab, using linear mixed models (Fig. 2). The slope of the model in this analysis was not statistically significantly different from zero. The estimated value of the slope was −0.00207, showing a small negative association between concentration of ramucirumab and the change from baseline in QTcF. Mean ramucirumab concentration-time profiles at cycles 1 and 3 were very similar, with slightly higher mean concentrations for cycle 3, reflecting a small amount of accumulation following 3 doses of ramucirumab.

Safety analyses included all treated patients (n = 66). Most treatment-emergent adverse events (TEAEs) in patients receiving ramucirumab were consistent with the known adverse event (AE) profile. Sixty-five patients experienced at least one TEAE, regardless of causality. Forty-two patients (63.6%) experienced at least one TEAE considered related to ramucirumab; the most common were headache (16.7%; 1.5% grade 3), nausea (15.2%), hypertension (10.6%; 4.5% grade 3), and vomiting (10.6%).

This phase II study demonstrated that ramucirumab did not produce a prolongation of QTcF. The 90% two-sided (95% one-sided) upper confidence limit did not exceed 10 milliseconds. This conclusion is also supported by concentration-QTcF modeling, which showed a visible but not significant negative association between concentration of ramucirumab and change from baseline in QTcF.

Trial Information	
Disease	Advanced Cancer/Solid Tumor Only
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	No designated number of regimens
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	To determine the effect of ramucirumab on the QT/QTc interval in patients with advanced cancer.
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	Patients who experienced ongoing clinical benefit may have continued to receive study therapy until there was documented progression of disease, intolerable toxicity, or withdrawal of consent. A follow-up evaluation was conducted including adverse event assessment. Routine monitoring, including radiographic evaluation of disease, was continued as necessary to confirm patient eligibility to continue in the trial.
Investigator's Analysis	Active and should be pursued further.

Drug Information

Drug 1	
Generic/Working name	Ramucirumab
Trade name	Cyramza
Company name	Eli Lilly and Company
Drug type	Antibody
Drug class	Angiogenesis - VEGF
Dose	10 mg/kg
Route	IV
Schedule of Administration	Every 21 days

Patient Characteristics

Number of patients, male	37
Number of patients, female	31
Age	Median (range): 63.5 years (19–86 years)
Performance Status: ECOG	0 — 17 1 — 46 2 — 3 Unknown — 2

Primary Assessment Method

Control Arm: Total Patient Population	
Number of patients screened	76
Number of patients enrolled	68
Number of patients evaluable for toxicity	66
Number of patients evaluated for efficacy	0

Adverse Events

Adverse Events at All Dose Levels, All Cycles

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue	68%	15%	14%	3%	0%	0%	32%
Nausea	67%	17%	14%	2%	0%	0%	33%
Dyspnea	69%	12%	14%	5%	0%	0%	31%
Abdominal pain	72%	9%	11%	8%	0%	0%	28%
Headache	72%	18%	5%	5%	0%	0%	28%
Diarrhea	76%	21%	3%	0%	0%	0%	24%
Vomiting	77%	9%	11%	3%	0%	0%	23%
Dehydration	81%	2%	11%	6%	0%	0%	19%
Constipation	84%	8%	6%	2%	0%	0%	16%
Dizziness	84%	14%	2%	0%	0%	0%	16%
Hypertension	85%	0%	9%	6%	0%	0%	15%
Fever	85%	12%	3%	0%	0%	0%	15%
Anorexia	67%	17%	14%	2%	0%	0%	33%
Edema limbs	81%	12%	5%	2%	0%	0%	19%
Cough	79%	18%	3%	0%	0%	0%	21%

Adverse Events Legend
Treatment-emergent adverse events reported for ≥10 patients regardless of causality (safety population, $n = 66$)
*No Change from Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Gastrointestinal hemorrhage	2	Possible
Infusion-related reaction	2	Probable
Hepatic failure	4	Possible
Dehydration	3	Unrelated
Pulmonary embolism	3	Unrelated
Deep vein thrombosis	3	Possible
Hypertension	2	Definite

