Original Article

Efficacy and Safety Results of Depatuxizumab Mafodotin (ABT-414) in Patients With Advanced Solid Tumors Likely to Overexpress Epidermal Growth Factor Receptor

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BACKGROUND: Epidermal growth factor receptor (*EGFR*) alterations are associated with multiple cancers. Current EGFR-directed therapies have led to increased efficacy but are associated with specific side effects. The antibody-drug conjugate depatuxizumab mafodotin (depatux-m) targets EGFR with a monoclonal antibody linked to a cytotoxin, and is highly tumor-specific. **METHODS:** This phase 1/2 study evaluated the safety, pharmacokinetics, and efficacy of depatux-m in patients who had advanced solid tumors with known wild-type *EGFR* overexpression, amplification, or mutated *EGFR* variant III. A 3 + 3 dose escalation was used, and 2 dosing schedules were evaluated. Depatux-m also was manufactured under an alternate process to reduce the drug load and improve the safety profile, and it was tested at the maximum tolerated dose (MTD). In another cohort, prolonged infusion time of depatux-m was evaluated; and a cohort with confirmed *EGFR* amplification also was evaluated at the MTD. **RESULTS:** Fifty-six patients were treated. The MTD and the recommended phase 2 dose for depatux-m was 3.0 mg/kg. Common adverse events (AEs) were blurred vision (48%) and fatigue (41%). A majority of patients (66%) experienced 1 or more ocular AEs. Grade 3 or 4 AEs were observed in 43% of patients. One patient with *EGFR*-amplified, triple-negative breast cancer had a partial response. Stable disease was observed in 23% of patients. Pharmacokinetics revealed that depatux-m exposures were approximately dose-proportional. **CONCLUSIONS:** Depatux-m resulted in infrequent nonocular AEs but increased ocular AEs. Patient follow-up confirmed that ocular AEs were reversible. Lowering the drug-antibody ratio did not decrease the number of ocular AEs. A partial response in 1 patient with *EGFR*-amplified disease provides the opportunity to study depatux-m in diseases with a high incidence of *EGFR* amplification. ***Cancer*** **2018;124:2174-83**.

KEYWORDS: ABT-414, antibody-drug conjugate, epidermal growth factor receptor (EGFR), depatuxizumab mafodotin (depatux-m).

INTRODUCTION

Alterations in the epidermal growth factor receptor (*EGFR*) gene play an important role in the development of many human cancers.[1] Overexpression, activation, and/or mutations of *EGFR* are associated with an aggressive cancer phenotype and are implicated in tumor progression through a variety of cellular processes, including cell proliferation, apoptosis, angiogenesis, and metastasis.[1]

EGFR was first proven as a viable oncology target in studies that used EGFR-directed monoclonal antibodies, such as cetuximab, for the treatment of colorectal[2] and head and neck[3] cancers. These and other targeted EGFR therapies, including tyrosine kinase inhibitors (such as erlotinib and gefitinib) in patients with *EGFR*-activating mutations have gained widespread use in several tumor types, notably lung[4] and head and neck[3] cancers, leading to an increase in progression-free and overall survival of patients.

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Depatuxizumab (depatux) (formerly ABT-806) is a veneered, humanized, recombinant immunoglobulin G1κ (IgG1κ) monoclonal antibody targeting a unique conformation of human EGFR that is exposed due to EGFR overexpression (increased receptor density), high levels of gene amplification, or a mutant form of *EGFR* with deletion of exons 2 through 7 (*EGFR* variant III [*EGFRvIII*]).[5] This EGFR epitope is largely inaccessible when *EGFR* is expressed normally, contributing to limited binding of depatux in normal tissues.[5] An initial phase 1 study demonstrated that depatux had high tumor specificity,[6] with no dose-limiting acneiform skin rashes or diarrhea that commonly occur with EGFR-directed therapies.[7]

Antibody-drug conjugates (ADCs) belong to a class of drugs that harness the targeting property of a monoclonal antibody and link it to a potent, cytotoxic drug. A major advantage of ADCs is their ability to deliver a toxic payload directly to a tumor, bypassing downstream resistance mechanisms.[8] Depatuxizumab mafodotin (depatux-m) (formerly ABT-414) is a novel ADC targeting EGFR in which cysteine (cys) residues of the depatux antibody were conjugated to a potent antimicrotubule agent, monomethyl auristatin F (MMAF), through a noncleavable maleimidocaproyl (mc) linker (mc-MMAF [mafodotin]).[5,9] The antibody selectively binds the depatux tumor-selective EGFR epitope on the surface of the cell, is internalized and degraded, and releases Cys-mcMMAF (Cys-mafodotin). MMAF binds to the microtubule network, leading to cell cycle arrest and cell death. Preclinical studies indicate that depatux-m has antitumor activity in cell lines and mouse xenograft models.[9]

The drug-antibody ratio (DAR) refers to the number of toxin molecules covalently linked to the antibody backbone of an ADC. The average DAR of depatux-m is approximately 4. However, in a purification process (process B) that eliminates higher order DAR species, another version of depatux-m was manufactured with an average DAR of 3. Decreasing the DAR of an ADC has been thought to help decrease adverse side effects, and previous work has indicated that a reduction in DAR does not lead to a decline in antitumor activity.[10] To our knowledge, this is the first clinical evaluation of the safety and efficacy of 2 different DAR species of the same ADC.

