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First-in-Human Phase I Study of ABBV-085, an Antibody–Drug Conjugate Targeting LRRC15, in Sarcomas and Other Advanced Solid Tumors

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ABSTRACT

Purpose: Leucine-rich repeat containing 15 (LRRC15) is expressed on stromal fibroblasts in the tumor microenvironment of multiple solid tumor types and may represent an interesting target for therapy, particularly in patients with sarcomas where LRRC15 is also expressed by malignant cells. ABBV-085 is a monomethyl auristatin-E antibody–drug conjugate that targets LRRC15 and showed antineoplastic efficacy in preclinical experiments. Herein, we report findings of ABBV-085 monotherapy or combination therapy in adult patients with sarcomas and other advanced solid tumors.

Patients and Methods: This first-in-human phase I study (NCT02565758) assessed ABBV-085 safety, pharmacokinetics/pharmacodynamics, and preliminary antitumor activity. The study consisted of two parts: dose escalation and dose expansion. ABBV-085 was administered by intravenous infusion at 0.3 to 6.0 mg/kg every 14 days.

Results: In total, 85 patients were enrolled; 45 patients received the recommended expansion dose of 3.6 mg/kg ABBV-085 monotherapy, including 10 with osteosarcoma and 10 with undifferentiated pleomorphic sarcoma (UPS). Most common treatment-related adverse events were fatigue, nausea, and decreased appetite. The overall response rate for patients with osteosarcoma/UPS treated at 3.6 mg/kg was 20%, including four confirmed partial responses. No monotherapy responses were observed for other advanced cancers treated at 3.6 mg/kg. One patient treated with ABBV-085 plus gemcitabine achieved partial response.

Conclusions: ABBV-085 appeared safe and tolerable at a dose of 3.6 mg/kg every 14 days, with preliminary antitumor activity noted in patients with osteosarcoma and UPS. Given the high unmet need in these orphan malignancies, further investigation into targeting LRRC15 in these sarcomas may be warranted.

Introduction

In cancer, the tumor microenvironment (TME) contains a complex mixture of different types of nonmalignant cells, including immunologic and blood cells, endothelial cells, and cancer-associated fibroblasts (CAFs), that can interact in a multidimensional network with the tumor cells themselves (1). Tumor stroma represents an important part of the TME and has a role in tumorigenesis, progression of cancer, and resistance to therapy (2). Many anticancer therapies impact the malignant cells without clear effects on the surrounding stroma (2). Extracellular matrix proteins produced by CAFs have been found in the cancer stroma and have been implicated in the immunosuppressive environment that characterizes many solid tumors. CAFs have also demonstrated a role in preventing the uptake of chemotherapy agents, which results in chemoresistance (1, 3). An interest in targeting CAFs as part of antitumor strategies led to a search for markers that are present on CAFs but not on normal tissue cells.

Leucine-rich repeat containing 15 (LRRC15) is a membrane protein detected on the cell surface of stromal fibroblasts in multiple types of solid tumors, such as breast, lung, and pancreatic cancers, while having low expression in most normal tissues. Expression of LRRC15 is regulated by transforming growth factor beta; LRRC15 can bind collagen, which supports its role in cell-to-cell adhesion and tissue structure. Several classes of cancers [e.g., breast, head and neck, and non–small cell lung cancer (NSCLC)] exhibit high expression of LRRC15 on CAFs in the stroma by IHC. Importantly, sarcomas, which originate from mesenchymal cells with certain subtypes exhibiting fibroblastic differentiations, also express LRRC15 directly on the cancer cells themselves (4). Strong LRRC15 expression was observed

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Translational Relevance

LRRC15 (leucine-rich repeat containing 15) is a membrane protein expressed on the surface of stromal fibroblasts in the tumor microenvironment of multiple solid tumor types, while most normal tissues exhibit low or no expression. In sarcomas, LRRC15 expression is detected directly on tumor cells with strong expression noted in several subtypes of soft tissue and bone sarcomas, for which effective new therapies are needed. The antibody–drug conjugate ABBV-085 was developed to target LRRC15 and showed efficacy in preclinical experiments. Herein, we describe the phase I, first-in-human study of ABBV-085 monotherapy in patients with sarcomas and other advanced solid tumors. A promising overall response rate of 20% was seen in patients with osteosarcoma or undifferentiated pleomorphic sarcoma, including four confirmed partial responses with a median duration of response of 8 (range, 4–15) months. Further investigation appears warranted to target LRRC15 as a therapeutic strategy in these patients with sarcomas.