Serious Adverse Events Legend
Serious adverse events considered related to study drug (safety population, $n = 66$)

Pharmacokinetics/Pharmacodynamics, cycle 1

n	61
C_{max}	485 μg/mL
AUC	67,400 μg $\times$ h/mL
Half-life	148 hours
Volume of distribution	2,290 mL
Clearance	11.6 mL/h

Pharmacokinetics/Pharmacodynamics, cycle 3

n	47
C_{max}	571 μg/mL
AUC	69,900 μg $\times$ h/mL
Half-life	189 hours
Volume of distribution	2,560 mL
Clearance	10.7 mL/h

Note: Please refer to Table 2 for summary of major pharmacokinetic parameters.

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Correlative Endpoints Met
Investigator's Assessment	Active and should be pursued further

Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2) contribute to angiogenesis, which plays a role in tumor growth and metastasis. Ramucirumab is a recombinant human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to VEGFR-2, inhibiting VEGF-mediated signaling [1]. The International Conference on Harmonization E14 guidance specifies that all drugs should undergo a formal clinical evaluation early in clinical development to assess the potential for QT/QTc prolongation [2]. The exact timing of QT/QTc prolongation following ramucirumab administration, if existent, was not known before initiating this study. This was a multicenter, open-label, single active-arm, phase II study to determine if treatment with ramucirumab (10 mg/kg) caused prolongation of the QT/QTc interval in patients with advanced cancer.

A total of 68 patients (37 men and 31 women) between the ages of 19 and 86 years with advanced cancer of solid-tumor origin enrolled in this study (Table 1). Patients with an implantable pacemaker or automatic implantable cardioverter defibrillator were not eligible for this study. Patients with a congenital long QT syndrome; a prolonged QTc interval on pretreatment electrocardiogram (ECG) of longer than 450 milliseconds, using both Bazett's (QTcB) and Fridericia's (QTcF) QT correction; a clinically relevant abnormality on the ECG that prevented an accurate measurement of the QT interval; or using a medication that was known to prolong the ECG QT interval were excluded. Patients with a history of risk factors for ventricular tachycardia or torsades de pointes, fainting, unexplained loss of consciousness, or convulsions were also excluded from participation. Patients received 10 mg/kg of ramucirumab every 21 days. Sixty-six patients received at least one dose of study drug and comprised the safety population. Fifty-one patients received at least 9 weeks of therapy (the complete QTc evaluation period). Patients who experienced ongoing clinical benefit may have continued to receive study therapy until there was documented progression of disease, intolerable toxicity, or withdrawal of consent. A follow-up evaluation was conducted, including adverse event assessment. Routine monitoring, including radiographic evaluation of disease, was continued as necessary to confirm patient eligibility to continue in the trial.

Serial blood samples were taken from patients following the initial infusion (cycle 1) and the third infusion (cycle 3).

Ramucirumab serum concentrations were measured by a bridging enzyme-linked immunosorbent assay, as previously described [3]. Profiles were very similar, with slightly higher mean concentrations for cycle 3, reflecting the small amount of accumulation following 3 doses of ramucirumab (Fig. 3). Major pharmacokinetic parameters following intravenous infusion of 10 mg/kg ramucirumab in cycles 1 and 3 are summarized in Table 2.

The QTcF change from baseline was the primary endpoint for this study. QT/QTc prolongation was determined with triplicate ECGs at multiple time points after the initial dose, and at steady state at a therapeutic dose level. The first 16 patients enrolled in the study received 1 dose of moxifloxacin (400 mg orally), an antibiotic associated with mild QTc prolongation, 1 week before receiving ramucirumab treatment, to demonstrate assay sensitivity. The mean moxifloxacin-induced QTcF prolongation exceeded 10 milliseconds and the lower 90% confidence intervals (CIs) exceeded 5 milliseconds at 8 postdose time points (Fig. 4).