On the basis of the history of EGFR-targeted therapy and more recent data, we undertook a study of depatux-m at 2 different DARs in patients who had advanced solid tumors likely to overexpress *EGFR*. Here, we present safety, pharmacokinetics (PKs), and preliminary efficacy data on depatux-m in a refractory population.

MATERIALS AND METHODS

Study Design

Study M13-379 (clinicaltrials.gov identifier NCT01741727) was designed as a phase 1 and 2, open-label study to evaluate the safety, PKs, and efficacy of depatux-m in patients with advanced solid tumors; however, the study sponsor ultimately decided not to extend the study into the phase 2 expansion cohort, and no patients were enrolled in that phase. The study design (Fig. 1) was intended to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RPTD) and to evaluate depatux-m in patients who had tumors with *EGFR* overexpression to determine efficacy in that population. In addition, several techniques were evaluated to determine potential improvements in the toxicity profile, including 2 depatux-m drug manufacturing processes (the original process A and alternate process B), 2 administration schedules (dosing every 3 weeks and 2 weeks on/1 week off dosing), and prolonged infusion times (approximately 6 hours).

This trial was approved by the independent ethics committees/institutional review boards at all participating sites. Written, informed consent from all patients or their legal representative was obtained before enrollment. The study was conducted in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and the Declaration of Helsinki and its later amendments.

Patient Eligibility Criteria

Eligible patients were aged $\geq$18 years; had a solid tumor type known to overexpress wild-type *EGFR*, to express *EGFRvIII*, or to be *EGFR*-amplified; had disease that could not be treated by surgical resection or other approved therapeutic options with curative intent; and had an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients provided either an archived, diagnostic, formalin-fixed, paraffin-embedded or frozen tumor tissue sample or a tumor biopsy sample that was collected before the first dose of depatux-m, to be available for pharmacodynamics analyses. Patients had adequate bone marrow, renal, and hepatic function (patients with liver metastasis could have aspartate and alanine transferase levels $\leq$5.0 times the upper normal limit). Women of childbearing potential and men who agreed to use adequate contraception before, during, and 3 months after the completion of therapy were allowed. Patients were ineligible if they had uncontrolled metastases to the central nervous system; received anticancer therapy or underwent major surgery within 28 days before the first dose of depatux-m; or received a prior

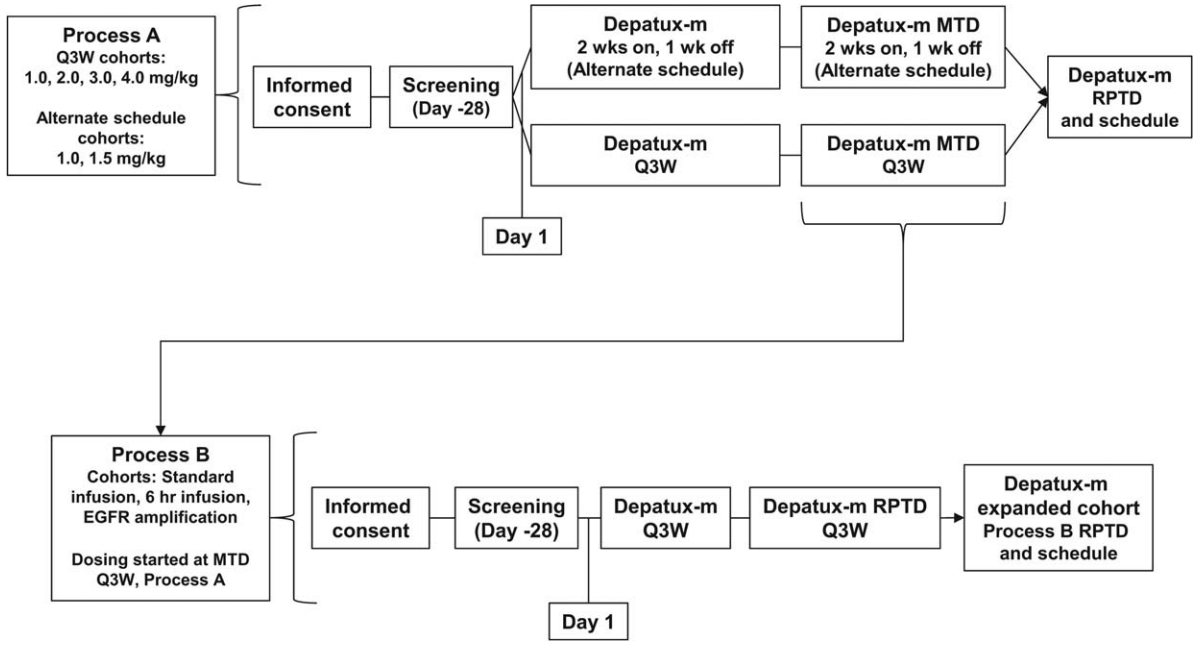

Figure 1. The study schema is illustrated. EGFR indicates epidermal growth factor receptor; MTD, maximum tolerated dose; Q3W, once every 3 weeks; RPTD, recommended phase 2 dose.

