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Phase 1 study of narnatumab, an anti-RON receptor monoclonal antibody, in patients with advanced solid tumors

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Abstract

Purpose—Macrophage-stimulating 1-receptor (RON) is expressed on macrophages, epithelial cells, and a variety of tumors. Narnatumab (IMC-RON8; LY3012219) is a neutralizing monoclonal antibody that blocks RON binding to its ligand, macrophage-stimulating protein (MSP). This study assessed safety, maximum tolerated dose (MTD), pharmacokinetics, pharmacodynamics, and efficacy of narnatumab in patients with advanced solid tumors.

Methods—Narnatumab was administered intravenously weekly at 5, 10, 15, or 20 mg/kg or every 2 weeks at 15, 20, 30, or 40 mg/kg in 4-week cycles.

Results—Thirty-nine patients were treated, and 1 dose-limiting toxicity (DLT) (grade 3 hyponatremia, 5 mg/kg) was reported. The most common narnatumab-related adverse events (AEs) were fatigue (20.5%) and decreased appetite, diarrhea, nausea, and vomiting (10.3% each). Except for 2 treatment-related grade 3 AEs (hyponatremia, hypokalemia), all treatment-related AEs were grade 1 or 2. Narnatumab had a short half-life (<7 days). After Cycle 2, no patients had

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Compliance with Ethical Standards

Conflict of Interest Disclosures

P. M. LoRusso, M. Gounder, S. I. Jalal, and E. G. Chiorean disclosed no potential conflicts of interest. V. André, S. R. P. Kambhampati, N. Loizos, T. R. Holzer, A. Nasir, and J. Kauh are employees of Eli Lilly and Company. J. Cosaert and J. Hall were employed by Eli Lilly and Company during the conduct of the study but are now employed by Sotio (Prague, Czech Republic) and Boehringer Ingelheim (Ridgefield, CT), respectively.

Ethical Approval

This study was conducted in accordance with applicable laws and regulations, Good Clinical Practices, and the Declaration of Helsinki and with approval by the local Institutional Review Boards of participating institutions.

Informed Consent

Patients provided written informed consent before participating in the study.

Supplementary Materials

The following supplementary materials give readers additional information about the work.

concentrations above 140 µg/mL (concentration that demonstrated antitumor activity in animal models), except for 1 patient receiving 30 mg/kg biweekly. Eleven patients had a best response of stable disease, ranging from 6 weeks to 11 months. Despite only 1 DLT, due to suboptimal drug exposure, the dose was not escalated beyond 40 mg/kg biweekly. This decision was based on published data reporting that mRNA splice variants of RON are highly prevalent in tumors, accumulate in cytoplasm, and are not accessible by large-molecule monoclonal antibodies.

Conclusions;—Narnatumab was well tolerated and showed limited antitumor activity with this dosing regimen.

Keywords

Narnatumab; IMC-RON8; Macrophage-stimulating protein receptor; RON; Solid tumors; Phase 1

Introduction

Macrophage-stimulating 1-receptor (RON) is a member of the c-Met receptor tyrosine kinase family. As is the case for its better known family member, c-Met, several lines of evidence suggest a role for RON in cancer [1]. First, it is highly expressed in several epithelial tumors such as colon [2], lung [3], breast [4, 5], stomach [6], ovary [7], pancreas [8], bladder [9], liver [10], and kidney [11, 12]. RON is also coexpressed and can cross-talk with other growth factor receptors such as c-Met and epidermal growth factor receptor (EGFR) [5, 9, 13, 14]. Recent mRNA analysis has shown RON splice variants RON 165 and RON 155 (but not RON 160) to be constitutively active in the cytoplasm and RON 165 expression to be highly prevalent in diverse tumor types [15]. Second, macrophage-stimulating protein (MSP) and RON have been shown to cause the migration and invasion of cancer cells [2, 4]. Third, RON has been shown to have oncogenic potential in cultured cell lines [16, 17, 18] and in transgenic mice [19, 20, 21], where overexpression of RON led to a profound increase in proliferation and tumorigenesis, respectively, and to play a central role in suppressing Th1-mediated inflammation [22].