Pretreatment with diphenhydramine (25–50 mg) was required before the administration of ramucirumab for cycles 1–4. The 90% CI of change from time-matched baseline (day −1) for QTcF at cycle 3 is shown in Figure 1. The diphenhydramine infusion occurred between 00:00 and 00:15, and the ramucirumab infusion occurred between 00:15 and 1:15. Using the time-matched QTcF values from day −1 as the baseline, repeated-measures analysis of covariance showed that the upper limit of the two-sided 90% CI of the least square means of change from baseline for QTcF values was less than 10 milliseconds at all study time points in cycle 3. Categorical outlier analysis for cycle 3 showed 2 patients (3 time points) with a QTcF value of longer than 450 milliseconds and no longer than 480 milliseconds. No patient had a QTc value of longer than 480 milliseconds or QT, QTcB, or QTcF values of 500 milliseconds or longer in this population.

Time-matched concentration change from baseline in QTcF analysis demonstrated the slope of the model in this analysis was not statistically significantly different from zero. The estimated value of the slope was −0.00207, showing a small negative association between ramucirumab concentration and the change from baseline in QTcF (Fig. 2). The estimated value of mean change in QTcF was 2.8 milliseconds (90% CI: −3.8 to 9.5) at a geometric mean maximum serum concentration (C_{max}) of 571 μg/mL (range: 272–1820 μg/mL) during cycle 3.

Sixty-five patients experienced at least one treatment-emergent adverse event (TEAE), regardless of causality. The TEAEs, regardless of causality, reported for at least 10% of patients are presented in Table 3. Forty-two patients (63.6%) had at least 1 TEAE that was considered related to ramucirumab. The most common grade 3 TEAE considered related to ramucirumab was hypertension ($n = 3$; 4.5%). Eleven patients (16.7%) experienced at least 1 serious adverse event (SAE) considered related to ramucirumab; 8 (12.1%) were grade ≥3 (Table 4). Thirty-two patients (48.5%) experienced at least 1 SAE regardless of causality. Sixteen patients died during the study. Eleven patients died within 30 days of the last dose of ramucirumab; 5 patients died more than 30 days after the last dose of ramucirumab. Disease progression was indicated as the primary cause of all of these deaths.

Ramucirumab is approved by the U.S. Food and Drug Administration for metastatic gastric cancer (REGARD and RAINBOW trials), non-small cell lung cancer (REVEL trial), and metastatic colorectal cancer (RAISE trial) [4–7]. Some VEGF inhibitors can prolong the QTc interval. Vandetanib, which inhibits VEGFR and epidermal growth factor receptor signaling, significantly prolonged QTc interval [8]. An evaluation of sunitinib, a multitargeted tyrosine kinase inhibitor, demonstrated a dose-dependent effect on QT interval [9]. Based on the overall assessment, this study demonstrated that ramucirumab at a dose of 10 mg/kg administered every 21 days for 3 cycles did not produce a prolongation of QTcF. This was also supported by time-matched concentration change from baseline in QTcF analysis, which showed a visible but not significant negative association between ramucirumab concentration and change from baseline in QTcF.

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

References

1. Spratlin JL, Cohen RB, Eadens M et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28:780–787.

2. U.S. Department of Health and Human Services. Guidance for industry: E14: clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073153.pdf. Accessed September 22, 2015.

3. Chiorean EG, Hurwitz HI, Cohen RB et al. Phase I study of every 2- or 3-week dosing of ramucirumab, a human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2 in patients with advanced solid tumors. Ann Oncol 2015;26:1230–1237.

4. Fuchs CS, Tomasek J, Yong CJ et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31–39.

5. Wilke H, Muro K, Van Cutsem E et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–1235.

6. Garon EB, Ciuleanu TE, Arrieta O et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): A multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665–673.

7. Tabernero J, Yoshino T, Cohn AL et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): A randomised, double-blind, multicentre, phase 3 study [published correction appears in Lancet Oncol 2015;16:e262]. Lancet Oncol 2015;16:499–508.

8. Liu Y, Liu Y, Fan ZW et al. Meta-analysis of the risks of hypertension and QTc prolongation in patients with advanced non-small cell lung cancer who were receiving vandetanib. Eur J Clin Pharmacol 2015;71:541–547.

