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Safety and Clinical Activity of MEDI1873, a Novel GITR Agonist, in Advanced Solid Tumors

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ABSTRACT

Purpose: The safety and preliminary efficacy of MEDI1873, an agonistic IgG1 fusion protein targeting glucocorticoid-induced TNF receptor–related protein (GITR), were evaluated in an open-label, first-in-human, phase I, dose escalation study in previously treated patients with advanced solid tumors.

Patients and Methods: Two single-patient cohorts at 1.5 and 3 mg i.v. were followed by 3+3 dose escalation in six cohorts at 7.5, 25, 75, 250, 500, and 750 mg, all every 2 weeks, for up to 52 weeks. Primary endpoints were safety and tolerability, dose-limiting toxicities (DLT), and MTD. Secondary endpoints included antitumor activity, pharmacokinetics, immunogenicity, and pharmacodynamics.

Results: Forty patients received MEDI1873. Three experienced DLTs: grade 3 worsening tumor pain (250 mg); grade 3 nausea, vomiting, and headache (500 mg); and grade 3 non-ST segment elevation myocardial infarction (750 mg). An MTD was not reached and treatment was well tolerated up to 500 mg. Most common treatment-related adverse events were headache (25%), infusion-related reaction (17.5%), and decreased appetite (17.5%). MEDI1873 exposure was dose proportional. Antidrug–antibody incidence was low. MEDI1873 increased peripheral $CD4^+$ effector memory T-cell proliferation as well as cytokines associated with effector T-cell activation at dose levels ≥75 mg. The best response was stable disease (SD) in 17 patients (42.5%), including 1 unconfirmed partial response. Eight patients (20.0%) had SD ≥24 weeks.

Conclusions: MEDI1873 showed acceptable safety up to 500 mg i.v. every 2 weeks with pharmacodynamics activity, and prolonged SD in some patients. However, further development is not planned because of lack of demonstrated tumor response.

Introduction

Antibodies against cytotoxic T-lymphocyte antigen (CTLA-4), programmed cell death-1 (PD-1), and programmed cell death ligand-1 (PD-L1) are now approved for multiple tumor types (1). However, only a subset of patients respond and additional strategies are needed (2).

Activating costimulatory receptor ligands to enhance the effector immune response can potentiate antitumor activity (3). Glucocorticoid-induced TNF receptor family–related protein (GITR), a T-cell costimulatory receptor, is expressed on $CD25^+$/$FoxP3^+$ regulatory T cells (Treg) and is upregulated on $CD4^+$ and $CD8^+$ effector T cells (4, 5). Interaction of GITR with its ligand (GITRL) enhances the proliferation of effector T cells in response to tumor antigens and modulates the activity of intratumoral Tregs (5–7). Targeting GITR directly delivers activating signals that augment those received through the T-cell receptor and overcomes local immunosuppression (8, 9).

Agonists of GITR have shown promising antitumor activity in preclinical tumor models both as a monotherapy and in combination with vaccines, chemotherapy, and immunotherapies (10–13). MEDI1873 is a novel, GITRL/IgG1 agonist fusion protein that binds to GITR on $CD4^+$ and $CD8^+$ effector T cells and Tregs (14). It is predicted to induce an antitumor response by stimulating the activation and proliferation of effector memory T cells and by decreasing Treg tumor infiltration.

Here, we present safety, pharmacokinetics, preliminary efficacy, and pharmacodynamics data in patients treated during the dose escalation phase of a phase I, first-in-human study of MEDI1873 in advanced solid tumors (NCT02583165).

Patients and Methods

Patients

Patients were eligible for enrollment if they were ≥18 years of age with histologically or cytologically confirmed advanced solid tumors with at least one measurable lesion according to the RECIST version 1.1 (RECIST v1.1); if they had received at least one, but not more than three, prior lines of systemic treatment for recurrent or metastatic disease (which could include checkpoint inhibitors); and if they had adequate organ function.

Patients were excluded if they had received any anticancer therapy within 4 weeks prior to the first dose of MEDI1873 (in the case of mAbs, 6 weeks prior); live, attenuated vaccine within 28 days prior to the first dose of MEDI1873; or any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Trial registration number: NCT02583165.

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Translational Relevance

Glucocorticoid-induced TNF receptor–related protein (GITR) is a T-cell costimulatory receptor. GITR agonists have been shown to stimulate antitumor immunity in preclinical models. This phase I study of MEDI1873, a novel GITR ligand/IgG1 agonist fusion protein, demonstrated engagement of GITR on circulating memory T cells, thereby enhancing effector T-cell function through inducing peripheral IFNγ, IFNγ-induced protein 10 (IP-10), IFN-inducible T-cell alpha chemoattractant, and monokine induced by IFNγ, and increasing circulating Ki67$^+$ CD4$^+$ cells in patients with advanced solid tumors. MEDI1873 also reduced intratumoral GITR$^+$ FoxP3$^+$ cells. Several patients had prolonged stable disease, exceeding 1 year in two cases. Although some findings were encouraging, there are no plans for further clinical exploration of MEDI1873.

cancer; or if they had unresolved toxicities from prior anticancer therapy.