In addition to being expressed on epithelial tumor cells, RON is also expressed on tissue-resident macrophages including Kupffer cells, mesangial cells, Langerhans cells, microglia, alveolar macrophages, and peritoneal macrophages, but not on inflammatory M1 macrophages. Tumor-associated M2 macrophages (TAMs), which originate from the tissue-resident macrophage population, represent a substantial portion of a growing tumor and are associated with poor prognosis in many human tumors [23, 24, 25]. Preclinical experiments in control and RON^{-/-} animal models have demonstrated that RON expression in TAMs of the control animals promotes tumor growth, while in RON^{-/-} animals tumor growth is significantly decreased [22].

In light of the foregoing observations, inhibiting RON with an antibody is thought to be a viable therapeutic strategy for cancer. Narnatumab (IMC-RON8; LY3012219), a neutralizing monoclonal antibody to human RON, was generated and examined in preclinical studies for its potential as a novel cancer treatment (see Supplementary Materials for details). The recombinant human monoclonal antibody narnatumab has a dissociation constant (K_d) of 32 pM and blocks the RON ligand, MSP, from binding to RON. In addition to blocking ligand-

induced receptor phosphorylation, narnatutumab inhibits phosphorylation of downstream signaling molecules in RON-expressing tumor cells and in a RON-transfected cell line. In vitro studies demonstrated that narnatutumab inhibits MSP-induced migration of human lung and breast cancer cell lines. In addition, narnatutumab inhibits the MSP-induced mitogenic response of a pancreatic cancer cell line. In vivo antitumor activity of narnatutumab was demonstrated in colon, lung, pancreas, and breast xenograft tumor models in athymic mice. In pharmacokinetic (PK)/pharmacodynamic (PD) mouse studies, narnatutumab had a terminal half-life ($t_{1/2}$) of 5.2 days and achieved antitumor effects at a steady-state plasma trough level of approximately 140 $\mu\text{g/mL}$. To establish the potential benefits of combining narnatutumab with cytotoxic therapy, narnatutumab was combined with docetaxel and was shown to have additive antitumor effects in a human breast xenograft model. Together, these preclinical results demonstrate that narnatutumab possesses antitumor activity and suggest that it may be effective as a single agent or in combination with cytotoxic therapy for the treatment of cancer.

Here, we report the results of a phase 1 trial of narnatutumab in patients with advanced solid tumors.

Patients and Methods

Patient Selection

Eligible patients were ≥ 18 years of age; had advanced solid tumors (measurable and/or nonmeasurable) refractory to standard therapies or for which no standard therapy was available; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; and had not received cancer-directed therapy within 28 days before the first dose of study drug. Excluded were patients with known sensitivity to monoclonal antibodies, patients previously treated with agents targeting RON ligand or receptor (within 6 weeks before the first study dose), and patients with brain or leptomeningeal metastases.

Study Design

This was a phase 1, multicenter, open-label, dose-escalation study conducted at 3 centers in the U.S. The primary objective of the study was to establish the safety profile and maximum tolerated dose (MTD) of narnatutumab. Secondary objectives included assessments of the PK, PD, immunogenicity, and antitumor activity of narnatutumab.

The planned enrollment was approximately 40 patients.

This study was conducted in accordance with applicable laws and regulations, Good Clinical Practices, and the Declaration of Helsinki and with approval by the local Institutional Review Boards of participating institutions. Patients provided written informed consent before participating in the study. The ClinicalTrials.gov identifier for this study is NCT01119456.

Treatment Cohorts

Narnatutumab was administered intravenously once weekly (cohorts 1–3) or biweekly (cohorts 4–7). In cohorts 1–3, the weekly doses were 5, 10, and 15 mg/kg, respectively. In

cohorts 4–7, the biweekly doses were 15, 20, 30, and 40 mg/kg. In cohort 8, the weekly dose was 20 mg/kg.