EGFR-directed monoclonal antibody within 4 weeks before the first dose of depatux-m, including depatux.

Treatment Regimen

Depatux-m was administered intravenously at a starting dose of 1.0 mg/kg over 30 to 40 minutes. Dosing proceeded in sequential cohorts with a 3 + 3 design and evaluated dose-limiting toxicities (DLTs). Two dosing schemes were evaluated in parallel: once every 3 weeks and an alternate schedule of 2 weeks on/1 week off, both under the original manufacturing process (process A). For the once every 3 weeks schedule, doses of 1.0, 2.0, 3.0, and 4.0 mg/kg were tested (cohorts 1-4). For the alternate schedule, 1.0 and 1.5 mg/kg doses were tested (cohorts 1A and 2A). Evaluation of the alternative manufacturing process (process B) started at the MTD of once every 3 weeks dosing (3.0 mg/kg; cohort 1B), as determined by process A. A 6-hour, prolonged infusion time was evaluated in a separate cohort at the same MTD (cohort 2B). The RPTD was selected based on the types of DLTs that occurred and the determined MTD. An additional cohort of patients who had tumors with confirmed *EGFR* amplification was evaluated at the RPTD (3.0 mg/kg, once every 3 weeks; cohort 3B) determined from process B.

A steroid ophthalmic solution was implemented at a depatux-m dose of $\geq$2.0 mg/kg to improve tolerability to the ocular side effects. Dexamethasone 0.1% solution, with 2 drops in each eye every 8 hours starting 3 days before depatux-m dosing and continuing for 10 days, was recommended. Further materials and methods are detailed in the supporting information.

RESULTS

Patient Demographics

In total, 56 patients with various tumor types who had received a median of 3 prior therapies (range, 0-7 prior therapies) were enrolled in the study (Table 1). Twenty-one of those patients (38%) had tumors that overexpressed *EGFR*, and 10 (18%) had a confirmed Kirstin rat sarcoma virus oncogene (*KRAS*) mutation.

Safety of Depatux-M

In total, 55 of 56 patients (98%) experienced at least 1 adverse event (AE) (Table 2). Common AEs included blurred vision in 27 of 56 patients (48%) and fatigue in 23 of 56 patients (41%). Thirty-seven patients (66%) experienced some type of ocular side effect. The descriptions of the ocular side effects from various ophthalmologists involved in the study were identical to what was observed in subsequent depatux-m clinical trials and with other ADCs, termed microcystic keratopathy.[11-13] The most frequent ocular AEs observed in the study, such as blurred vision, dry eye, and photophobia, were consistent with the pathology and symptomology described for

TABLE 1. Patient Demographics

Characteristic	No. of Patients									
	Process A				Alternate Schedule		Process B	6-Hour Infusion	*EGFR*-Amplified	
	C1	C2	C3	C4	C1A	C2A	C1B	C2B	C3B	
	1.0 mg/kg, n = 3	2.0 mg/kg, n = 10	3.0 mg/kg, n = 5	4.0 mg/kg, n = 5	1.0 mg/kg, n = 6	1.5 mg/kg, n = 1	3.0 mg/kg, n = 11	3.0 mg/kg, n = 7	3.0 mg/kg, n = 8	Total No. (%), N = 56
Sex										
Women	2	3	3	4	4	0	8	5	3	32 (57)
Men	1	7	2	1	2	1	3	2	5	24 (43)
Age, y										
<40	0	0	0	0	0	0	1	0	0	1 (2)
40 to <60	1	5	3	1	4	1	6	3	3	27 (48)
≥60	2	5	2	4	2	0	4	4	5	28 (50)
Tumor type										
Anal	0	0	0	0	0	0	1	1	0	2 (4)
Breast	0	0	0	1	0	0	1	0	1	3 (5)
Cervical	1	0	0	0	0	0	0	0	0	1 (2)
Cholangio.	0	0	0	0	0	0	1	0	0	1 (2)
Colon	0	3	0	1	0	1	2	1	2	10 (18)
Esophageal	0	0	0	0	0	0	0	1	0	1 (2)
Gastric	0	0	0	0	1	0	0	0	0	1 (2)
Head & neck	2	1	1	0	0	0	4	0	2	10 (18)
NSCLC	0	5	4	2	3	0	1	1	2	18 (32)
Pancreatic	0	0	0	1	0	0	0	0	0	1 (2)
Pelvic	0	0	0	0	0	0	0	1	0	1 (2)
Penile SCC	0	0	0	0	1	0	0	0	0	1 (2)
Rectal	0	0	0	0	0	0	0	1	0	1 (2)
Skin	0	0	0	0	0	0	0	1	0	1 (2)
Thymic	0	1	0	0	0	0	0	0	0	1 (2)
Tonsil	0	0	0	0	0	0	0	0	1	1 (2)
Vulvar	0	0	0	0	0	0	1	0	0	1 (2)
Vulvar SCC	0	0	0	0	1	0	0	0	0	1 (2)
EGFR overexpression[a]										
Yes	2	3	2	2	2	0	5	1	4	21 (38)
No	1	6	2	3	3	1	4	1	3	24 (42)
Unknown	0	1	1	0	1	0	2	5	1	11 (20)
KRAS mutation										
Yes	0	3	0	1	0	0	3	2	1	10 (18)
No	1	4	1	1	1	1	2	1	3	15 (27)
Unknown	2	3	4	3	5	0	6	4	4	31 (55)
ECOG score										
0	1	3	1	3	4	0	3	1	1	17 (30)
1	2	7	3	2	2	1	8	6	7	38 (68)
2	0	0	1	0	0	0	0	0	0	1 (2)