on several histologic subtypes of soft tissue sarcomas (STS) and bone sarcomas, including undifferentiated pleomorphic sarcoma (UPS) and osteosarcoma (5). Direct expression of LRRC15 by sarcoma cells may increase the susceptibility of these mesenchymal tumors to LRRC15-targeted therapy. These findings support LRRC15 as an interesting target for anticancer therapy, particularly in some sarcomas where this protein will be expressed in the tumor stroma as well as by the malignant cells.

Antibody–drug conjugates (ADCs) represent a successful technology for targeted delivery of chemical payloads to cells expressing a specific antigen. Antibodies that selectively bind cell surface antigens are joined via a linker to the chemical compound (6). For ADCs developed as cancer therapeutics, the target molecules should ideally either be expressed exclusively on the tumor cells, or be overexpressed in relation to normal cells, as is the case for LRRC15. There are currently several approved ADCs that are used in oncology, and multiple recent approvals have further expanded the application of ADCs as important anticancer therapeutic agents (7, 8). ABBV-085 links an anti-LRRC15 humanized immunoglobulin G1 antibody (PR-1498487) to the antimitotic drug monomethyl auristatin E (MMAE) through a protease-cleavable valine–citrulline linker. An additional process step is then applied to enrich for ADC molecules that contain two MMAE molecules per antibody, resulting in an average drug-to-antibody ratio of 2 (4). While higher numbers of MMAE molecules can be loaded per antibody, this does not necessarily increase efficacy and may result in increased toxicity (4, 9). MMAE blocks tubulin depolymerization and demonstrates more selective activity against cells that are actively dividing, with a good therapeutic window for aggressively dividing cancer cells versus nondividing normal cells (10).

In preclinical experiments, ABBV-085 was able to kill LRRC15-positive (+) cancer cells in *in vitro* systems and demonstrated *in vivo* efficacy in multiple solid tumor models representing different LRRC15^{+} solid tumor indications (4). ABBV-085 had significant antitumor activity in LRRC15-expressing STS and bone sarcoma patient-derived xenograft tumor models, including complete responses (CR) and cures (4, 5). A second study investigated ABBV-085 treatment in several different osteosarcoma patient-derived xenograft models and found that ABBV-085 significantly inhibited tumor growth in six out of seven models, and improved event-free survival in five out of seven models; response was seen to correlate with LRRC15 expression (11). In addition, treatment with ABBV-085 was tested preclinically in combination with multiple anticancer therapies that have varying mechanisms of action, including cytotoxic chemotherapy (e.g., gemcitabine, docetaxel), radiation, and immune-therapy [anti-programmed cell death protein 1 (PD-1)]; these combinations were more effective than using either compound individually (4). The addition of either gemcitabine or anti–PD-1 antibodies significantly improved the antitumor activity of ABBV-085 in mouse models (4), indicating these combinations may also be of interest in patient care.

Herein, we report the findings of a first-in-human phase I study that investigated the safety and preliminary antitumor activity of ABBV-085 monotherapy in patients with sarcoma and other advanced solid tumors. Exploratory pilot cohorts were also included for investigation of ABBV-085 in combination with the anti–PD-1 mAb nivolumab, as well as gemcitabine with or without *nab*-paclitaxel. Pharmacodynamics and predictive biomarkers were evaluated for association with pharmacokinetics (PKs), safety, and preliminary antitumor activity. Results from dose-escalation and dose-expansion cohorts are presented.

Patients and Methods

Study design and treatment

The primary objectives of this phase I first-in-human, open-label, multicenter study (trial registration ID: NCT02565758) were to assess safety and tolerability, evaluate the PK, and determine the maximum tolerated dose and recommended phase I expansion dose of ABBV-085 as monotherapy, and also in combination with nivolumab or gemcitabine ± *nab*-paclitaxel. Secondary objectives were to assess preliminary antitumor activity of ABBV-085 as monotherapy, as well as pilot combinations with nivolumab or gemcitabine ± *nab*-paclitaxel. Exploratory objectives were evaluation of pharmacodynamics and predictive biomarkers for association with PK, safety, and efficacy.

