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Phase I Dose-Escalation Study of MEDI-573, a Bispecific, Antiligand Monoclonal Antibody against IGFI and IGFII, in Patients with Advanced Solid Tumors

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Abstract

Purpose: This phase I, multicenter, open-label, single-arm, dose-escalation, and dose-expansion study evaluated the safety, tolerability, and antitumor activity of MEDI-573 in adults with advanced solid tumors refractory to standard therapy or for which no standard therapy exists.

Experimental Design: Patients received MEDI-573 in 1 of 5 cohorts (0.5, 1.5, 5, 10, or 15 mg/kg) dosed weekly or 1 of 2 cohorts (30 or 45 mg/kg) dosed every 3 weeks. Primary end points included the MEDI-573 safety profile, maximum tolerated dose (MTD), and optimal biologic dose (OBD). Secondary end points included MEDI-573 pharmacokinetics (PK), pharmacodynamics, immunogenicity, and antitumor activity.

Results: In total, 43 patients (20 with urothelial cancer) received MEDI-573. No dose-limiting toxicities were identified, and only 1 patient experienced hyperglycemia related to treatment. Elevations in levels of insulin and/or growth hormone were not observed. Adverse events observed in >10% of patients included fatigue, anorexia, nausea, diarrhea, and anemia. PK evaluation demonstrated that levels of MEDI-573 increased with dose at all dose levels tested. At doses >5 mg/kg, circulating levels of insulin-like growth factor (IGF)-I and IGFII were fully suppressed. Of 39 patients evaluable for response, none experienced partial or complete response and 13 had stable disease as best response.

Conclusions: The MTD of MEDI-573 was not reached. The OBD was 5 mg/kg weekly or 30 or 45 mg/kg every 3 weeks. MEDI-573 showed preliminary antitumor activity in a heavily pretreated population and had a favorable tolerability profile, with no notable perturbations in metabolic homeostasis. *Clin Cancer Res; 20(18); 4747–57. ©2014 AACR.*

Introduction

The insulin-like growth factor (IGF) signaling system is an ubiquitous, complex, tightly regulated pathway that has potent effects on cell proliferation, survival, differentiation, and transformation (1). Two circulating ligands, IGFI and IGFII (1), are tightly regulated by at least 6 circulating IGF-binding proteins (IGFBP; ref. 2). Both IGFI and IGFII transduce signaling through the type 1 IGF receptor (IGF1R), a transmembrane receptor tyrosine kinase (1, 3). The insulin receptor isoform A (IR-A) is also an IGF signaling receptor through the binding of IGFII (4). Conversely, the insulin receptor isoform B (IR-B) is a purely metabolic isoform capable of binding only insulin at physiologic concentrations (4). Further mitogenic regulation of IGFII occurs via a nonsignaling membrane receptor, IGFIIR (5). Adding to the complexity of the system, insulin receptors and IGF1R can form hybrid receptors that have varying affinities for IGF ligands as well as insulin (6).

Increased expression of IGF1R, IGFI, and IGFII has been demonstrated in a number of cancers, including breast, colorectal, thyroid, bladder, hepatocellular carcinoma, and osteosarcoma (7–11). In urothelial cancer cells, increased expression of IGF1R has been associated with promoting motility and invasion of cancer cells (8), suggesting the potential therapeutic value of an agent that targets the IGF signaling pathway in this population. There is compelling

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Translational Relevance

This article reports the findings of a phase I, multicenter, open-label study evaluating the safety, tolerability, and antitumor activity of MEDI-573 in adult patients with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Pharmacodynamic evaluations demonstrated that MEDI-573 was effective at sequestering insulin-like growth factor (IGF)-I and IGFII ligands at doses well below the dose that could be safely administered to patients. Importantly, MEDI-573 treatment demonstrated a favorable toxicity profile, with no metabolic derangements. This is important for the clinical–translational potential of MEDI-573, as lack of these metabolic adverse events may favor this IGF-targeting strategy over other approaches in patients with cancer. Of 39 patients evaluable for response, 13 had stable disease as best response. Based on these findings, MEDI-573 continues to be investigated in patients with cancer.

evidence in multiple tumor types, models, and clinical samples that dysregulation of IGF signaling has a substantial impact on cancer growth, survival, and resistance to clinically useful cancer therapies. For example, IGF signaling has been implicated in resistance to hormonal therapy in breast cancer (12, 13). Blockade of IGF signaling may enhance the effects of hormonal therapy (14, 15). Similarly, dysregulated IGF signaling has been implicated as a mechanism of resistance to therapies targeted against receptor tyrosine kinases (16), including trastuzumab (17). Multiple studies have also demonstrated that IGF signaling inhibition can enhance the effects of cytotoxic chemotherapy (18, 19), potentially expanding the scope of clinical benefit achieved with therapies that target IGF.