A standard 3+3 design was utilized. Patients who completed 1 cycle or discontinued due to drug-related toxicities were considered eligible for toxicity evaluation. During the dose-limiting toxicity (DLT) assessment period (6 weeks for cohorts 1–3 and 4 weeks for remaining cohorts), if a DLT was observed the cohort was expanded per the standard 3+3 design to a total of 6 patients. No inpatient dose escalation was permitted.

Safety Assessments

All patients who received at least 1 dose of narnatumab were evaluated for safety and toxicity. Safety measures included adverse events (AEs), DLTs, dose adjustments, clinical laboratory test results, vital signs, and electrocardiograms. All AEs were classified and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.02).

A DLT was defined as any narnatumab-related grade 4 neutropenia lasting >7 days; any grade 3 or 4 neutropenia complicated by fever $\geq 38.5^{\circ}\text{C}$ or infection, grade 4 thrombocytopenia, or grade 3 thrombocytopenia complicated by hemorrhage; or any grade 3 or 4 nonhematologic toxicity (excluding alopecia, fatigue, anorexia, nausea, and vomiting that was controlled with antiemetics). The MTD was defined as the highest dose at which not more than 1 patient experienced a DLT.

Pharmacokinetic Assessments

Serial serum samples for PK analysis were collected. For patients on the weekly 5-, 10-, or 15-mg/kg dosing regimens, these samples were collected up to 168 hours after the end of infusion following the first dose and up to 336 hours following the fourth dose. For patients on the weekly 20 mg/kg dosing regimen, the samples were collected up to 168 hours. For patients on the biweekly regimen, the samples were collected up to 336 hours after the end of infusion following the first dose and fifth dose.

Samples collected during the study were analyzed for narnatumab by using a validated enzyme-linked immunosorbent assay method at ICON Development Solutions, LLC (Whitesboro, NY). Pharmacokinetic parameters for narnatumab were calculated by standard noncompartmental analysis (NCA) using Phoenix WinNonlin 6.3 (Pharsight Corporation).

Immunohistochemical Assessments

Archival tumor tissue samples were collected at baseline, if available, and stained for assessment of RON protein expression in tumor cells by immunohistochemistry (IHC), using a rabbit monoclonal anti-RON antibody (EP1132Y, Abcam, ab52927) directed against the extracellular domain of RON in a CLIA-certified laboratory. The primary antibody was used at a concentration of 28 $\mu\text{g/mL}$, antigen retrieval was performed in citrate buffer (pH 6.2), and slides were stained on a Leica Bond-III automated stainer. Each stained slide was blindly interpreted without any knowledge of clinicopathologic patient data or dosing information and manually scored by an experienced American Board-certified anatomic

pathologist with expertise in immunohistopathology. Positive RON protein staining appeared as unequivocal, crisp, brown staining in tumor cell membranes and/or cytoplasm against an acceptable/clean stromal background. A well-established semiquantitative IHC scoring scheme (H-score), based on the levels of intensity of combined tumor cell membrane and cytoplasmic staining [0 (none), 1+ (weak), 2+ (intermediate), 3+ (intense)] and the proportion of stained tumor cells at each level of staining intensity was used. For each stained section, an H-score was then calculated as the weighted sum of % 1+ cells, twice the % 2+ cells, and three times the % 3+ cells (range, 0–300).

Pharmacodynamic Assessments

Potential treatment-induced effects of narnatumab on cytokine expression were assessed against an interleukin panel for Th1/Th2 plus IL-6. The resulting data were plotted against time.

Efficacy Assessments

Tumor response was evaluated every 6 weeks (cohorts 1–3) or every 8 weeks (cohorts 4–8), according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Change in tumor size was defined as the percent change in tumor size from baseline. Progression-free survival (PFS), overall survival (OS), and best response were determined. Best overall response was summarized, and the clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD]) was determined.

Statistical Analysis

Continuous data were summarized by patient numbers, mean, median, standard deviation, minimum, and maximum as applicable. Categorical data were summarized by patient numbers, frequency, and percentages. Missing data were not imputed.