Study design

In this first-in-human, phase I, multicenter, global, open-label study, the dose escalation phase consisted of two single-patient cohorts at the two lowest MEDI1873 doses (1.5 and 3 mg), followed by 3+3 dose escalation in six additional cohorts 7.5, 25, 75, 250, 500, and 750 mg. Patients received treatment intravenously every 2 weeks for up to 52 weeks. Patients who completed the initial 52 weeks of treatment and then progressed, were given the option of retreatment. The dose-limiting toxicity (DLT) period was 15 days for the single-patient cohorts and 28 days for the 3+3 cohorts.

The starting dose was based on cynomolgus monkey nonclinical safety studies, as this species was considered the only pharmacologically relevant model. MEDI1873 was generally associated with pharmacologically mediated enhancement of proliferation and expansion of T-cell subpopulations, antidrug–antibody (ADA)-mediated impact on drug exposure, and ADA-mediated morbidity and mortality. Safety margins were calculated on the basis of a highest non-severely toxic dose of 15 mg/kg and adequate safety margins for the proposed clinical doses were attained. Therefore, a two-compartment pharmacodynamics model of MEDI1873 in humans was based on cynomolgus monkey pharmacokinetics data. MEDI1873 7.5 mg every 2 weeks was proposed as the human starting dose, as the predicted trough levels were below the EC_{10} for *in vitro* and *in vivo* activity (no effect level) and the predicted C_{max} was below the EC_{90} for *in vivo* CD4$^+$ T-cell proliferation. Following discussions with the FDA, two additional single-patient cohorts of 1.5 mg every 2 weeks and 3 mg every 2 weeks were introduced into the protocol.

Intratumoral and peripheral pharmacodynamic changes were explored in separate pharmacodynamic cohorts in patients with non–small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), or colorectal cancer receiving MEDI1873 75 or 250 mg. Mandatory pretreatment and on-treatment tumor biopsies were collected from the patients in the pharmacodynamic confirmation cohorts (6 patients in the 75 mg cohort and 8 patients in the 250 mg cohort), but not during dose escalation. In addition, the poor quality of either the pretreatment or posttreatment biopsy in a matched pair rendered many pairs unevaluable, resulting in only 5 pairs of evaluable biopsies. All patients had flow cytometric assessment of lymphocytes pre- and on-treatment up to day 43. Peripheral cytokines and blood gene expression was also measured in all patients.

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation/Good Clinical Practice, and applicable regulatory requirements. All patients provided written informed consent. The protocol, any amendments, and informed consent forms were reviewed and approved by the institutional review boards/independent ethics committees.

Endpoints and assessments

The primary endpoints were to assess the safety and tolerability of MEDI1873, describe the DLTs, and determine the MTD or highest protocol-defined dose. The safety profile was assessed through the number of patients experiencing adverse events (AE), serious AEs (SAE), DLTs, abnormal laboratory parameters, vital signs, and electrocardiogram results.

A secondary endpoint was preliminary antitumor activity based on RECIST v1.1 evaluated every 8 weeks; expressed as rates of complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and SD ≥24 weeks. Additional secondary endpoints included pharmacokinetic measures (maximum observed concentration, AUC-time curve, drug clearance, and elimination half-life); immunogenicity assessed as the number and percentage of patients with detectable ADAs, and pharmacodynamic measurements including changes from baseline in the number and activation status of intratumoral lymphocyte populations, assessed by matched biopsies from pretreatment and day 29, evaluated for intratumoral CD8, FoxP3, and GITR, and tumoral PD-L1 expression by IHC. Peripheral blood from all patients was monitored for type-2 IFN cytokine levels, gene expression, and lymphocyte phenotype by flow cytometry up to day 43. Blood was collected for pharmacokinetics assessments at every visit for the first 13 visits, except for visits 6, 8, and 10; from visit 14 onwards blood was collected every 4 weeks (±3 days) starting on day 99.

Statistical analyses

All data analyses were conducted using the SAS System version 9.3 or higher (SAS Institute Inc.) in a UNIX environment and validated according to AstraZeneca SAS Programming standards. Antitumor activity analyses were based on investigator assessment by RECIST 1.1. Objective response rate was estimated with a 95% confidence interval (CI) using the exact probability method. Noncompartmental pharmacokinetics data analysis of serum MEDI1873 concentration–time data was performed using the validated computer software package Phoenix WinNonlin (version 8.1, Certara, L.P.) in accordance with MedImmune SOP MSP-RES-010048, "Non-compartmental Pharmacokinetic/Toxicokinetic Data Analysis."