In clinical studies, monoclonal antibodies directed against IGF1R have been the focus of most strategies targeting IGF (20–24). However, emerging data suggest that IGF signaling through IR-A, which is not blocked by IGF1R-targeted monoclonal antibodies, may be as important as IGF1R-mediated IGF signaling. For example, the IR-A receptor has been shown to be the predominant IGF signaling receptor in breast cancer (25, 26), suggesting that the blockade of IGF signaling through IGF1R inhibition may be an inadequate treatment strategy. Expression of IR-A also is common in ovarian carcinoma (27), osteosarcoma (28), acute myelogenous leukemia (29), and other malignancies (30–32), suggesting that IGF blockade through both IGF1R and IR-A may be warranted (21).

MEDI-573 is a dual-targeting human monoclonal antibody that neutralizes the IGFI and IGFII ligands, resulting in inhibition of IGF signaling through both IGF1R and IR-A in a number of cancer cell lines; importantly, metabolic insulin action through IR-B is not altered using this approach (33). Thus, we hypothesized that the antiligand approach of MEDI-573 may improve on the incomplete IGF signaling blockade that occurs with IGF1R-directed monoclonal antibodies. Here we report the results of the first clinical study of MEDI-573 in adults with advanced solid tumors refractory to standard therapy or for which no standard therapy exists.

Materials and Methods

Patient population

Men and women ages 18 years or older with histologically confirmed advanced solid tumors for which no curative or standard therapies were available were eligible for inclusion. Patients were required to have a Karnofsky performance status $\geq$60, life expectancy of at least 12 weeks, and adequate hematologic (hemoglobin $\geq$10 g/dL, absolute neutrophil count $\geq$1,500/mm^3, platelet count $\geq$100,000/mm^3) and organ function [serum aspartate aminotransferase and alanine aminotransferase levels $\leq$2 times institutional upper limit of normal (ULN), serum bilirubin levels $\leq$1.5 times ULN, and creatinine clearance $\geq$60 mL/min]. Prior radiation therapy was allowed, provided that exposure did not exceed 25% of total marrow space, and toxicities from any previous cancer therapies must have recovered to grade <2 before enrollment. Patients were excluded if they received any concurrent therapy for cancer, chemotherapy, or small molecule–targeted therapy within 4 weeks of first MEDI-573 dose, immunotherapy or biologic therapies within 6 weeks of study treatment, or previous therapy with monoclonal antibodies directed against IGF1R. Additional exclusion criteria included: poorly controlled diabetes mellitus; New York Heart Association grade $\geq$2 congestive heart failure; history of myocardial infarction, unstable angina, transient ischemic attack, or stroke within 6 months of treatment with study medication; history of other invasive malignancy within 5 years (except for cervical carcinoma *in situ*, nonmelanomatous carcinoma of the skin or ductal carcinoma *in situ* of the breast that has been surgically cured) or documented brain metastasis; evidence of significant active infection; use of immunosuppressive medications or systemic steroids within 7 days of first dose of MEDI-573; pregnancy or lactation; clinically significant electrocardiogram (ECG) abnormality; or evidence of any condition that may have compromised patient safety during the study.

Objectives

The primary objectives were to determine the maximum tolerated dose (MTD) and optimal biologic dose (OBD) of MEDI-573 in patients with solid tumors. The end points included dose-limiting toxicity, adverse events (AE), and serious AEs (SAE). Secondary objectives included determination of the pharmacokinetic (PK) and immunogenic properties of MEDI-573, pharmacodynamic (PD) effects of MEDI-573 on circulating plasma levels of IGFI and IGFII, and the antitumor activity in response to MEDI-573 administration in patients with solid tumors. Exploratory analyses were conducted to evaluate the relationship of IGF pathway–related components at the mRNA and miRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment, and to identify and characterize

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associations between baseline circulating tumor cells (CTC) and clinical response.

Study design and dose-escalation cohorts

This phase I, multicenter, open-label, single-arm, dose-escalation, and dose-expansion study was conducted at 6 sites in the United States from March 2009 to July 2011 (ClinicalTrials.gov registry number: NCT00816361). The study protocol was approved by the ethics committee at each participating center, and all patients provided written informed consent before study participation.

Patients were assigned to sequential cohorts of 3 to 6 evaluable patients each receiving 1 of 5 doses of MEDI-573 (0.5, 1.5, 5, 10, or 15 mg/kg) every 7 days in 21-day cycles (escalation cohorts 1–5). If the first 3 patients in the 1.5 mg/kg cohort did not experience a dose-limiting toxicity (DLT) after 21 days of treatment, then enrollment in the 5 mg/kg cohort would begin. Higher-dose cohorts were enrolled following the same process. If 2 or more subjects within a cohort experienced a DLT within the first 21 days of treatment, then the MTD was exceeded and no further subjects were enrolled in that cohort. If 0 of 3 or fewer than 1 of 6 patients in cohort 5 experienced a DLT within the first 21 days of treatment, subsequent patients were enrolled in cohorts receiving 30 or 45 mg/kg of MEDI-573 every 3 weeks (escalation cohorts 6 and 7). Enrollment in the 45 mg/kg cohort was dependent on PK, PD, immunogenicity, and safety assessments of MEDI-573 at the 30 mg/kg dose level. Intrapatient dose escalation was not allowed. MEDI-573 was administered as a 60-minute intravenous infusion once every 7 days at doses $\leq$15 mg/kg; or one 90-minute intravenous infusion for the 30 and 45 mg/kg doses. For cohorts 1 to 5, after the first cycle, a dose could be delayed up to 7 days based on hematologic and nonhematologic toxicities; however, administration of all doses was required for the cycle to be considered complete. Dose delays were not allowed in the 30 and 45 mg/kg cohorts. Patients who did not receive all required doses within a cycle did not advance to the next cycle and were removed from the study. Treatment with MEDI-573 continued until unacceptable toxicity, disease progression, or other reasons for withdrawal were observed.