All patients who received at least 1 dose of narnatumab were referred to as the All Treated Patients Population. Safety and efficacy were analyzed overall and by cohort using this population.

PFS was defined as the time from the date of study enrollment to the date of progressive disease or death due to any cause, whichever occurred first. OS was defined as the time from the date of study enrollment to the date of death from any cause. For patients not known to have died as of the data cutoff date, OS time was censored at the last contact date on which the patient was known to be alive prior to the cutoff date. Best response was determined from a sequence of responses assessed. The 95% confidence interval (CI) for the clinical benefit rate was calculated using the Clopper-Pearson exact method.

Results

Patients

This study was conducted from May 2010 to November 2013. Overall, 39 patients were treated and received at least 1 dose of study drug. See Table 1 for patient baseline

characteristics (including demographics and prior therapies) and Fig. 1 for patient disposition.

Among all cohorts, the median number of cycles received was 2 (range, 1–12). There were no dose reductions or modifications in the study. The most common reason for discontinuation was progressive disease (87.2%, 34/39 patients).

Safety and Tolerability

Only 1 DLT was observed during the study (grade 3 hyponatremia in cohort 1 that was considered possibly related to study treatment). Therefore, the MTD was not determined.

Overall, 37 patients (94.9%) experienced at least 1 AE. The most common treatment-emergent AEs (TEAEs) were fatigue (46.2%), decreased appetite (38.5%), nausea (28.2%), vomiting (28.2%), and cough (25.6%). Overall, 23 patients (59.0%) experienced an AE of grade 3. The most common grade 3 TEAE was hyperglycemia (10.3%, all grade 3).

Overall, 19 patients (48.7%) experienced at least 1 treatment-related TEAE (see Table 2); fatigue was the most common (8 patients, 20.5%). However, with the exception of 2 grade 3 treatment-related AEs (hyponatremia in cohort 1 and hypokalemia in cohort 6), all treatment-related AEs were grade 1 or 2. No clinically relevant changes in laboratory values (other than the grade 3 AEs of hyponatremia and hypokalemia noted above), electrocardiogram parameters, or vital sign parameters were noted during this study.

Twelve deaths were reported during this study, and six of the reported deaths occurred within 30 days after the last dose of study drug was administered. The primary cause of death in 11 cases was progressive disease. The remaining patient died while in hospice, but no cause of death was cited.

Sixteen patients experienced a total of 29 serious adverse events (SAEs). The only SAE that was considered related to study drug was the event of grade 3 hyponatremia (cohort 1) that was declared a DLT, as discussed above.

One patient (cohort 5) discontinued study treatment due to an AE of disease-related grade 2 ascites that was considered serious and required hospitalization, study drug discontinuation, and treatment. In addition, another patient (cohort 8) discontinued study treatment after withdrawing consent. A few days before discontinuation, this patient experienced a grade 3 AE of anemia that was considered serious but unrelated to study drug by the investigator.

As is the case for other monoclonal antibodies, infusion-related/hypersensitivity reactions may occur during or after narnatumab administration. In this study, individual AEs of grade 2 infusion-related reaction (cohort 1, definitely related) and grade 1 hypersensitivity (cohort 2, possibly related) were reported. Both events were considered nonserious and required no change in dose level before resolving.

Since narnatumab is a modulator of macrophage function, blood monocyte levels were monitored as part of clinical laboratory evaluations. This monitoring revealed one grade 2

AE of leukocytosis that was considered unrelated to the study drug, but no grade 3 AEs of leukocytosis or grade 3 AEs associated with lymphocytes, neutrophils, or monocytes.

Pharmacokinetics

Narnatumab concentrations exhibited a multiphasic decline (Fig. 2). The PK parameters of narnatumab for weekly and biweekly regimens are presented in Table 3. After multiple doses, narnatumab had a geometric mean clearance of approximately 0.02–0.05 L/hr and a short $t_{1/2}$ (<7 days). The PK of narnatumab may not have been adequately characterized by noncompartmental methods because of the relatively short PK sampling time. Therefore, these PK parameters should be interpreted with caution.