Data availability

Data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Results

Patients and treatment

As of the final database lock on February 19, 2019, 40 patients were enrolled and treated. Demographic and disease characteristics are summarized in **Table 1**. Most patients were heavily pretreated. Of the 20 patients with colon cancer, 15 were microsatellite stable, 1 was

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Table 1. Demographic and baseline characteristics.

Characteristic	Total ($N = 40$)
Median age, years (range)	58.3 (32.0–81.0)
Sex, *n* (%)	
Female	17 (42.5)
Male	23 (57.5)
Race, *n* (%)	
Asian	1 (2.5)
Black or African American	6 (15.0)
White	33 (82.5)
ECOG performance status, *n* (%)	
0	22 (55.0)
1	18 (45.0)
Tumor type, *n* (%)	
Colorectal cancer	20 (50.0)
Mesothelioma	3 (7.5)
Neuroendocrine tumor[a]	3 (7.5)
NSCLC	1 (2.5)
SCLC[b]	1 (2.5)
Soft-tissue sarcoma[b]	1 (2.5)
Other[c]	11 (27.5)
No. of prior lines of systemic therapy for metastatic disease/locally advanced disease, *n* (%)[d]	$N = 34$
1	5 (14.7)
2	13 (38.2)
3	14 (42.2)
4[e]	1 (2.9)
5[e]	1 (2.9)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[a]Includes neuroendocrine cancer ($n = 1$, 2.5%) and pancreatic neuroendocrine cancer ($n = 2$, 5%).
[b]Coded as NSCLC in original database.
[c]Includes HNSCC lip and oral cavity ($n = 1$, 2.5%), adenoid cystic carcinoma ($n = 1$, 2.5%), breast ($n = 1$, 2.5%), cervical ($n = 2$, 5.0%), endometrial ($n = 1$, 2.5%), metastatic HPV$^+$ oropharyngeal squamous cell carcinoma ($n = 1$, 2.5%), mucinous adenocarcinoma of appendix with omental caking ($n = 1$, 2.5%), pancreatic cancer ($n = 1$, 2.5%), prostate cancer ($n = 1$, 2.5%), and undifferentiated epithelioid malignant neoplasm ($n = 1$, 2.5%).
[d]Five patients had received prior PD-1/PD-L1 therapy (four for metastatic disease and one in the adjuvant setting). One had HNSCC lip and oral cavity (pembrolizumab, best response PD), one had prostate cancer (atezolizumab, best response PD), one had NSCLC (atezolizumab, best response SD), one had soft-tissue sarcoma (nivolumab, best response SD), and one had HPV$^+$ oropharyngeal squamous cell carcinoma (nivolumab, best response PD).
[e]The study protocol restricted the number of lines of prior therapy, but the database collected the number of prior regimens. Because a line of therapy could contain more than one regimen if those regimens were planned ahead of time, the two subjects with four and five prior treatments were eligible for the study as the number of "lines of therapy" was within the entry criteria per protocol.

microsatellite unstable (MSI-low), 1 had indeterminate microsatellite status, and microsatellite status was not reported in 3 patients.

Median duration of exposure was 8 weeks (range, 2–54.3) and median duration of follow-up was 18.3 months (range, 0.6–37.1). Three patients (7.5%) completed 52 weeks of study treatment; the most common reason for discontinuation was PD (72.5%), and withdrawal of consent and AEs (7.5% each).

Safety and tolerability

Three patients (7.5%) experienced DLTs: grade 3 SAE of worsening tumor pain on day 8, which resolved after 14 days but led to dose omission (250 mg); grade 3 SAEs of nausea, vomiting, and headache on day 1, which resolved after 3 days but vomiting led to treatment discontinuation (500 mg); and grade 3 non-ST segment elevation myocardial infarction following the initial infusion, which resolved after 2 days but led to permanent treatment discontinuation (750 mg). Because of the severity of the event that occurred at 750 mg, this dose was not considered tolerated, even though a formal MTD was not reached.

Any-grade treatment-related AEs occurred in 82.5% of patients (**Table 2**), most commonly headache (25.0%), infusion-related reaction (IRR, 17.5%), and decreased appetite (17.5%). grade 3/4 treatment-related AEs occurred in 8 patients (20.0%), predominantly at doses ≥250 mg; none were reported in >1 patient. There were no treatment-related grade 5 AEs. Five patients (12.5%) had a treatment-related SAE: 3 of 15 patients (20.0%) in the 250 mg group (pain, ejection fraction decreased, and pneumonitis); 1 of 7 patients (14.3%) in the 500 mg group (nausea and vomiting); and 1 of 1 patient (100%) in the 750 mg group (acute myocardial infarction). Three patients (7.5%) had a treatment-related AE that led to permanent discontinuation of MEDI1873: 1 of 15 patients (6.7%) in the 250 mg group (grade 3 pneumonitis); 1 of 7 patients (14.3%) in the 500 mg group (grade 3 vomiting); and 1 of 1 patient (100%) in the 750 mg group (grade 3 acute myocardial infarction).