Abbreviations: C, cohort; Cholangio., cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene; NSCLC, non-small cell lung carcinoma; SCC, squamous cell carcinoma.

[a] EGFR expression was determined by the H-score for immunohistochemistry; an H-score ≥150 was considered overexpression.

TABLE 2. Adverse Events

Adverse Event	No. of Patients										Total No. (%), N = 56
	Process A				Alternate Schedule		Process B	6-Hour Infusion	*EGFR*-Amplified		
	C1	C2	C3	C4	C1A	C2A	C1B	C2B	C3B		
	1.0 mg/kg, n = 3	2.0 mg/kg, n = 10	3.0 mg/kg, n = 5	4.0 mg/kg, n = 5	1.0 mg/kg, n = 6	1.5 mg/kg, n = 1	3.0 mg/kg, n = 11	3.0 mg/kg, n = 7	3.0 mg/kg, n = 8		
Any AE in ≥20% total patients	3	10	5	4	5	1	11	7	8		55 (98)
Nonocular											
Fatigue	1	5	2	2	3	0	5	4	1		23 (41)
Nausea	0	4	1	2	2	1	7	5	0		22 (39)
Vomiting	1	3	0	2	2	1	5	4	0		18 (32)
Decreased appetite	0	2	2	3	0	0	4	3	1		15 (27)
Ocular											
Vision blurred	0	6	3	4	3	0	5	5	1		27 (48)
Dry eye	1	7	3	1	2	0	3	2	1		20 (36)
Keratitis	0	2	1	1	1	0	5	3	0		13 (23)
Photophobia	1	2	1	2	2	0	3	2	0		13 (23)

Abbreviations: AE, adverse event; C, cohort; EGFR, epidermal growth factor receptor.

microcystic keratopathy (Supporting Table 1). Twenty-four patients (43%) experienced a grade 3 or 4 AE (Table 3), and 8 of 56 patients (14%; all ocular in nature) had grade 3 or 4 AEs that were deemed possibly related to depatux-m by either the investigator or the sponsor. However, the only grade 4 event was an instance of hyponatremia in 1 patient from cohort 3, which was unrelated to depatux-m.

Serious AEs were reported in 19 of 56 patients (34%). The only serious AEs observed in more than 1 patient were pneumonia in 3 of 56 patients (5%) and disease progression and dyspnea (both in 2 of 56 patients; 4%). DLTs were reported in 2 of 56 patients (4%), including 1 patient in cohort 2 with eye pain and 1 in cohort 1B with facial swelling (Supporting Table 2). Two of 56 patients (4%) had AEs that led to a dose reduction in depatux-m, including 1 patient in cohort 2 who experienced dry eye and eye pain and 1 in cohort 2B who had keratitis (Supporting Table 1). Eleven patients (20%) had an AE that led to discontinuation of depatux-m treatment (Supporting Table 2). Five patients had AEs resulting in death, with 4 of the events caused by disease progression and the other as a result of cardiac arrest that was not treatment-related or because of disease progression.

Of 56 patients, discontinuation of depatux-m occurred because of progressive disease radiographic (64.3%), progressive disease clinical (21.4%), AE related to progression (10.7%), AE not related to progression (8.9%), withdrawal of consent (7.1%), loss to follow-up (5.4%), or other reasons (7.1%).