Dose-expansion cohorts

The dose-expansion phase was designed to evaluate the PK and PD parameters and to determine tumor response in 2 cohorts of approximately 10 patients each with advanced urothelial cancer (e.g., bladder cancer) at dose levels of 5 or 15 mg/kg every 7 days. The first 10 patients enrolled into the dose-expansion phase were treated with MEDI-573 15 mg/kg. The decision to continue enrollment in the lower 5-mg/kg dose-expansion cohort was based on PD assessments. The dosing schedule was the same as for the dose-escalation cohorts.

Safety assessments

Patient safety and tolerability were assessed through physical examinations, vital signs, ECGs, routine laboratory evaluations, and assessment of treatment-related AE and SAEs and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All AEs occurring within 30 days after the last dose of MEDI-573 were reported by the investigator. Serious AEs included any AE that resulted in death, was immediately life-threatening (i.e., an event wherein the patient was at risk of dying at the time of the event), required inpatient hospitalization or prolongation of hospitalization, resulted in persistent or substantial disability/incapacity, resulted in a congenital anomaly in the offspring of a patient, or may have jeopardized the patient or required medical intervention to prevent one of the previously mentioned outcomes. Complete physical examinations were performed at screening, after every 2 cycles, and at the end of treatment. A physical examination for the purpose of disease evaluation was completed at screening and on the first day of each cycle. ECGs were performed at screening, on day 1 of the first treatment cycle before and at completion of infusion, and 6 hours after completion (in the MEDI-573 0.5, 1.5, 5.0, 10.0, and 15.0 mg/kg and dose-expansion cohorts only), on day 1 of all subsequent cycles before dosing, at end of treatment, and 30 days following the last dose of MEDI-573. Vital signs were assessed immediately before MEDI-573 infusion, every 15 minutes during the infusion, at the end of the infusion ($\pm$5 minutes), and 30 and 60 minutes ($\pm$5 minutes) postinfusion. Routine laboratory evaluations, including serum chemistry and hematological assessments of complete blood count with differential and platelet count occurred at screening, on days 1, 3, 8, and 15 of the first treatment cycle, on days 1, 8, and 15 of subsequent cycles, and at end of treatment. In the dose-escalation cohorts, these were assessed on days 1, 3, and 8 of the first treatment cycle, and on days 1 and 8 of subsequent cycles. Hemoglobin A1c levels were evaluated at screening and at the end of treatment. Urine samples were assessed at screening, on each treatment day of every cycle, and at the end of treatment; in the dose-escalation cohort, urinalysis occurred at screening, on the first day of each treatment cycle, and at the end of treatment.

PK and immunologic evaluations

Blood samples were collected immediately before and following MEDI-573 infusions (all cycles), as well as 2 and 6 hours postinfusion (0.5, 1.5, 5.0, 10.0, and 15.0 mg/kg and dose-expansion cohorts only) on day 1 of cycle 1. Additional samples were collected 24 and 48 hours ($\pm$2 hours) following the first infusion of cycle 1, and pre- and postinfusion ($\pm$5 minutes) for each subsequent treatment. Samples for evaluation of anti–MEDI-573 antibodies were collected at screening and before each infusion. Free MEDI-573 in serum was quantitated using a validated electrochemiluminescence assay in which unlabeled and ruthenium-labeled mouse anti-idiotype monoclonal antibodies were used as the capture and detection reagents, respectively. The PK parameters, including C_{max}, T_{max}, and AUC, were determined using PK data after the first dose only using a noncompartmental approach with WinNonlin Professional

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version 5.2 (Pharsight Corp.). Plasma concentrations of free IGFI and IGFII were measured using an electrochemiluminescence assay in which biotinylated MEDI-573 was used as the capture reagent and a ruthenium-labeled polyclonal antibody was used as the detection reagent. The OBD was defined as the dose at which all circulating free IGFI and IGFII ligands was sequestered by MEDI-573.

Antitumor activity

Disease evaluations were performed by computed tomography (CT) or magnetic resonance imaging (MRI) at screening, every 2 cycles, at end of treatment or until progressive disease during treatment, and at the discretion of the investigator. For patients who discontinued treatment for reasons other than progressive disease or initiation of alternative treatment, disease evaluations were performed every 3 months until progressive disease. Tumor measurements and assessments were based on Response Evaluation Criteria in Solid Tumors (RECIST; ref. 34). Antitumor activity was assessed based on objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

Survival and posttherapy follow-up

Every 3 months (±2 weeks) after the last dose of MEDI-573, survival status was assessed and complete physical examinations and disease evaluations were performed until the end of study or patient death. Presence of anti–MEDI-573 antibodies, serum concentrations of MEDI-573, and levels of blood biomarkers were assessed 3 months following the last dose of MEDI-573.