Headache and vomiting were grade 3 in only 1 patient. Generally, headaches were managed with analgesics, such as acetaminophen and caffeine supplements. Headaches were mostly self-limiting and transient. Nausea and vomiting were generally low grade and manageable with prescription medications. None of the events required special precautions or modifications to AE management plans.

Further investigation into cardiac-related AEs revealed that the myocardial infarction occurred in a patient with a medical history of chest pain, obesity, hypertension, hyperlipidemia, and bilateral edema in lower extremities, who was hospitalized 3 hours after study drug administration with chest pain and later recovered. In addition, a patient with a medical history of hypertension, arrhythmia, and type 2 diabetes receiving 250 mg had a decreased ejection fraction (25%–30% from a baseline of 30%–35%) along with severe hypocalcemia. Cardiology consult reported that the event could represent an abnormality related to coronary artery disease of left bundle branch block and might be stress related given his progressive cancer. However, contribution from study drug exposure could not be ruled out.

Efficacy

Best overall response was SD in 17 patients (42.5%), including 1 patient with unconfirmed PR and 8 (20.0%) with SD ≥24 weeks (95% CI, 9.8–38.2; **Table 3**; **Fig. 1**). Of these 17 patients, the response of SD by tumor type was as follows: colon (7/20, 35.0%), NSCLC (1/1, 100%), small-cell lung cancer (SCLC; 1/1, 100%), soft-tissue sarcoma (1/1, 100%), adenoid cystic carcinoma (1/1, 100%), mesothelioma (2/3, 66.7%), neuroendocrine cancer (1/1, 100%), pancreatic neuroendocrine tumor (2/2, 100%, including the patient with unconfirmed PR), and cervical cancer (1/2, 50%). Of the 8 patients with SD ≥24 weeks, the responses by tumor type were colon (3/20, 15.0%), pancreatic neuroendocrine tumor (2/2, 100%), SCLC (1/1, 100%), adenoid cystic carcinoma (1/1, 100%), and mesothelioma (1/3, 33.3%). Three patients had SD >1 year (1 each with SCLC, pancreatic neuroendocrine tumor, and mesothelioma).

Five patients had received prior PD-1/PD-L1 therapy (4 for metastatic disease and 1 in the adjuvant setting). None had SD ≥24 weeks with MEDI1873 (**Fig. 1**). Their tumor types were HNSCC lip and oral cavity ($n = 1$), prostate ($n = 1$), NSCLC ($n = 1$), soft-tissue sarcoma ($n = 1$), and human papillomavirus-associated (HPV$^+$) oropharyngeal squamous cell carcinoma ($n = 1$). Median progression-free survival (PFS)

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Table 2. Treatment-related AEs (any grade events occurring in >10% of patients, and all grade 3/4 events).

	MEDI1873 dose								
***n* (%)**	**1.5 mg *n* = 1**	**3.0 mg *n* = 1**	**7.5 mg *n* = 3**	**25 mg *n* = 3**	**75 mg *n* = 9**	**250 mg *n* = 15**	**500 mg *n* = 7**	**750 mg *n* = 1**	**Total *N* = 40**
Any grade AEs with incidence >10%	1 (100)	1 (100)	3 (100)	2 (66.7)	4 (44.4)	14 (93.3)	7 (100)	1 (100)	33 (82.5)
Headache				1 (33.3)	1 (11.1)	2 (13.3)	5 (71.4)	1 (100)	10 (25.0)
Decreased appetite			1 (33.3)			4 (26.7)	2 (28.6)		7 (17.5)
IRR					1 (11.1)	5 (33.3)	1 (14.3)		7 (17.5)
Fatigue			1 (33.3)	2 (66.7)	1 (11.1)	2 (13.3)			6 (15.0)
Nausea			1 (33.3)		1 (11.1)	1 (6.7)	2 (28.6)	1 (100)	6 (15.0)
Vomiting						2 (13.3)	3 (42.9)	1 (100)	6 (15.0)
Diarrhea			1 (33.3)	1 (33.3)		3 (20.0)			5 (12.5)
Grade 3/4 AEs		1 (100)				5 (33.3)	1 (14.3)	1 (100)	8 (20)
Acute myocardial infarction								1 (100)	1 (2.5)
Amylase increased		1 (100)							1 (2.5)
Aspartate aminotransferase increased						1 (6.7)			1 (2.5)
Dyspnea						1 (6.7)			1 (2.5)
Ejection fraction decreased						1 (6.7)			1 (2.5)
Headache							1 (14.3)		1 (2.5)
Nausea							1 (14.3)		1 (2.5)
Pain						1 (6.7)			1 (2.5)
Pneumonitis						1 (6.7)			1 (2.5)
Rash						1 (6.7)			1 (2.5)
Tumor pain						1 (6.7)			1 (2.5)
Vomiting							1 (14.3)		1 (2.5)

was 1.9 months (95% CI, 1.8–3.6) and median overall survival (OS) was 16.2 months (95% CI, 8.0–not estimable).