The study consisted of two parts: dose escalation and dose expansion (Supplementary Fig. S1). The dose-escalation phase followed a 3 + 3 design and was composed of three arms (A–C). In arm A, ABBV-085 was administered by intravenous infusion to groups of three to six patients at 0.3 up to 6.0 mg/kg on day 1, once every 2 weeks until disease progression or unacceptable toxicity. Dose-limiting toxicities (DLTs) were defined as any grade 3 or higher ABBV-085–related event occurring during the first cycle of 28 days. The maximum tolerated dose was defined as the highest dose at which fewer than two of six patients experienced a DLT. For dose escalation arms B and C, the starting dose of ABBV-085 was one level below the highest safe dose identified in arm A. In arm B, the approved dosing schedule of nivolumab was applied in addition to ABBV-085, and in arm C, standard doses of gemcitabine alone or with *nab*-paclitaxel were included. Similar dose-escalation guidelines were used in dose-escalation arms B and C as in arm A.

ABBV-085 monotherapy was further evaluated in a dose-expansion phase composed of three arms (A1, A3, and A4) with different operational elements and patient selection: A1 – squamous cell carcinoma of the head and neck, or NSCLC, or breast cancer; A3 – STS or osteosarcoma; A4 – a dose-expansion arm implemented at a single center that was focused on selecting tumors for tissue collection before and after initiation of ABBV-085 treatment (Supplementary Fig. S1). Planned additional cohorts for dose expansion with ABBV-

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085 monotherapy for patients with adenocarcinoma of the pancreas and for dose expansion in combination (with nivolumab and gemcitabine alone or with *nab*-paclitaxel) were not enrolled, on the basis of sponsor decision to truncate the trial. However, data were collected from the combination treatment patients from the dose-escalation phase.

The study protocol and informed consent form were approved by the Institutional Review Board at each participating site. Written informed consent was obtained from each individual participating in the study. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, as defined by the International Conference on Harmonisation.

Patient eligibility

Eligible patients were ≥18 years of age with Eastern Cooperative Oncology Group performance status 0 to 2, measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) version (v) 1.1 (12), and an advanced solid tumor that was not amenable to surgery or alternative approved therapies. All patients had to consent to provide archived diagnostic formalin-fixed paraffin-embedded (FFPE) tumor tissue or undergo a biopsy. Patients with sarcomas had histologic or cytologic documentation of sarcoma subtype. A positive LRRC15 stain was required for enrollment in certain arms of the study. Detailed eligibility criteria are listed in Supplementary Table S1.

Safety

Safety assessments performed during the study included monitoring of adverse events (AEs) and concomitant medication, vital signs, physical examination, electrocardiogram, and laboratory tests. AEs were coded using the Medical Dictionary for Regulatory Activities and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. Treatment-emergent AEs (TEAEs) were defined as any AE occurring after the first dose of ABBV-085 until 60 days after study drug discontinuation, or until start of another anticancer therapy.

Pharmacokinetics

Blood samples for PK evaluation of ABBV-085 were collected during cycle 1 and 3 at days 1 (predose and 15 minutes, 3, 6, and 24 hours after infusion), 3, 5, 8, and 15. For all other cycles, samples were collected at days 1 and 15. Samples for antidrug antibody analysis were collected at cycle 1 day 1 (predose) and 15, at all subsequent cycles on day 1 (predose), and at final visit. Serum concentrations of conjugate (ABBV-085) and total mAb were determined using validated electrochemiluminescence immunoassay methods. Validated liquid chromatography–mass spectrometry was applied to determine the plasma levels of unconjugated MMAE. PK parameters, including maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), area under the concentration–time curve (AUC), and terminal elimination half-life ($t_{1/2}$), were estimated using noncompartmental analysis (Phoenix WinNonlin 8.0).

Antitumor activity

Radiologic assessments consisted of CT or MRI scans, performed within 28 days prior to cycle 1 day 1, and every two treatment cycles thereafter to determine tumor burden. Baseline evaluations were performed as close as possible to the start of study drug but no more than 4 weeks before the beginning of treatment. For patients in the dose-escalation cohort, or patients who had received ABBV-085 treatment for more than 52 weeks in the expansion cohorts, tumor assessments could be decreased in frequency to every three treatment cycles. Efficacy endpoints included objective response rate (ORR), progression-free survival (PFS), and duration of objective response (DOR). ORR was determined according to RECIST v1.1 (12).