Correlative studies

To understand the effects of MEDI-573 on IGF1R pathways as well as proliferation and invasion in human cancer, we studied the mRNA expression profiles in biopsy samples from patients with bladder cancer before and after treatment with MEDI-573 (see Supplementary Methods).

CTC analysis

CTC analysis was performed on samples from patients in the MEDI-573 30 and 45 mg/kg dose-escalation cohorts and in the expansion cohorts with available baseline CTC values ($n = 24$, including 18 patients with bladder cancer and 6 patients with other solid tumors from the MEDI-573 30 and 45 mg/kg escalation cohorts). Methods were described previously (35), but this analysis used the CellSearch CXC Kit (Janssen Diagnostics). For evaluating CTCs as a prognostic marker for survival, patients were grouped by baseline CTC values of either less than 5 or 5 or more, as these cutoffs have been established as prognostic for breast cancer (36) and prostate cancer (37). The cutoff of 5 CTCs was used in this case, although the majority of CTC data were from patients with bladder cancer, because no cutoff point has been established for CTCs in bladder cancer. However, it should be noted that using a cutoff of 3 CTCs, which has been used for colorectal cancer (38, 39), yielded similar findings with this dataset.

Statistical analysis

For the dose-escalation phase, a minimum of 21 evaluable patients (3 patients in each dose cohort) were required if no DLTs occurred. The safety population included all patients who received at least 1 dose of MEDI-573. The efficacy evaluable population included all patients who received any MEDI-573 treatment and had at least 1 post-baseline tumor assessment. The MTD evaluable population included patients who completed at least 1 full cycle of MEDI-573 (3 doses in cohorts 1–5 or 1 dose in cohorts 6–7, and followed ≥21 days after the first dose) or discontinued because of DLTs. Nonevaluable patients were replaced in the same cohort. All DLTs were assessed during the first treatment cycle and were defined as any grade 3 or higher toxicity for which a cause other than treatment with MEDI-573 could not be reasonably justified. Exceptions were fasting serum glucose abnormalities of up to grade 3 with duration <24 hours, grade 3 fever not considered an SAE that resolved to normal or baseline within 24 hours of treatment, or grade 3 rigors or chills that responded to optimal therapy.

All safety end points were summarized descriptively. AEs and SAEs were summarized by cohort, system organ class, severity, and relationship to MEDI-573 treatment for 30 days following the last dose. PK and immunogenic assessments were summarized descriptively. For MTD and OBD assessments, descriptive statistics were used to summarize the occurrence of DLTs by cohort. The TTR, DR, TTP, PFS, and OS were evaluated using Kaplan–Meier methods. For the CTC analysis, time-to-event data were visualized using Kaplan–Meier curves and were evaluated with log-rank (Mantel–Cox) tests.

Results

Patients

A total of 43 patients, including 23 in the dose-escalation phase and 20 in the dose-expansion phase with urothelial (bladder) cancer, received MEDI-573 (Fig. 1). The patient population was predominantly white (90.7%) and male (58.1%), with a mean age of 62.6 years and a mean weight of 82.8 kg (Table 1). The most common tumor type was bladder (39.5% of patients) because of the dose-expansion cohorts. Approximately 91% of patients presented with stage IV tumors.

Safety

The MTD was not reached after enrolling patients through the highest dose level on the weekly (15 mg/kg) or every 3 week (45 mg/kg) schedules. No DLTs (≥grade 3 AE during the first cycle) were observed at any dose level. Overall, the most common AEs were decreased appetite (46.5%), fatigue (41.9%), nausea (32.6%), diarrhea (25.6%), vomiting (23.3%), and abdominal pain (20.9%). The most common treatment-related AEs were fatigue (27.9%), decreased appetite (23.2%), nausea