Of the 39 patients treated in this study, 1 patient receiving the 30 mg/kg biweekly regimen had trough concentrations following the previous infusion that exceeded 140 µg/mL (the target trough concentration that demonstrated antitumor activity in a preclinical animal model).

RON Immunohistochemistry

Combined immunohistochemical expression of RON protein in tumor cell membrane and cytoplasm was scored in a total of 26 archived tumor tissue samples. The resulting median H-score was 92 (range, 0–200). Across all dose groups, significant (although variable) levels of RON protein expression were found in the majority of patients in whom pretreatment tumor tissue specimens were available for RON IHC. Since post-dose tumor tissue samples were not available, the level of post-treatment change in RON protein expression induced by narnatumab could not be characterized.

Pharmacodynamics

Assessment of potential treatment-induced effects on cytokine expression against an interleukin panel for Th1/Th2 plus IL-6 revealed no changes over time or across doses for all analytes examined.

Efficacy

Fig. 3 displays the minimum percent change in tumor size from baseline at the time of best response. Of the 39 patients evaluated, 29 (74.4%) had measurable disease. Most of the patients had an increase in tumor burden, but 5 patients had a slight reduction in tumor size that did not qualify for a tumor response according to the RECIST criteria. The maximum reduction in tumor size (12%) was observed in a patient with a rectal adenocarcinoma.

There were no CRs or PRs in this study. Among 39 evaluable patients, 11 patients (28.2%) had a best response of SD. This resulted in a clinical benefit rate (CR+PR+SD) of 28.2% (95% CI, 15.0%, 44.9%).

In the subset of 11 patients whose best response was SD, PFS ranged from 6 weeks to 48 weeks (approximately 11 months). Six patients in this subset had a PFS of >3 months, ranging from 13 weeks (approximately 3 months) to 48 weeks (approximately 11 months).

Cancer types in these 6 patients included colorectal (n = 3), breast (n = 1), lung (n = 1), and hepatocellular (n = 1).

A total of 21 patients (53.9%) had a best response of progressive disease. In each case, progression occurred within the first 2 cycles.

Discussion

In this dose-finding phase 1 study of narnatumab, an anti-RON receptor monoclonal antibody, 39 patients with advanced refractory solid tumors were treated on a weekly or biweekly schedule. Overall, narnatumab was safe and well tolerated. Less than half of patients (49%) experienced a treatment-related AE. Only 1 DLT was observed during the study (grade 3 hyponatremia), and no MTD was determined.

All 12 deaths reported in the study were deemed unrelated to study treatment. SAEs were reported in 41% of patients, but only 1 of those SAEs (the grade 3 hyponatremia in cohort 1) was considered possibly treatment related.

Narnatumab did not appear to affect macrophage circulating blood cells: only 1 blood monocyte-related event of grade 2 (i.e., non-treatment-related grade 2 leukocytosis) was observed during the study.

Following 5–20 mg/kg weekly or 15–40 mg/kg biweekly doses after Cycle 2, only 1 patient (in the 30 mg/kg biweekly dosing cohort) had a trough concentration that exceeded the target trough concentration of 140 µg/mL (i.e., the trough concentration at which narnatumab demonstrated antitumor activity in preclinical animal models).

Despite the occurrence of only 1 DLT in this study, given the suboptimal drug exposure levels, the sponsor decided not to proceed with further dose escalation beyond 40 mg/kg biweekly. This decision was based on published data showing that mRNA splice variants of RON are highly prevalent in tumors [26] and accumulate in the cytoplasm [27] and are not accessible by large molecule monoclonal antibodies but are better targeted with small molecule inhibitors that penetrate the cell membrane. One such agent, merestinib (LY2801653), has been shown to inhibit RON at nanomolar concentrations [28].

In 26 archived tumor tissue samples, RON was shown by IHC to be expressed in the majority of samples tested. Assessment of potential treatment-induced effects on cytokine expression against an interleukin panel for Th1/Th2 plus IL-6 revealed no changes over time or across doses for all analytes examined.