9. Bello CL, Mulay M, Huang X et al. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: Pharmacokinetic-pharmacodynamic evaluation of sunitinib. Clin Cancer Res 2009;15:7045–7052.

10. U.S. Department of Health and Human Services. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40. Accessed February 21, 2016.

Figures and Tables

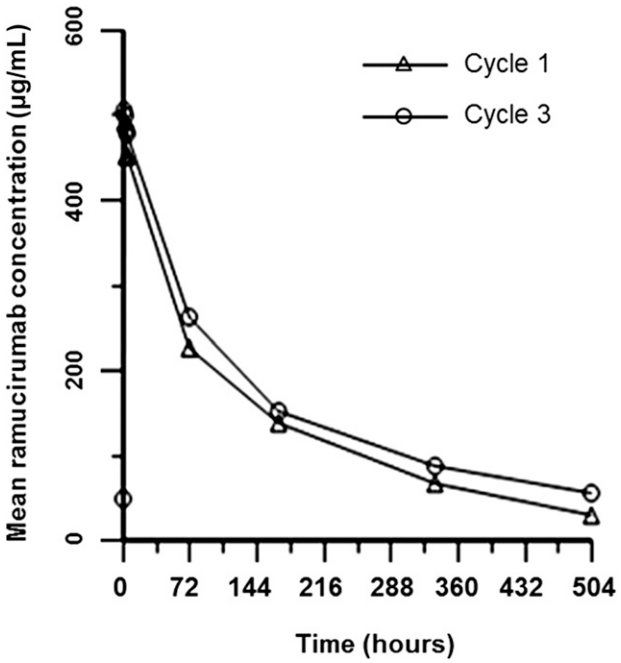

Figure 3. Mean ramucirumab concentration-time profiles following the first (cycle 1) or third (cycle 3) dose of 10 mg/kg ramucirumab.

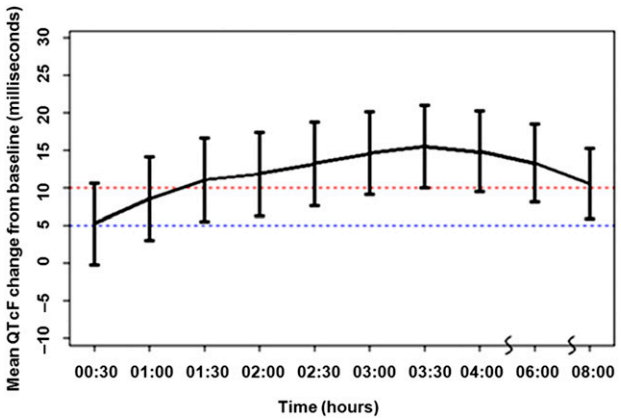

Figure 4. Graph showing 90% confidence interval of change from baseline for QTcF after moxifloxacin treatment. Red dotted line and blue dotted line indicate 10- and 5-millisecond time points, respectively. The scale of the *x*-axis (time) is non-uniform following the 4-hour measurement.

Abbreviation: QTcF, QT corrected by Fridericia's formula.

Table 1. Baseline patient characteristics (enrolled population, $n = 68$)

Characteristic	*n* (%)
Sex	
Male	37 (54.4)
Female	31 (45.6)
Age, years	
Median (range)	63.5 (19–86)
18 to <65	41 (60.3)
≥65	27 (39.7)
Race	
White	62 (91.2)
Black	5 (7.4)
Asian	1 (1.5)
Ethnicity	
Hispanic or Latino	4 (5.9)
Non-Hispanic or Latino	64 (94.1)
ECOG PS	
0	17 (25.0)
1	46 (67.6)
≥2	3 (4.4)
Missing	2 (2.9)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Summary of ramucirumab pharmacokinetic parameters following administration of 10 mg/kg ramucirumab