Two patients received MEDI1873 retreatment after the 52-week treatment period. One had mesothelioma and experienced an initial PFS of 534 days, a second PFS of 57+ days, and an OS of 633+ days. The other patient (the patient with an unconfirmed PR) had pancreatic neuroendocrine cancer and experienced an initial PFS of 716 days, a second PFS of 56+ days, and an OS of 890+ days.

Pharmacokinetics

Pharmacokinetics data were available for 40 patients. Exposure (C_{max}/D and AUC_{0-t}/D) was consistent across MEDI1873 doses of 1.5–750 mg, indicating linear kinetics (Supplementary Fig. S1). Geometric mean terminal half-life ($t_{1/2}$) ranged from 1.3 to 2.4 days. MEDI1873 clearance was similar across the 75–500 mg doses (where the apparent terminal elimination phase was better characterized), ranging from 2.88 to 3.96 L/day. The incidence of ADAs was approximately 20% and titers were generally low. The pharmacokinetics exposure of MEDI1873 was similar between patients with and without treatment-emergent ADAs, suggesting that the effect of immunogenicity on exposure was minimal.

Table 3. Tumor response.

Response	**Total (*N* = 40)**
Best overall response, *n* (%)	
CR	0
PR	0
SD	17 (42.5)
Unconfirmed CR	0
Unconfirmed PR	1 (2.5)
PD	20 (50.0)
Not available	3 (7.5)
SD ≥24 weeks, *n* (%)	8 (20.0)
95% CI	9.8–38.2

Pharmacodynamics

MEDI1873 engaged GITR as evidenced by >50% reductions in peripheral GITR-expressing memory $CD4^+$ T cells using a competitive target engagement assay (Supplementary Fig. S2). Changes from baseline in $GITR^+$ cells occurred at all dose levels tested (25, 75, 250, and 500 mg) on days 2 and 3. The duration of $GITR^+$ T-cell suppression correlated with MEDI1873 dose. In the 25 and 75 mg cohorts, $GITR^+$ cell levels returned to baseline on day 15 and thereafter. No substantial decrease in total effector memory T cells was detected (data not shown).

MEDI1873 increased peripheral $CD4^+$ effector memory T-cell proliferation at dose levels ≥75 mg on day 15, as shown by increases in baseline normalized $Ki67^+$ $CD4^+$ T cells (Supplementary Fig. S3A). $GITR^+$ levels on $CD8^+$ T cells were significantly lower than on $CD4^+$ T cells and no elevations in $CD8^+$ $Ki67^+$ T cells were detected (data not shown).

MEDI1873 induced an increase in peripheral IFNγ, which was associated with GITR engagement. Maximum target engagement, characterized by a reduction in GITR expression, coincided with peak cytokine secretion (Supplementary Fig. S3B). At doses ≥75 mg, peripheral IFNγ, IFNγ-induced protein 10 (IP-10), IFN-inducible T-cell alpha chemoattractant, and monokine induced by IFNγ were elevated on days 2 and 3. Following the first dose, patients receiving MEDI1873 75–250 mg every 2 weeks had higher and/or more sustained increases in type-2 IFNγ than those receiving lower doses (Supplementary Fig. S4). Patients with SD ≥24 weeks showed Ki67 and cytokine changes similar to their respective dose cohorts.

In the tumor, MEDI1873 reduced tumoral $GITR^+$ $FoxP3^+$ cells at doses ≥75 mg, consistent with its expected mechanism of action (**Fig. 2**). All 5 patients with evaluable paired biopsies showed a ≥25% decrease in $GITR^+$ cell populations ($GITR^+/FoxP3^+$ and