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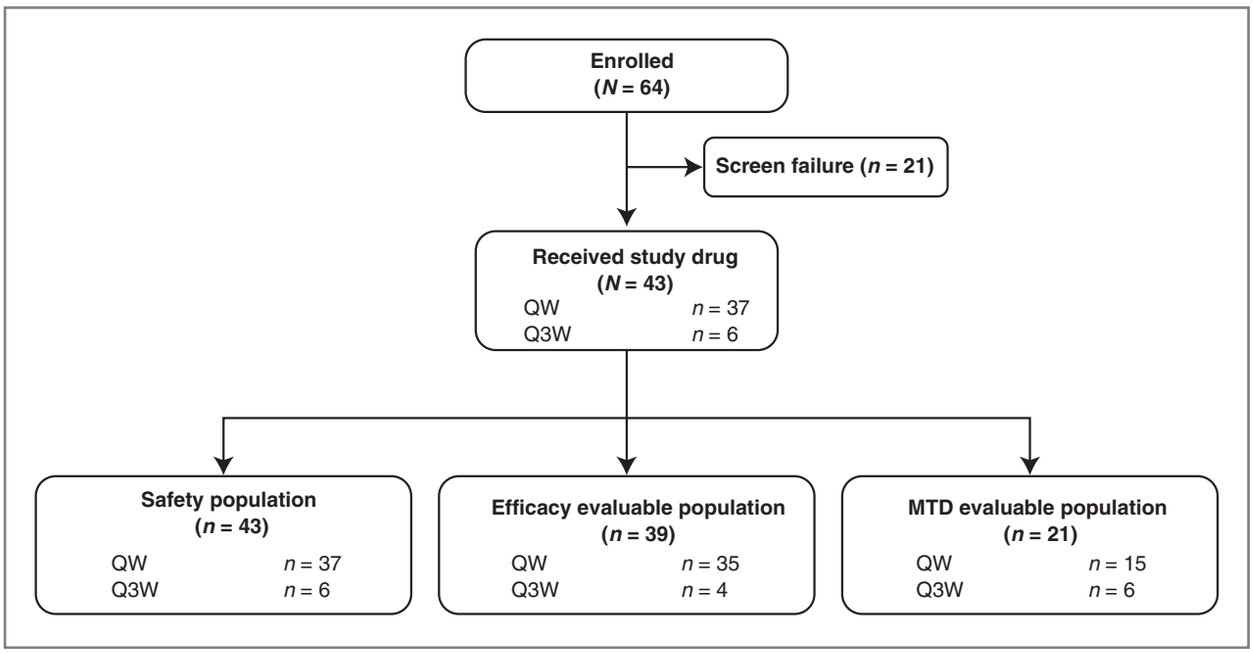

Figure 1. Patient disposition. Abbreviations: QW, once weekly; Q3W, every 3 weeks.

(18.6%), diarrhea (16.3%), and anemia (11.6%). Most AEs were ≤ grade 2 (Table 2). Overall, 34 SAEs occurred in 17 patients; 1 patient treated with 15.0 mg/kg experienced 2 treatment-related SAEs (Table 3). Five of 43 patients (11.6%) in the dose-escalation phase and 1 of 20 patients (5.0%) in the dose-expansion phase discontinued

Table 1. Baseline characteristics and disease status (safety population)

Variable	Cohorts 1–5, 0.5–15 mg/kg QW ($n = 37$)	Cohorts 6–7, 30–45 mg/kg Q3W ($n = 6$)	Total ($N = 43$)
Age (y), mean (SD)	62.6 (11.5)	62.0 (12.7)	62.6 (11.6)
Sex, *n*, male/female	23/14	2/4	25/18
Primary tumor type, *n*			
Bladder	20	—	20
Breast (adenocarcinoma)	1	—	1
Cervical	—	1	1
Colorectal	1	1	2
Colon	1	—	1
Esophageal	1	—	1
Ewing's sarcoma	1	—	1
Gastroesophageal	—	1	1
Non–small cell lung	—	1	1
Ovarian	—	1	1
Prostate	3	—	3
Other[a]	9	1	10
Baseline Karnofsky performance status			
70	6	3	9
80	13	3	16
90	13	—	13
100	5	—	5

Abbreviations: QW, once weekly; Q3W, every 3 weeks.

[a]Includes anal cancer, adrenal cortical carcinoma, leiomyosarcoma, uterine cancer, pancreatic carcinoma, angiosarcoma, liposarcoma, appendiceal adenocarcinoma, and adenocarcinoma of unknown primary origin.

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Table 2. Treatment-related[a] AEs by severity, according to CTCAE criteria

	Cohorts 1–5, 0.5–15 mg/kg QW ($n = 37$)		Cohorts 6–7, 30–45 mg/kg Q3W ($n = 6$)	
AE, *n* (%)	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
Fatigue	10 (27)	0	1 (17)	1 (17)
Decreased appetite	9 (24)	0	1 (17%)	0
Nausea	7 (19)	0	1 (17)	0
Diarrhea	5 (14)	0	2 (33)	0
Anemia	5 (14)	0	0	0
Vomiting	3 (8)	0	1 (17)	0
Rash	2 (5)	0	1 (17)	0
Pruritus	1 (3)	0	2 (33)	0
Myalgia	2 (5)	0	0	0
Leukopenia	2 (5)	0	0	0
Thrombocytopenia	2 (5)	0	0	0
Abdominal pain	2 (5)	0	0	0
Stomatitis	0	0	2 (33)	0
Increased alkaline phosphatase	1 (3)	0	1 (17)	0
Constipation	1 (3)	0	0	0
Dry mouth	1 (3)	0	0	0
Peripheral edema	1 (3)	0	0	0
Pyrexia	1 (3)	0	0	0
Thirst	1 (3)	0	0	0
Increased serum creatinine	1 (3)	0	0	0
Increased growth hormone	1 (3)	0	0	0
Increased insulin	1 (3)	0	0	0
Decreased weight	1 (3)	0	0	0
Hypocalcemia	1 (3)	0	0	0
Hypomagnesemia	1 (3)	0	0	0
Hypophosphatemia	1 (3)	0	0	0
Back pain	1 (3)	0	0	0
Somnolence	1 (3)	0	0	0
Exertional dyspnea	1 (3)	0	0	0
Pneumothorax	1 (3)	0	0	0
Alopecia	1 (3)	0	0	0
Early satiety	0	0	1 (17)	0
Hypoglycemia	0	1 (3)	0	0
Systolic hypertension	1 (3)	0	0	0

[a]Related is defined as possibly, probably, or definitely related to study drug.

treatment because of AEs. Three deaths occurred during the study, all because of progressive disease and none considered related to MEDI-573 treatment. Clinically, significant changes in serum glucose related to study treatment were rare, observed in 1 of 43 patients. No clinically significant changes to insulin or somatotropin levels, hematologic parameters, or in ECGs were observed. No neutralizing antibodies against MEDI-573 were detected in any patient sample.