LRRC15 IHC

LRRC15 staining of patient samples was performed as previously described (4). All samples were processed at Mosaic Laboratories. Staining was evaluated by a pathologist, and evaluation of reactivity involved a combination of the following: staining intensity, subcellular localization, and percentage of cells staining positive in the primary component of the tissue type of interest (cancer cells and stroma). The LRRC15 (mouse clone AD210.40.9) assay was evaluated on a semi-quantitative scale, and recorded as 0 (unstained), 1+ (weak staining), 2+ (moderate staining), or 3+ (strong staining). An H-score was calculated using the following equation:

(3 × percentage of cell staining at 3+) + (2 × percentage of cells staining at 2+) + (1 × percentage of cells staining at 1+)

Other cell types evaluated (maximum staining intensity recorded only) when observed included normal adjacent tissue, endothelial cells, smooth muscle cells, fibroblasts, inflammatory cells, and nerve cells.

Gene expression profiling

Pre- and posttreatment paired biopsies were collected for TME characterization. The nCounter PanCancer Immune Profiling Panel with added custom genes (including LRRC15; NanoString Technologies, Inc., XT-CSO-HIP1–12) was applied for immune gene expression profiling.

IHC and multiplex immunofluorescence

IHC and multiplex immunofluorescence analysis was performed on FFPE tumor tissue samples at MD Anderson Cancer Center. All tumor tissue samples were collected in accordance with the clinical trial protocol, and written informed consent was obtained from each individual participating in the study. Deidentified FFPE tumor tissue samples were shipped to MD Anderson Cancer Center for analysis. Pre- and posttreatment tissue samples consisting of 4-μm sections were stained with hematoxylin and eosin. IHC studies were performed using antibodies against CD3 (Dako, A0452) and CD8 (Thermo Fisher Scientific, MS-457-S). Sections were processed with peroxidase-conjugated avidin/biotin and 3′-3-diaminobenzidine substrate (Leica Microsystem). For multiple immunofluorescence staining, the Tyramide Signal Amplification and detection method (Akoya Biosciences) was utilized with the following markers: CD68 (Dako, M0876, 1:250 dilution) with subsequent visualization using fluorescein Cy5.5, CD3 (Dako, A0452, 1:100) with subsequent visualization using fluorescein Cy3.5, PD-1 ligand 1 (Cell Signaling Technology, CST13684, 1:100) with subsequent visualization using fluorescein Cy3, and HLA-DR (CD74; Cell Signaling Technology, CST77274, 1:500) with subsequent visualization using fluorescein isothiocyanate; nuclei were visualized using DAPI (1:2,000). The slides were scanned using the Vectra slide scanner (Akoya Biosciences) and images were acquired at ×10 magnification. Subsequently, the regions of interest were selected and zoomed in to acquire images at ×40 magnification. Nuance spectral analysis software (PerkinElmer) was used for the multispectral analysis.

Statistical analyses

The safety analysis population consisted of all patients who received at least one dose of study drug. All safety summaries were descriptive, without statistical inference. The efficacy-evaluable population in the dose-expansion part of the study included all patients who received at

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least one dose of study drug and had at least one postdose tumor assessment. ORR was defined as the proportion of patients with a confirmed partial response (PR) or CR according to RECIST v1.1. The two-sided confidence interval (CI; 80%) for ORR, CR, and PR rates was computed using the exact Clopper–Pearson method. PFS was defined as time from first date of administration of study drug to disease progression or death, whichever occurred first. PFS was censored at time of last tumor assessment for patients without PFS events. The median PFS and its 80% CI were estimated using the Kaplan-Meier method. DOR was defined as time from initial objective response to disease progression or death, whichever occurred first; if neither occurred, DOR was censored at time of last tumor assessment. DOR was summarized using similar methods as PFS.