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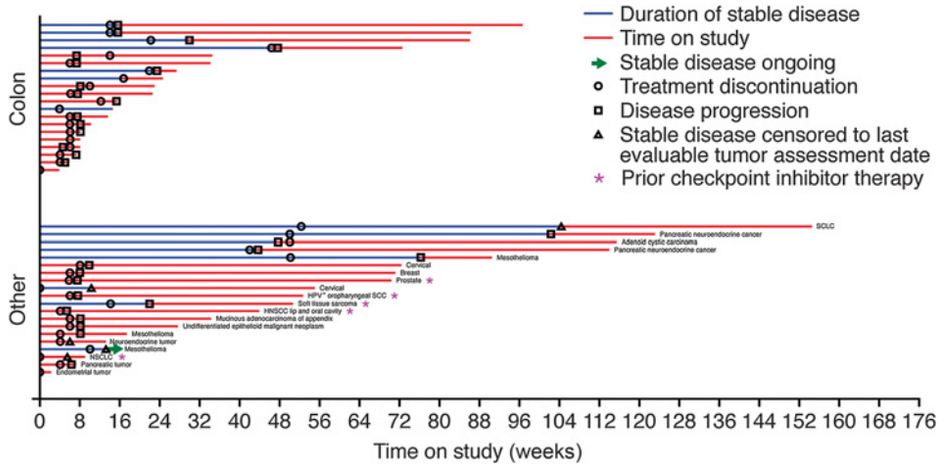

Figure 1.
Time on study drug and duration of SD for all tumor types. The duration of SD (blue) and the total time on study drug (red), are shown for patient cohorts with colon cancer or other cancers.

GITR$^+$/FoxP3$^-$; **Fig. 2A**), and 1 of 8 evaluable patients showed a more than 2-fold increase in CD8$^+$ and PD-L1$^+$ cells (**Fig. 2B**). This patient also had the highest baseline levels of peripheral blood GITR expression on CD4$^+$ T cells. Patients with high (≥median) baseline GITR levels had a sustained elevation of peripheral blood Ki67$^+$ CD4$^+$ T cells to day 43 (**Fig. 3**).

Discussion

GITR agonists have demonstrated therapeutic potential in preclinical models (10–13). In this first-in-human study, MEDI1873, a GITR ligand/IgG1 agonist fusion protein, was well tolerated at doses up to 500 mg every 2 weeks in patients with advanced solid tumors. While no formal MTD was reached, the maximum administered dose (750 mg) was not considered tolerated because of the nature and severity of the observed DLT (myocardial infarction) at that dose level. While concomitant comorbid conditions may have contributed, a study drug etiology could not be ruled out. Immediately following the myocardial infarction, cardiac catherization showed complete occlusion of the left anterior descending coronary artery with evidence of collaterals. Another patient receiving 250 mg had a decreased ejection fraction. In both cases, the events were deemed possibly drug-related, but they may not have been immune-induced events or related to the target.

MEDI1873-related AEs were generally mild or moderate in severity, and the AE profile was, as expected, based on early clinical studies of other GITR agonists (15). There were no on-study deaths and the immunogenicity profile was acceptable. No patients had a CR or confirmed PR. However, 17 patients (42.5%) had a best response of SD, including 1 unconfirmed PR. Eight (20%) SD patients had prolonged SD ≥24 weeks across several tumor types. Similar findings were reported among patients with advanced solid tumors in a phase I first-in-human study of the GITR agonist TRX-518 (16). Although some patients with prolonged SD in this study had cancers that typically have an indolent course, such as pancreatic neuroendocrine cancer and adenoid cystic carcinoma, it is unlikely to account for the prolonged SD with MEDI1873, as all of these patients were progressing rapidly on previous treatment (Supplementary Table S1). Despite this, these data suggest that GITR agonist monotherapy may not be sufficient to produce a robust anticancer effect in a heavily pretreated population and that combinations with checkpoint inhibitors or other drug classes may be required to evaluate its anticancer potential.