Pharmacokinetics

Three analytes (depatux-m, total depatux, and Cys-mafodotin) were measured to characterize the PKs of the ADC (Fig. 2). Depatux-m serum concentrations were moderately lower than those of total depatux, and circulating plasma concentrations of Cys-mafodotin were significantly lower than those of depatux-m (Fig. 2A). The maximum concentrations of depatux-m and total depatux typically were achieved soon after the end of infusion. The systemic exposures, maximum serum concentrations (C_{max}), and areas under the curve on day 21 ($AUC_{day\ 21}$) of depatux-m achieved after the first administration of depatux-m by intravenous infusion were dose-proportional (Fig. 2B,C). The harmonic mean terminal half-life of depatux-m, total depatux, and Cys-mafodotin were approximately 10, 12, and 4 days, respectively. The PKs for depatux-m, total depatux, and Cys-mafodotin also were determined at depatux-m dose levels of 1.0 to 4.0 mg/kg (Supporting Table 3). The depatux-m PKs were linear, and no target-mediated disposition was observed within the dose ranges administered.

TABLE 3. Grade 3 and 4 Adverse Events

	No. of Patients									
	Process A				Alternate Schedule		Process B	6-Hour Infusion	*EGFR*-Amplified	
	C1	C2	C3	C4	C1A	C2A	C1B	C2B	C3B	
Grade 3/4 AEs	1.0 mg/kg, n = 3	2.0 mg/kg, n = 10	3.0 mg/kg, n = 5	4.0 mg/kg, n = 5	1.0 mg/kg, n = 6	1.5 mg/kg, n = 1	3.0 mg/kg, n = 11	3.0 mg/kg, n = 7	3.0 mg/kg, n = 8	Total No. (%), N = 56
Any grade 3/4 AE in >1 patient	0	4	1	2	3	1	4	5	4	24 (43)
Nonocular										
Hyponatremia										
Grade 3	0	0	0	0	1	0	1	1	2	5 (9)
Grade 4	0	0	0	1	0	0	0	0	0	1 (2)
Dyspnea										
Grade 3	0	0	0	0	0	0	1	2	1	4 (7)
Anemia										
Grade 3	0	0	0	0	0	0	0	2	1	3 (5)
Pneumonia										
Grade 3	0	0	0	0	1	0	0	1	1	3 (5)
Fatigue										
Grade 3	0	0	0	1	0	0	1	0	0	2 (4)
Ocular										
Keratitis										
Grade 3	0	1	0	1	0	0	2	0	0	4 (7)
Vision blurred										
Grade 3	0	0	0	1	1	0	0	1	1	4 (7)
Dry eye										
Grade 3	0	0	0	1	0	0	0	0	1	2 (4)

Abbreviations: AE, adverse event; C, cohort; EGFR, epidermal growth factor receptor.