Results

Patient demographics and baseline characteristics

In total, 85 patients were enrolled and treated with one or more doses of ABBV-085 (data cutoff 05 Aug 2019). The dose-escalation cohorts included 53 patients total: 46 patients were enrolled in arm A, three in arm B, and four in arm C (Supplementary Fig. S1). ABBV-085 doses ranged from 0.3 mg/kg to 4.8 mg/kg. Seven patients received combination therapy: three patients received 2.7 mg/kg every 2 weeks ABBV-085 with nivolumab (arm B), and four patients received 1.8 mg/kg every 2 weeks ABBV-085 with gemcitabine with ($n = 2$) or without ($n = 2$) *nab*-paclitaxel (arm C). A total of 32 patients were enrolled in dose expansion and treated with 3.6 mg/kg ABBV-085 (Supplementary Fig. S1; arms A1, A3, A4). In dose-escalation arm A and dose-expansion arm A3, a total of 10 patients with osteosarcoma and 10 with UPS were treated at the 3.6 mg/kg dose. The median age of the total patient population was 58 years (range, 21–84). The most common primary tumor type was sarcoma ($n = 37$). Further details of sarcoma patients treated at 3.6 and 4.2 mg/kg dose levels ($n = 29$) are listed in Supplementary Table S2. Other primary tumor types reported in more than five patients were NSCLC ($n = 9$), pancreatic cancer ($n = 9$), and breast cancer ($n = 6$). Patient demographics and baseline characteristics for all patients, patients with nonsarcoma and sarcoma treated at all doses, and patients with osteosarcoma and UPS treated at 3.6 mg/kg are summarized in Supplementary Table S3.

Safety

At the time of data cutoff, all 85 patients had discontinued treatment; the most common reasons included disease progression ($n = 67$) and AEs ($n = 11$). DLTs were reported in four patients who received ABBV-085 monotherapy [grade 3 anemia (3.6 mg/kg), grade 3 hypertriglyceridemia (4.2 mg/kg), grade 3 nausea (4.8 mg/kg), and grade 2 ileus (4.8 mg/kg)]. The dose for the expansion phase was defined as 3.6 mg/kg every 2 weeks on the basis of overall safety and tolerability profiles.

All TEAEs occurring in ≥10% of patients and treatment-related AEs (TRAE) occurring in ≥5% of patients on ABBV-085 monotherapy are summarized in **Table 1**. The incidence of reported TEAEs was highest in patients receiving ≥4.2 mg/kg ABBV-085; no dose dependency was observed at lower concentrations. TRAEs of any grade were reported in 62 (80%) patients on ABBV-085 monotherapy. The most common ABBV-085–related AEs were fatigue (30%), nausea (19%), and decreased appetite (17%; **Table 1**). For the combination arms, two cases of treatment-related diarrhea were reported in the nivolumab

Table 1. TEAEs occurring in ≥10% of patients, and TRAEs occurring in ≥5% of patients receiving ABBV-085 monotherapy.

	Related or unrelated to ABBV-085				Related to ABBV-085			
	Any grade		Grade ≥3		Any grade		Grade ≥3	
MedDRA preferred term, *n* (%)	All doses *N* = 78	3.6 mg/kg *n* = 45	All doses *N* = 78	3.6 mg/kg *n* = 45	All doses *N* = 78	3.6 mg/kg *n* = 45	All doses *N* = 78	3.6 mg/kg *n* = 45
Any AE	77 (99)	45 (100)	56 (72)	36 (80)	62 (80)	34 (76)	19 (24)	14 (31)
Fatigue	38 (49)	23 (51)	6 (8)	5 (11)	23 (30)	13 (29)	3 (4)	3 (7)
Nausea	24 (31)	15 (33)	2 (3)	0	15 (19)	10 (22)	1 (1)	0
Anemia	20 (26)	14 (31)	11 (14)	6 (13)	9 (12)	8 (18)	2 (3)	2 (4)
Vision blurred	19 (24)	12 (27)	0	0	10 (13)	6 (13)	0	0
Decreased appetite	18 (23)	10 (22)	0	0	13 (17)	8 (18)	0	0
Diarrhea	15 (19)	7 (16)	0	0	8 (10)	1 (2)	0	0
Abdominal pain	14 (18)	7 (16)	5 (6)	3 (7)	3 (4)	1 (2)	1 (1)	0
Dyspnea	14 (18)	12 (27)	2 (3)	2 (4)	1 (1)	1 (2)	0	0
Pyrexia	14 (18)	5 (11)	1 (1)	0	1 (1)	0	0	0
Constipation	12 (15)	10 (22)	1 (1)	1 (2)	4 (5)	4 (9)	0	0
Vomiting	12 (15)	7 (16)	0	0	6 (8)	2 (4)	0	0
Neuropathy peripheral	11 (14)	11 (24)	1 (1)	1 (2)	10 (13)	10 (22)	1 (1)	1 (2)
Peripheral sensory neuropathy	11 (14)	6 (13)	1 (1)	1 (2)	10 (13)	6 (13)	1 (1)	1 (2)
ALT increased	10 (13)	5 (11)	2 (3)	2 (4)	7 (9)	3 (7)	0	0
AST increased	9 (12)	5 (11)	2 (3)	2 (4)	8 (10)	4 (9)	1 (1)	0
Hypokalemia	9 (12)	4 (9)	2 (3)	1 (2)	3 (4)	1 (2)	0	0
Myalgia	9 (12)	7 (16)	1 (1)	1 (2)	3 (4)	1 (2)	1 (1)	1 (2)
Weight decreased	9 (12)	8 (18)	0	0	5 (6)	4 (9)	0	0
Alopecia	8 (10)	4 (9)	0	0	8 (10)	4 (9)	0	0
Arthralgia	7 (9)	4 (9)	0	0	4 (5)	3 (7)	0	0
Neutropenia	7 (9)	3 (7)	4 (5)	1 (2)	7 (9)	3 (7)	4 (5)	1 (2)
White blood cell count decreased	5 (6)	3 (7)	0	0	5 (6)	3 (7)	0	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities.