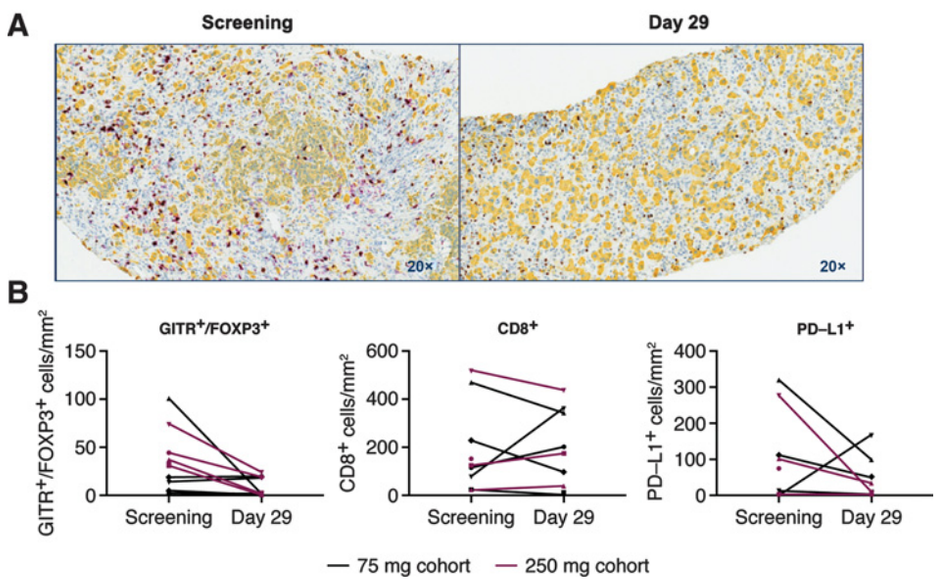

Figure 2.
Changes in tumoral biomarkers. Several tumoral biomarkers were assessed at screening and on day 29. **A,** Representative multiplex IHC staining of a tissue biopsy from a colorectal cancer liver metastasis. GITR is stained purple, FOXP3 is stained brown, and cytokeratin is stained yellow. **B,** Changes in expression of tumoral GITR$^+$ FoxP3$^+$ cells, CD8$^+$ cells, and PD-L1$^+$ cells, in the 75 and 250 mg cohorts.

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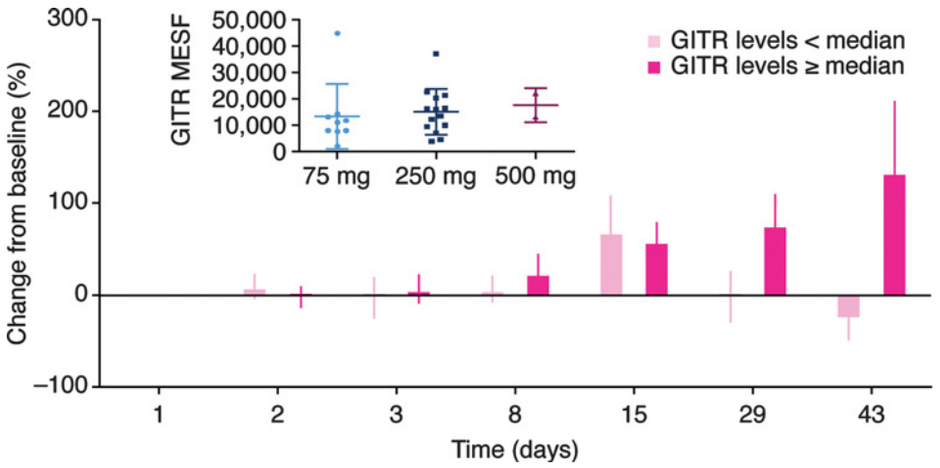

Figure 3.
Changes in peripheral blood T cells. Percent changes from baseline in $Ki67^+$ $CD4^+$ cells stratified by baseline GITR in the pooled 75, 250, and 500 mg cohorts. MESF, molecule equivalents of soluble fluorescence.

MEDI1873 was shown to engage with GITR on circulating memory T cells, and the duration of activity was dose related. The interaction between MEDI1873 and GITR induced robust pharmacodynamic effects, enhancing effector T-cell function and reducing Treg activity. These pharmacodynamic effects are consistent with the molecule's mechanism of action and may be enhanced in patients with high baseline GITR expression. In preclinical models, at least a 50% increase in proliferation (Ki67) or IFN-producing cells was observed in the periphery, and tumoral Tregs were depleted by >75%. The effects were greater in preclinical models than in humans, but this is also true of other immune checkpoint inhibitors such as CTLA-4 and PD-1 blockers.

Two other GITR agonists, MK-4166 and AMG-228, have a longer half-life than MEDI1873, but have been used at doses that saturate GITR receptor occupancy over the dosing cycle (15, 17, 18). The shorter half-life (2 days) and high agonistic potency of MEDI1873 (14) suggest that not having 100% GITR occupancy on circulating T cells over the whole dosing cycle may be beneficial. This concept is further supported by the clinical benefits (prolonged SD) observed at doses lower than 250 mg in this study. In addition, $Ki67^+$ T-cell activation and IFNγ-related cytokine release occurred at doses of 7.5–25 mg; loss of GITR expression was observed at a dose of 75 mg and for 1 patient there was an increase in intratumoral $CD8^+$ cells at this dose (intratumoral effects were not examined at lower doses). The potential benefit of a dosing schedule that does not require 100% occupancy and enables T-cell activation followed by a period of recovery before restimulation, are also supported by the high IFNγ production observed in patients with high baseline GITR levels, suggesting that a return of GITR to the high baseline levels may be beneficial for clinical effect. Tolerability of the agent is better at lower doses, which may be beneficial for combination regimens.