Narnatumab did not show any clinically significant antitumor activity, producing no responses. However, 11 patients had SD, resulting in a clinical benefit rate (CR+PR+SD) of approximately 28%. In the patients with SD, the PFS times ranged from 6 weeks to approximately 11 months. Stable disease for >3 months was noted in 6 patients whose primary tumor types included colorectal (n = 3), breast (n = 1), lung (n = 1), and hepatocellular (n = 1). The presence of significant (though variable) levels of RON protein expression in the available pretreatment tumor tissue samples points toward the potential

relevance of RON IHC for assessing both the pharmacodynamic effect of narnatumab and the value of tumor RON protein expression levels in predicting which patients may receive clinical benefit from narnatumab therapy.

Although narnatumab was well tolerated, its limited efficacy as a single agent in this study does not warrant further investigation in the monotherapy setting with the current dosing schedule.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Patient disposition.

Abbreviations: N = number of patients providing consent; n = number of patients; q2w = once biweekly; qw = once weekly.

^aReasons for patients not treated: symptomatic deterioration: 2 patients, adverse event: 1 patient.

^bMaximum number of cycles received per patient: 1 (16 patients, 41.0%), 2 (15 patients, 38.5%), 3 (3 patients, 7.7%), 4 (3 patients, 7.7%), 8 (1 patient, 2.6%), 12 (1 patient, 2.6%).

^cCohort 1 (5 mg/kg qw) 7 patients; Cohort 2 (10 mg/kg qw) 3 patients; Cohort 3 (15 mg/kg qw) 3 patients; Cohort 4 (15 mg/kg q2w) 4 patients; Cohort 5 (20 mg/kg q2w) 3 patients; Cohort 6 (30 mg/kg q2w) 3 patients; Cohort 7 (40 mg/kg q2w) 3 patients; Cohort 8 (20 mg/kg qw) 13 patients.

Figure 2.

Mean serum concentration-time profiles of narnatumab after single intravenous infusion (first administration) and multiple intravenous infusions (fourth administration on weekly [qw] schedule and fifth administration on biweekly [q2w] schedule) over 1.0–2.5 hours. NOTE: Following multiple infusions, the plot for 15 mg/kg q2w represents data from 1 patient and the plot for 40 mg/kg q2w represents mean of data from 2 patients.

Figure 3.
Minimum percent change in tumor size from baseline at the time of best response.

Table 1

Patient Baseline Characteristics

Characteristic	All patients (N = 39)
Median age (range), years	64 (24, 81)
Sex, n (%)	
Male	22 (56.4)
Female	17 (43.6)
Race, n (%)	
Asian	1 (2.6)
Black or African American	4 (10.3)
Other	1 (2.6)
White	33 (84.6)
ECOG PS, n (%)	
0	12 (30.8)
1	25 (64.1)
2	2 (5.1)
Primary tumor type, n (%)	
Colorectal	15 (38.5)
Lung	7 (17.9)
Urological	6 (15.4)
Liver	3 (7.7)
Head and neck	2 (5.1)
Other ^a	6 (15.4)
Prior therapy, ^b n (%)	
Radiotherapy	20 (51.3)
Curative	12 (60.0)
Palliative	10 (50.0)
Systemic therapy	39 (100)
Surgery	37 (94.9)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status

^aOther malignancies included soft tissue sarcoma, gastroesophageal junction, breast, neuroendocrine, melanoma, and endocrine (1 case each).

^bPatients may have had more than one prior cancer therapy.