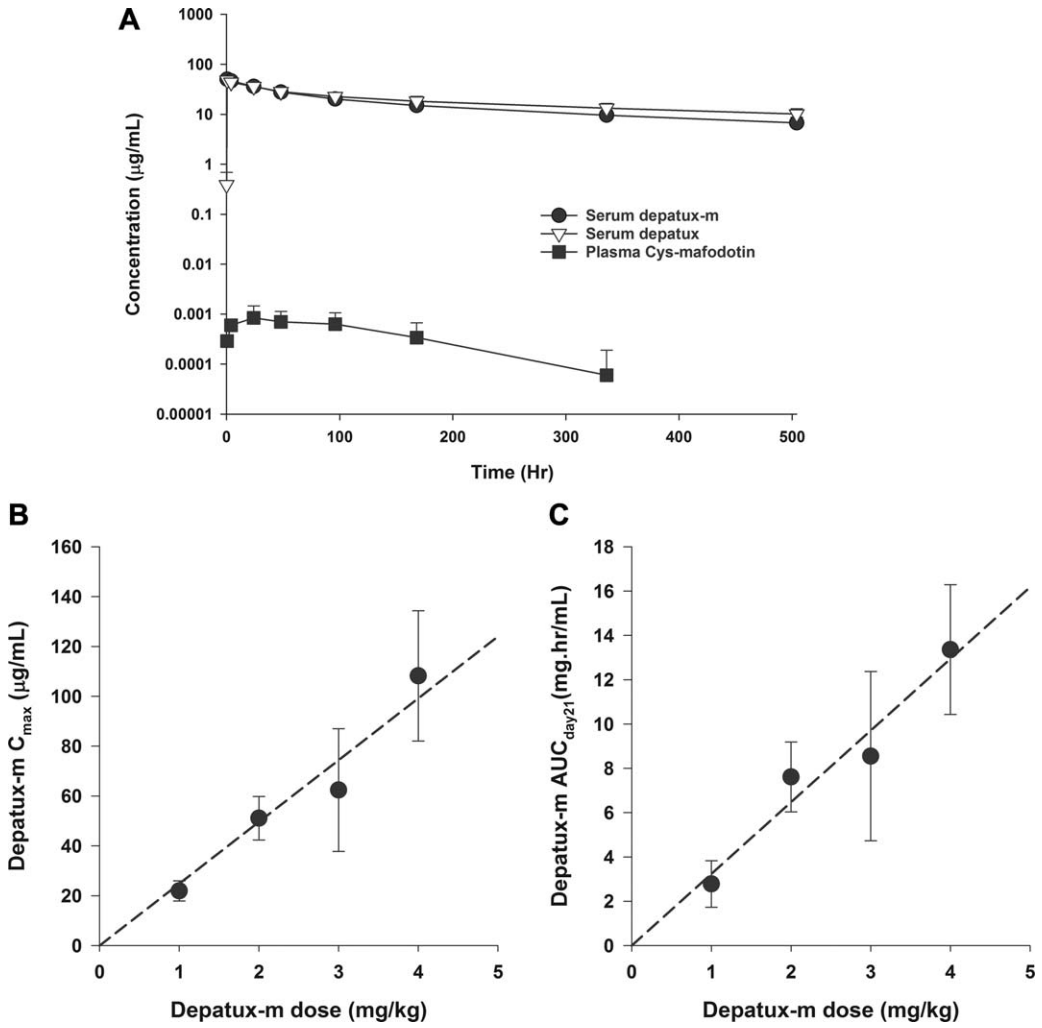

Figure 2. The pharmacokinetics of depatuxizumab mafodotin (depatux-m), total depatux, and Cys-mafodotin are illustrated. (A) Concentration-time profiles are illustrated for each analyte after the first intravenous infusion of depatux-m at 2 mg/kg. Mean ± standard deviation values are shown for the depatux-m (B) maximum serum concentration (C_{max}) and (C) area under the curve on day 21 ($AUC_{day\ 21}$) versus the depatux-m dose.

Biomarker Analysis

A range of EGFR protein expression was observed across tumors. Tumors from 21 patients had H-scores ≥150, and 24 tumors had H-scores <150 (Table 1). Of the 35 patients whose tumor samples underwent fluorescence in situ hybridization analysis to determine *EGFR* amplification, 6 had *EGFR*-amplified tumors, including 1 who had a confirmed partial response (PR) (Fig. 3). Only 1 patient in cohort 2 was positive for the *EGFRvIII* mutation and also had *EGFR* amplification.

Efficacy of Depatux-M

Across all cohorts, the median duration of depatux-m exposure was 22 days. Twenty-one of 56 patients (38%) received treatment for 0 to 3 weeks, and 26 of 56 (46%) received treatment for >3 weeks and up to 6 weeks.

Fifty-two of 56 patients had data available to assess response to treatment (Fig. 3). The remaining 4 patients did not have a follow-up scan after their initial baseline assessment. A PR was observed in 1 patient (2%) who had triple-negative breast cancer that was also *EGFR*-amplified (Fig. 3). Stable disease was observed in 12 of 52 patients, (23%) and 39 of 52 patients (75%) had progressive disease.

DISCUSSION

This phase 1 study of patients with advanced solid tumors demonstrated that depatux-m was generally well tolerated in this refractory population. Aside from ocular side effects and fatigue, the AEs observed in this population

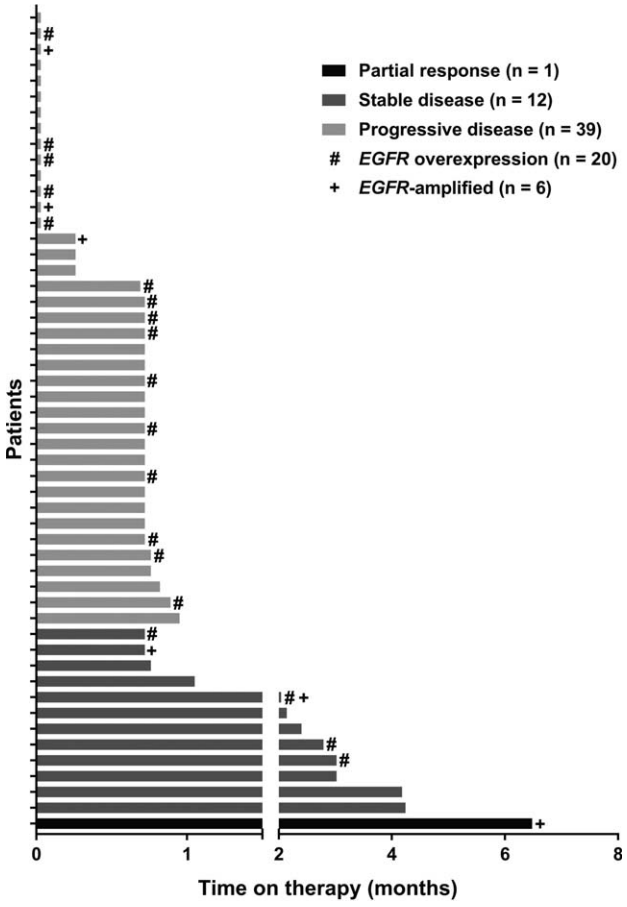

Figure 3. Best response and time on therapy are illustrated. The best responses, as determined by the investigator, and the time on depatuxizumab mafodotin (depatux-m) therapy are shown for 52 of 56 patients who had data available. EGFR indicates epidermal growth factor receptor.

were consistent with what would be expected in patients with the advanced cancers studied.