PKs and PDs

The MEDI-573 serum concentration–time profile is presented in Fig. 2A. PK parameters determined by noncompartmental analysis are summarized in Table 4. Serum concentrations of MEDI-573 increased with dose. The OBD, defined as full suppression of both IGFI (Fig. 2B) and IGFII (Fig. 2C) in the plasma of patients receiving MEDI-573, was achieved at a once weekly dose of 5.0 mg/kg or higher and at 30.0 or 45 mg/kg every 3 weeks.

Antitumor activity

Four patients in the dose-escalation phase were not included in the efficacy evaluable population: 2 because of AEs, 1 because of withdrawal of consent, and 1 who entered hospice care. No partial or complete responses were observed on study. Stable disease occurred in 13 of 39 (33%) patients in the dose-escalation cohorts and 4 of 20 (20%) patients in the dose-expansion cohorts with

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Table 3. Serious adverse events

Dose, mg/kg	Number of patients/ number of cohort ($n = 17$)	SAEs ($n = 34$)
0.5	2/4	Increased blood creatinine, dehydration, fatigue, decreased GFR, neoplasm (disease progression)
1.5	1/3	Neoplasm (disease progression)
5.0	4/14	Abdominal pain, diarrhea, device-related infection, urinary tract infection, cholangitis, urinary tract obstruction
10.0	1/3	Neoplasm (disease progression)
15.0	6/13	Hypoglycemia, decreased weight,[a] decreased appetite,[a] urosepsis, small intestine obstruction, hypercalcemia, bacteremia, device-related infection, confusional state, hemoptysis, deep vein thrombosis
30.0	0/3	—
45.0	3/3	Abdominal distention, abdominal pain, vomiting, musculoskeletal chest pain, neoplasm (disease progression), renal failure, respiratory failure

Abbreviation: GFR, glomerular filtration rate.
[a]Considered by investigators to be treatment related; occurred in the same patient.

urothelial cancer. Stable disease lasting at least 12 weeks was reported in 8 of 39 (21%) efficacy evaluable patients, 3 of whom were in the dose-expansion cohorts. The median TTP and PFS were 1.4 months in both the overall efficacy evaluable patients and the dose-expansion cohorts. The median OS were 4.8 and 4.0 months in the overall efficacy evaluable population and dose-expansion cohorts, respectively.

Correlative studies

Eleven pairs of pretreatment and posttreatment mRNA biopsy samples from the dose-expansion cohorts were studied. Six pairs of samples were from the 5-mg/kg cohort and 5 pairs were from the 15-mg/kg cohort. A trend toward inhibition was observed with MEDI-573 on cancer proliferation genes (*AURKA*, *CCNB1*, *MKI67*, and *MYBL2*), cancer invasion genes (*CTSL2* and *MMP11*), and the bladder cancer marker UPK3A, but these changes were not statistically significant (see Supplementary Fig. S1). The mRNA differential expression of IGF pathway genes, including *IGF1*, *IGF2*, *IGF1R*, and IR-A, were also studied, and no statistically significant differences were observed by comparing pretreatment and posttreatment samples in the 2 cohorts. A trend of dose-dependent decreases in mRNA expression of Grb2, AKT1, and mTOR was observed by comparing the 5 and 15 mg/kg cohorts, but these differences were not statistically significant owing to small sample sizes. The relationship between the mRNA differential expression and PFS also were investigated (data not shown). However, the results were not conclusive because of the limited sample size.

CTC analysis

Pretreatment CTC levels, ranging from 0 to 505 CTCs, were measured in patients participating in the dose-expansion cohorts and in the every 3 weeks dose-level groups (30 and 45 mg/kg). Six patients had 0 CTCs, 9 patients had 1 to 4 CTCs, and 3 patients had 5 or more CTCs in the dose-expansion cohorts. Of the 24 subjects with baseline CTC values, 8, 12, and 4 patients had 0 CTCs, 1 to 4 CTCs, and 5 or more CTCs, respectively. Overall survival was correlated with the number of pretreatment CTCs ($\geq$5/7.5 or <5/7.5 mL). For all patients with baseline CTC samples ($n = 24$), patients with at least 5 CTC/7.5 mL ($n = 4$) had inferior survival duration compared with patients with <5 CTC/7.5 mL ($n = 20$; 2.5 vs. 4.8 months, respectively; $P = 0.006$). When analyzed separately, patients in the expansion (urothelial cancer) cohorts ($n = 18$) with $\geq$5 CTC/7.5 mL ($n = 3$) had inferior survival duration compared with patients with <5 CTC/7.5 mL ($n = 15$; 3.2 months vs. 4.8 months, respectively; $P = 0.052$). These results should be interpreted with caution, given the small number of patients included in the analysis.