Table 2

Treatment-related adverse events (all grades)

Preferred term ^a	All cohorts (N = 39)	
	All grades	Grade 3
Anemia	3 (7.7)	0
Arthralgia	1 (2.6)	0
Blood amylase increased	1 (2.6)	0
Blood creatinine increased	1 (2.6)	0
Catheter site-related reaction	1 (2.6)	0
Constipation	1 (2.6)	0
Cough	1 (2.6)	0
Decreased appetite	4 (10.3)	0
Dehydration	1 (2.6)	0
Diarrhea	4 (10.3)	0
Dysgeusia	1 (2.6)	0
Fatigue	8 (20.5)	0
Feeling cold	1 (2.6)	0
Flatulence	1 (2.6)	0
Headache	1 (2.6)	0
Hypersensitivity	1 (2.6)	0
Hypogeusia	1 (2.6)	0
Hypokalemia	1 (2.6)	1 (2.6) ^b
Hypomagnesemia	2 (5.1)	0
Hyponatremia	2 (5.1)	1 (2.6) ^c
Infusion related reaction	1 (2.6)	0
Insomnia	1 (2.6)	0
Lipase increased	1 (2.6)	0
Mucosal inflammation	2 (5.1)	0
Nausea	4 (10.3)	0
Neuropathy peripheral	1 (2.6)	0
Paresthesia	1 (2.6)	0
Pyrexia	2 (5.1)	0
Thrombocytopenia	1 (2.6)	0
Vomiting	4 (10.3)	0

^a All treatment-related AEs in this study were grade 1 or 2, except as noted.^b Grade 3 hyponatremia, cohort 1 (NOTE: this treatment-related AE was the only dose-limiting toxicity observed in this study).^c Grade 3 hypokalemia, cohort 6.

Table 3
Narnatutumab pharmacokinetic parameters following intravenous infusion over 1.0–2.5 hours in patients with advanced solid tumors

PK Parameter	Geometric Mean (CV%) ^a					
	Weekly Regimen			Biweekly Regimen		
	5 mg/kg (N = 7)	10 mg/kg (N = 3)	15 mg/kg (N = 3)	20 mg/kg (N = 4)	20 mg/kg (N = 3)	40 mg/kg (N = 3)
Single dose	C _{max} (µg/mL)	111 (31)	183 (24)	369 (20)	437 (20)	506 (39)
	t _{max} ^b (hr)	2.00 (1.47–3.60)	1.68 (1.48–1.85)	2.00 (1.52–2.13)	1.60 (1.03–4.00)	2.63 (2.03–5.50)
	AUC _(0–last) ^c (µg·hr/mL)	8320 ^d (63)	12500 (14)	23800 (37)	29000 ^e (30)	35600 (22)
Multiple dose ^f	C _{max} (µg/mL)	139 ^g (50)	263 (17)	452 (29)	518 ^h (25)	560.965 ⁱ
	t _{max} ^b (hr)	1.02 (1.00–5.00) ^g	1.05 (1.03–1.52)	1.05 (1.00–1.50)	1.57 (1.00–5.50) ^h	1.53 ⁱ
	AUC _τ ^k (µg·hr/mL)	10400 ^g (87)	19400 (11)	31500 (51)	29900 ^j (47)	52700 ⁱ
					NA	NA
					NA	NA
					NA	1055.569; 711.984 ^j
					NA	3.72; 3.58 ^j
					NA	113000; 72200 ^j

Abbreviations: AUC = area under the concentration time curve; AUC_(0–last) = AUC from time zero to the last quantifiable concentration; AUC_τ = area under the concentration time curve during 1 dosing interval; C_{max} = maximum serum concentration; CV = coefficient of variation; hr = hour; N = number of patients who received at least 1 dose; NA= not available; n = number of observations; PK = pharmacokinetic; t_{max} = time of maximum observed drug concentration.

^aGeometric mean and geometric CV% are provided for n = 3; otherwise, actual values are provided.

^bMedian and range are provided for t_{max}.

^cLast nominal sample was collected at 168 hours from end of infusion for weekly regimen and 336 hours from end of infusion for biweekly regimen.

^dn = 4.

^en = 12.

^fFourth dose for weekly regimen and fifth dose for biweekly regimen.

^gn = 5.

^hn = 9.

ⁱn = 1.

regimen and 336 hours for biweekly regimen.

$$9 = u_f$$

$$1891 = 2_y$$

$$2 = u_f$$

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