ADCs are promising therapeutics for cancer treatment, but there are various side effects associated with their use. ADCs capitalize on the molecular binding of a monoclonal antibody and cytotoxic payload through a chemical linker, and toxicity can be caused by any component of the ADC. It is important that the antibody exhibit specific and efficient binding to the antigen on tumor cells with little to no binding on normal cells. Both the monoclonal antibody targeting EGFR (depatux) and the ADC in which it is used (depatux-m) demonstrated minimal binding in normal tissues and did not lead to the other toxicities[5,6,14] usually associated with EGFR-targeted therapies.[7,15] The linker is less likely to drive toxicity, although its stability can influence the toxicity derived from the payloads,[11] which are highly active because of their effects on cellular processes necessary for survival.

Ocular AEs were the most challenging side effects associated with depatux-m. The underlying factors leading to ocular side effects, specifically because of microcystic keratopathy, are unknown. We hypothesize that these effects may be 2-pronged: related to both the physiology of the eye and the properties of the ADC itself. The symptoms were limited to manifestations of microcyst formation in the cornea, which may be affected more than other tissues because of its robust blood supply, an abundance of cell surface receptors, and specific populations of rapidly dividing cells.[11,12] Studies of other ADCs have demonstrated similar ocular side effects, including those with mafodotin and DM4 (N[2′]-deacetyl-N[2′]-[4-mercapto-4-methyl-1-oxopentyl]-maytansine) payloads.[11,12] Notably, these ADCs have targets that are not expressed in ocular tissue/structures,[11,12] suggesting that the major component of the mechanism of action is not target-mediated.

Depatux-m uses mafodotin as its payload, a potent microtubule inhibitor that is associated with ocular side effects.[11] Other studies of ADCs using mafodotin with different targeted antibodies also have reported ophthalmic AEs. SGN-CD19A targets the B-lymphocyte antigen cluster of differentiation 19 (CD19), which commonly is expressed in patients with B-cell non-Hodgkin lymphoma. Phase 1 studies of patients with lymphoma and leukemia who received treatment with SGN-CD19A reported blurred vision and microcystic keratopathy.[16,17] SGN-75 targets CD70, which is expressed on immune cells, including activated T and B lymphocytes, and has been evaluated in studies of patients with renal cell carcinoma and non-Hodgkin lymphoma. Reported ocular side effects included iridocyclitis, dry eye, and corneal epitheliopathy.[18,19] In phase 1 studies of patients with renal cell carcinoma who received treatment with the ADC AGS-16M8F-MMAF or AGS-16C3F, keratopathy was primarily observed.[20]

Depending on the ADC and the dosage, a subset of patients across these studies did experience grade 3 or 4 ocular AEs. However, the majority resolved or improved upon administration of steroid eye drops or when patients entirely stopped taking the mafodotin-conjugated ADCs.[12] Resolution and/or improvement of ocular AEs were observed in this and other depatux-m trials.[21-24] However, calculating the median time to resolution has been unreliable because of limited patient numbers in this first-in-human study. Subsequent depatux-m trials have been conducted in patients with glioblastoma, in whom the ability to follow ocular AEs to complete resolution also has been difficult, because the majority of patients die

quickly after disease progression. Patients tended to recover from ocular side effects, but the length of time until resolution varied over several months. This is consistent with depatux-m studies conducted in cynomolgus monkeys and mice. In those studies, corneal epithelial effects occurred in a dose-dependent manner with respect to onset and severity, and the degree of resolution was correlated with the depatux-m dose (data on file; AbbVie, Inc). These lines of evidence suggest that ocular AEs are associated with mafodotin and occur with other ADCs, whether or not the ADC target is expressed in the eye; ocular AEs do not occur more frequently when treating a specific tumor type; and ocular AEs are limited to the cornea and are reversible.

Several mitigation strategies were used in an attempt to reduce the frequency and severity of the ocular side effects. Corticosteroid eye drops are commonly used with high-dose cytarabine administration to prevent the formation of epithelial microcysts.[12] It is thought that the steroid ophthalmic solution reduces the cellular turnover in the corneal epithelium and thus makes the cells more resistant to the effects of chemotherapy damage. The implementation of prophylactic steroid eye drops with every depatux-m infusion permitted continued dose escalation in this study. Traditionally, it has been assumed that reducing the DAR reduces toxicity associated with ADCs.[10] Depatux-m manufactured under process B did not significantly alter the frequency or severity of ocular side effects. An alternate dosing schedule (2 weeks on/1 week off) and a prolonged infusion time (6 hours) also did not significantly reduce the incidence or severity of ocular side effects.