Discussion

Effectively targeting the IGF system for the purposes of anticancer therapy has proven challenging. Numerous therapies have been developed targeting the pathway, which for the most part have been tolerable both as single agents and in combination with other agents. However, it is conceivable that the untoward metabolic consequence of IGF-targeting agents may not only lead to undesirable AEs, but also may be counterproductive to antitumor activity.

For example, hyperglycemia has been demonstrated to be a class effect AE in response to anti-IGF1R monoclonal antibodies; however, some agents are more likely to stimulate elevated glucose levels than others (20–22, 24). Although not fully understood, the proposed mechanism of glucose-level elevation is disruption of the negative feedback loop at the hypothalamic level by anti-IGF1R monoclonal antibodies, leading to increased growth hormone secretion and resultant hyperinsulinemia, insulin resistance, and, ultimately, hyperglycemia (40). Importantly, this mechanism is insulin receptor independent, as anti-IGF1R therapies do not bind to the insulin receptor, even at

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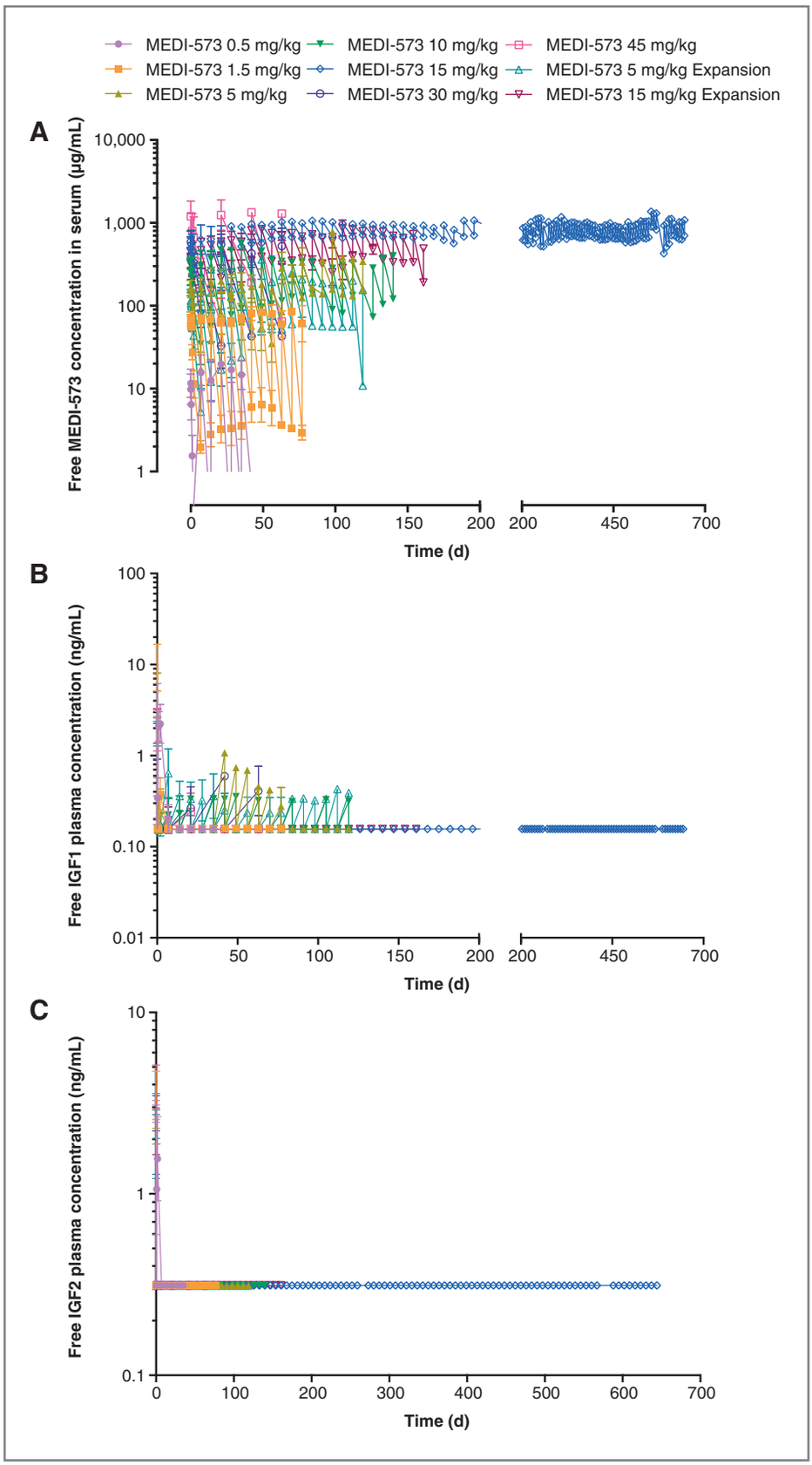

Figure 2. PK and PD effects of MEDI-573. The graphs illustrate free MEDI-573 concentrations in serum (A), the suppression of IGF1 (B), and the suppression of IGF2 (C). Values indicate the mean (SD) for each time point.