	Geometric mean (geometric CV%), 10 mg/kg every 3 weeks	
PK parameter	**Cycle 1: first dose ($N_{PK} = 61$)[a]**	**Cycle 3: third dose ($N_{PK} = 47$)[b]**
C_{max} or $C_{max,ss}$ (μg/mL)	485 (43)	571[b] (41)
$t_{1/2}$ (hours)	148[a] (36)	189[b] (33)
$AUC_{(0-\infty)}$ or $AUC_{\tau,ss}$ (μg × h/mL)	67,400[a] (38)	69,900[b] (41)
CL or CL_{ss} (mL/h)	11.6[a] (35)	10.7[b] (41)
V_{ss} (mL)	2,290[a] (36)	2,560[b] (46)
$R_{A,Cmax}$		1.12[b] (57)
$R_{A,AUC}$		1.11[b] (38)

[a]nPK = 59 for $t_{1/2}$; nPK = 58 for $AUC_{(0-\infty)}$, CL, and V_{ss}.
[b]nPK = 45 for $C_{max,ss}$, and $R_{A,Cmax}$; nPK = 38 for $AUC_{t,ss}$, CL_{ss}, and $R_{A,AUC}$; nPK = 37 for $t_{1/2}$; nPK = 34 for V_{ss}.
Abbreviations: AUC, area under the concentration-time curve; $AUC_{(0-\infty)}$, AUC from time 0 extrapolated to infinity; $AUC_{\tau,ss}$, AUC over the dosing interval at steady state; CL, total body clearance of drug calculated after intravenous administration; CL_{ss}, clearance at steady state; C_{max}, maximum observed serum concentration; CV%, percent coefficient of variation; N_{PK}, number of subjects used in pharmacokinetic analysis; nPK, number of pharmacokinetic observations; PK, pharmacokinetic; $R_{A,AUC}$, accumulation ratio based on AUC; $R_{A,Cmax}$, accumulation ratio based on C_{max}; $t_{1/2}$, apparent terminal elimination half-life; V_{ss}, volume of distribution at steady state.

Table 3. Treatment-emergent adverse events reported for at least 10% of patients regardless of causality (safety population, $n = 66$)

Preferred term	Any grade,[a] *n* (%)	Grade ≥3,[a] *n* (%)
Decreased appetite	21 (31.8)	1 (1.5)
Fatigue	21 (31.8)	2 (3.0)
Nausea	21 (31.8)	1 (1.5)
Dyspnea	20 (30.3)	3 (4.5)
Abdominal pain	18 (27.3)	5 (7.6)
Headache	18 (27.3)	3 (4.5)
Diarrhea	16 (24.2)	0 (0.0)
Vomiting	15 (22.7)	2 (3.0)
Cough	14 (21.2)	0 (0.0)
Dehydration	12 (18.2)	4 (6.1)
Edema peripheral	12 (18.2)	1 (1.5)
Constipation	10 (15.2)	1 (1.5)
Dizziness	10 (15.2)	0 (0.0)
Hypertension	10 (15.2)	4 (6.1)
Pyrexia	10 (15.2)	0 (0.0)
Chills	9 (13.6)	0 (0.0)
Abnormal weight loss	8 (12.1)	1 (1.5)
Arthralgia	7 (10.6)	0 (0.0)
Asthenia	7 (10.6)	0 (0.0)
Depression	7 (10.6)	0 (0.0)

[a]National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 was used for adverse event grading [10].

Table 4. Serious adverse events considered related to study drug (safety population, $n = 66$)

Serious adverse event	Any grade, *n* (%)	Grade ≥3, *n* (%)
Patients with any adverse event	11 (16.7)	8 (12.1)
Gastrointestinal hemorrhage	1 (1.5)	0 (0.0)
Infusion-related reaction	1 (1.5)	0 (0.0)
Hepatic failure	1 (1.5)	1 (1.5)
Dehydration	1 (1.5)	1 (1.5)
Pulmonary embolism	1 (1.5)	1 (1.5)
Deep vein thrombosis	2 (3.0)	2 (3.0)
Hypertension	1 (1.5)	0 (0.0)