With regard to efficacy, 1 patient had a confirmed PR to therapy, and there were no complete responses. It is noteworthy that the patient who had a PR had triple-negative breast cancer with *EGFR* amplification, which is an uncommon mutation in this cancer phenotype. This encouraging result provided evidence that depatux-m may be highly specific for tumor types with *EGFR* amplification, leading to further study of depatux-m in glioblastoma, in which nearly 50% of patients have *EGFR* amplification.[13] Encouraging efficacy of depatux-m has been observed in a phase 1 trial of patients with newly diagnosed and recurrent glioblastoma.[21-24] In addition, preliminary efficacy results from a large phase 2 trial of patients with recurrent glioblastoma (clinicaltrials.gov identifier NCT02343406) further support its development as a novel, targeted therapy that may improve outcomes for patients with *EGFR* amplification in a disease with very few treatment options.[25] Therefore, evaluation of depatux-m is ongoing.

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CONFLICT OF INTEREST DISCLOSURES

Glenwood D. Goss reports honoraria from AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly, Pfizer, and EMD Serono outside the submitted work. Everett E. Vokes reports personal fees from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Celgene, Eli Lilly, Genentech, Leidos, Merck, Regeneron, Serono, Takeda, and VentiRx outside the submitted work. Michael S. Gordon is a study investigator for AbbVie. Leena Gandhi reports personal fees from AstraZeneca, AbbVie, Pfizer, Genentech, Merck, and Ignyta and research funding from Bristol-Myers Squibb, all outside the submitted work. Kyriakos P. Papadopoulosis is an employee of South Texas Accelerated Research Therapeutics and reports research funding (to his institution) from AbbVie, MedImmune, Daiichi Sankyo, GlaxoSmithKline, Onyx, Sanofi, Novartis, Regeneron, ARMO BioSciences, ArQule, Amgen, Calithera Biosciences, Curagenix, Incyte, Merck, and Peloton Therapeutics outside the submitted work. Drew W. Rasco reports research funding from AbbVie outside the submitted work. JuDee S. Fischer, Katharine L. Chu, William W. Ames, Rajendar K. Mittapalli, Ho-Jin Lee, Jiewei Zeng, Lisa A. Roberts-Rapp, Lise I. Loberg, Peter J. Ansell, Edward B. Reilly, Christopher J. Ocampo, Kyle D. Holen are employees of AbbVie and may own stock/options in the company. Anthony W. Tolcher is a co-owner and employee of South Texas Accelerated Research Therapeutics and reports fees (to his institution) from for Bayer Schering Pharma, Blend Therapeutics, Celator, Janssen, Merus, Nanobiotix, Pierre Fabre, Symphogen, Heron, Asana Biosciences, Akebia Therapeutics, Genmab, Johnson and Johnson, Endocyte, Upsher-Smith, Ascentage, Bicycle Therapeutics, Boehringer Ingelheim, Ignyta, MEDIAN Technologies, OncoMed, Zymeworks, Elekta, Rigontec, and New B Innovation and research funding (to his institution) from AbbVie, ArQule, Asana Biosciences, Astex Pharmaceuticals, Cerulean Pharma, Dicerna, Endocyte, Gilead Sciences, Infinity Pharmaceuticals, Macrogenics, Pfizer, TaiRx, Inc., Bayer, Otsuka, and Plexxikon, all outside the submitted work.

AUTHOR CONTRIBUTIONS

Glenwood D. Goss: Conceptualization, investigation, writing–original draft, and writing–review and editing. **Everett E. Vokes:** Conceptualization, investigation, writing–original draft, and writing–review and editing. **Michael S. Gordon:** Investigation and writing–review and editing. **Leena Gandhi:** Investigation and writing–review and editing. **Kyriakos P. Papadopoulos:** Investigation and writing–review and editing. **Drew W. Rasco:** Investigation and writing–review and editing. **JuDee S. Fischer:** Resources, project administration, supervision, and writing–review and editing. **Katharine L. Chu:** Resources, project administration, supervision, and

writing–review and editing. **William W. Ames:** Data curation and writing–review and editing. **Rajendar K. Mittapalli:** Data curation and writing–review and editing. **Ho-Jin Lee:** Data curation, formal analysis, visualization, and writing–review and editing. **Jiewei Zeng:** Data curation, formal analysis, visualization, and writing–review and editing. **Lisa A. Roberts-Rapp:** Biomarker analysis, data curation, and writing–review and editing. **Lise I. Loberg:** Writing–original draft and writing–review and editing. **Peter J. Ansell:** Data curation and writing–review and editing. **Edward B. Reilly:** Data curation and writing–review and editing. **Christopher J. Ocampo:** Supervision, conceptualization, project administration, investigation, writing–original draft, and writing–review and editing. **Kyle D. Holen:** Supervision, methodology, conceptualization, project administration, investigation, writing–original draft, writing–review and editing, and funding acquisition. **Anthony W. Tolcher:** Conceptualization, investigation, writing–original draft, and writing–review and editing

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