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Table 4. PK parameters after first dose[a]

Dose (mg/kg)	Patients (*n*)	T_{max} (d)	C_{max} (μg/mL)	$AUC_{(0–7)}$ (day·μg/mL)
0.5 QW	3	0.04 (0.04–0.04)	11.6 (5.5)	9.59 (5.12)
1.5 QW	3	0.04 (0.04–0.04)	71.8 (12.5)	90.8 (18.6)
5 QW	3	0.04 (0.04–0.12)	166 (37.7)	431 (135)
5 QW expansion	9	0.04 (0.04–0.30)	115 (42.6)	227 (99.8)
10 QW	3	0.04 (0.04–0.14)	264 (121)	631 (288)
15 QW	3	0.28 (0.12–0.30)	560 (251)	1950 (917)
15 QW expansion	9	0.06 (0.04–0.30)	412 (141)	1280 (392)
30 Q3W	3	0.06 (0.06–0.06)	588 (213)	3510 (1230)
45 Q3W	3	0.06 (0.06–0.06)	1200 (621)	5790 (3390)

Abbreviations: $AUC_{0–7}$, area under the concentration–time curve from time zero to 7 days; $AUC_{0–21}$, area under the concentration–time curve from time 0 to 21 days; C_{max}, maximum observed serum concentration; T_{max}, time to maximum observed concentration.
[a]Table reflects data collected as of December 20, 2011. Parameters are presented as mean (standard deviation) except T_{max}, which is presented as median (minimum–maximum).

supraphysiologic levels (41–43). No occurrence of hyperinsulinemia or elevations in growth hormone was noted in patients receiving MEDI-573, and hyperglycemia was rare (1 case). These data suggest that an antiligand approach to targeting the IGF system may have less impact on metabolic homeostasis. However, further studies comparing such agents in a clinical study are necessary to confirm this finding. The observed lack of hyperglycemia in response to MEDI-573 also suggests that the negative feedback disruption mechanism described above, which should be disrupted by antiligand and anti-IGF1R monoclonal antibodies alike, is not a sufficient explanation. It should be noted that this difference may be because of differences in target interactions or in levels of blockade by the 2 different methods; however, these mechanisms require further study.

Insulin receptor activation by insulin may also explain the suboptimal therapeutic benefit of monoclonal antibodies targeting IGF1R. High insulin secretion and insulin receptor expression are associated with poor cancer outcomes and may attenuate the benefits of IGF1R targeting (44–48). Thus, the unopposed hyperinsulinemia stimulated by anti–IGF1R-directed monoclonal antibodies may be counterproductive to the antitumor effects of blocking IGF signaling through IGF1R (49). MEDI-573 has no interactions with insulin or insulin receptors (33). Thus, the antiligand approach may have an advantage over anti-IGF1R monoclonal antibodies in this regard. Of note, there was no clear modulation of insulin receptor isoforms or other IGF signaling–related proteins evaluated in response to MEDI-573. However, these results are limited by the number of patients evaluated. Although there was a correlation between patient outcomes and pretreatment CTC enumeration, it is likely that this is reflective of patients with poor prognoses as opposed to lack of benefit from MEDI-573, as previously described (50, 51).

MEDI-573 was clearly effective at clearing plasma IGFI and IGFII at doses greater than 5 mg/kg weekly. Suppression of IGF ligands at the tumor site, wherein the additional impact of acidic or hypoxic conditions exist, remains to be investigated (52–54). As no maximally tolerated dose was reached and AEs did not increase with increasing exposure of MEDI-573, we recommend the maximum administered dose for phase II investigations, which was 15 mg/kg on a weekly basis or 45 mg/kg every 3 weeks. This is supported by preclinical data indicating that complete IGF signaling blockade, but not IGF1R targeting alone, enhances the antitumor effects of hormonal therapy (14, 55). In mRNA expression studies in hormone receptor–positive and human epidermal growth factor receptor 2 (HER2)-negative tumor tissues, a positive correlation was found between mRNA ratios of IR-A and IR-B and the expression of multiple proliferation genes, and a more prominent IR-A:IR-B expression differential in luminal-B breast cancers (26). The association of increased IR-A:IR-B ratio with the luminal-B subtype suggests that these patients could potentially respond to therapy that targets both IGF1R and IR-A. In conclusion, this study suggests preliminary antitumor activity in the context of a heavily pretreated population and an acceptable safety profile with MEDI-573, thus warranting further clinical investigation. An ongoing phase I/II study (NCT01446159) is evaluating MEDI-573 in combination with hormonal therapy (an aromatase inhibitor) in patients with hormone receptor–positive, HER2-negative, metastatic breast cancer.

Disclosure of Potential Conflicts of Interest

T. LaVallee has ownership interest (including patents) in AstraZeneca. X.-Q. Yu and J. McDevitt are employees of MedImmune LLC. J. Huang is an employee of AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

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