The limited activity and overall good tolerance of MEDI1873 are consistent with recent data on other molecules targeting GITR as single agents or in combination with PD-1 inhibitors in patients with advanced solid tumors. In a study of 30 patients treated with AMG-228, an IgG1 mAb, tolerability was good, but T-cell activation and antitumor activity were not observed (15). The IgG1 mAb MK-4166 was well tolerated alone and in combination with pembrolizumab in a study of 113 patients, but responses were seen only with combination treatment (18). Similarly, the IgG1 mAb BMS-986156 showed good tolerability alone and in combination with nivolumab in a study of 292 patients, but there were no objective responses with monotherapy (19). Good tolerability was reported in a study of 37 patients treated with the IgG4 mAb MK-1248 alone or in combination with pembrolizumab; 1 patient had a CR and 2 had PRs (20).

Every 2 weeks regimen was selected for MEDI1873 for patient convenience. A dose-dependent increase in pharmacodynamics effect was demonstrated, especially the decrease in $GITR^+$ circulating cells, so more frequent administration was not required. The short half-life of MEDI1873 could have allowed exploration of alternate dosing schedules, but this was precluded by the lack of response. A recommended phase II dose was not formally established in this study, as further clinical development was stopped. A 250 mg dose administered every 3 weeks might be useful in that it would allow GITR and IFNγ levels to return to baseline before subsequent dosing.

In summary, MEDI1873 had an acceptable safety profile in patients with advanced solid tumors at doses ≤500 mg. Although the pharmacodynamics changes in blood and tumor and prolonged SD were encouraging, there are no plans for further clinical exploration of MEDI1873.

Disclosure of Potential Conflicts of Interest

A.S. Balmanoukian reports other from MedImmune/AstraZeneca (financial support for running the trial) during the conduct of the study, as well as other from Bristol-Myers Squibb (speakers bureau), Genentech (speakers bureau), AstraZeneca (speakers bureau), and Merck (speakers bureau) outside of the submitted work. J.R. Infante reports personal fees from Janssen Oncology (employee) during the conduct of the study and outside of the submitted work. R. Aljumaily reports other from AstraZeneca (payment to institution) during the conduct of the study, as well as other from Alliance Foundation Trials (payment to institution), Boston Biomedical (payment to institution), Syneos Health (payment to institution), Array BioPharma (payment to institution), Bristol-Myers Squibb (payment to institution), Huntsman Cancer Institute (payment to institution), Merck (payment to institution), AbbVie (payment to institution), Regeneron (payment to institution), G1 Therapeutics (payment to institution), F. Hoffman-La Roche AG (payment to institution), Genentech (payment to institution), MedImmune (payment to institution), GlaxoSmithKline (payment to institution), Novartis (payment to institution), Peloton Therapeutics (payment to institution), Baxalta (payment to institution), Eli Lilly (payment to institution), EMD Serono (payment to institution), Boehringer Ingelheim (payment to institution), Tesaro (payment to institution), Pfizer (payment to institution), and Checkpoint Therapeutics (payment to institution) outside the submitted work. A. Naing reports grants from MedImmune (research funding) during the conduct of the study, and grants from NCI (research funding), EMD Serono (research funding), Karyopharm Therapeutics (research funding), Incyte (research funding), Regeneron (research funding), Merck (research funding), Bristol-Myers Squibb (research funding), Pfizer (research funding), Neon Therapeutics (research funding), Calithera Biosciences (research funding), TopAlliance Biosciences (research funding), Eli Lilly (research funding), Kymab (research funding), PsiOxus (research funding), Arcus Biosciences (research funding), and NeoImmuneTech (research funding), grants and non-financial support from ARMO BioSciences (research funding, travel,

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Authors' Contributions

A.S. Balmanoukian: Conceptualization, resources, investigation, methodology, writing-review and editing. **J.R. Infante:** Conceptualization, resources, investigation, methodology, writing-review and editing. **R. Aljumaily:** Conceptualization, resources, investigation, methodology, writing-review and editing. **A. Naing:** Conceptualization, resources, investigation, methodology, writing-review and editing. **A.V. Chintakuntlawar:** Conceptualization, resources, investigation, methodology, writing-review and editing. **N.A. Rizvi:** Conceptualization, resources, investigation, methodology, writing-review and editing. **H.J. Ross:** Conceptualization, resources, investigation, methodology, writing-review and editing. **M. Gordon:** Conceptualization, resources, investigation, methodology, writing-review and editing. **P.R. Mallinder:** Conceptualization, methodology, writing-review and editing. **N. Elgeioushi:** Formal analysis, methodology, writing-review and editing. **I. González-García:** Formal analysis, methodology, writing-review and editing. **N. Standifer:** Formal analysis, investigation, methodology, writing-review and editing. **J. Cann:** Formal analysis, investigation, methodology, writing-review and editing. **N. Durham:** Formal analysis, investigation, methodology, writing-review and editing. **S. Rahimian:** Conceptualization, methodology, writing-review and editing. **R. Kumar:** Conceptualization, methodology, writing-review and editing. **C.S. Denlinger:** Conceptualization, resources, investigation, methodology, writing-review and editing.

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