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combination arm, and aspartate aminotransferase increased and alanine aminotransferase increased were reported by two patients in the gemcitabine ± *nab*-paclitaxel combination arm.

Serious AEs without regard to study drug attribution occurred in 38 (49%) patients, with abdominal pain, malignant neoplasm progression (8% each), pneumonia, and sepsis (4% each) the most frequently reported in patients receiving ABBV-085 monotherapy. Occurrence of serious AEs was increased in patients on higher doses (1.2–4.8 mg/kg) of ABBV-085 and rare in patients treated with lower doses (0.3 or 0.6 mg/kg) of ABBV-085. One patient in the nivolumab combination arm reported serious AEs of nausea, vomiting, and cardiac arrest, while sepsis and malignant neoplasm progression was reported in one patient in the gemcitabine ± *nab*-paclitaxel combination arm.

Nine (12.5%) patients who received ABBV-085 monotherapy died within 30 days of study drug administration; the most common attribution was progression of the underlying malignant neoplasm ($n = 5$). The remaining four deaths were attributed to the following (one each): acute respiratory failure, respiratory failure, septic shock, and death (unspecified). There was no clear relation between the occurrence of grade 5 AEs and dose level of ABBV-085, as the grade 5 AEs were experienced in patients receiving a dose range of 0.6 to 4.8 mg/kg. One patient in the nivolumab arm experienced cardiac arrest leading to death, and one patient in the gemcitabine ± *nab*-paclitaxel combination arm died due to progression of their malignancy.

Eye disorders and peripheral neuropathy were considered AEs of special interest, given the known safety profile of MMAE. In total, 20 patients treated with ABBV-085 monotherapy experienced an AE related to eye disorders [vision blurred (24%), dry eye (4%), corneal epithelial microcysts (3%)], and 24 patients (31%) experienced an AE related to peripheral neuropathy. All reported eye disorders were grade 1 to 2 and were reversible. The peripheral neuropathy was primarily low grade (one case of grade ≥3 in a patient treated at 3.6 mg/kg). The occurrence of eye disorders and peripheral neuropathy seemed to be related to the dose of ABBV-085 and were rare in patients treated at <3.6 mg/kg.

Pharmacokinetics

On the basis of available data by the analysis cutoff date, preliminary PK parameters were determined for the conjugate ($n = 39$), the total (unconjugated and conjugated) antibody ($n = 39$), and unconjugated MMAE ($n = 41$). The concentration–time profiles after the first dose in cycle 1 are reported for patients dosed at 3.6 mg/kg every 2 weeks (**Fig. 1**); the conjugate and the total antibody concentrations were highly correlated. The C_{max} and AUC were 62 μg/mL and 3,840 μg × h/mL for the conjugate and 58.3 μg/mL and 4,680 μg × h/mL for the total antibody, respectively. MMAE had a C_{max} of 3.99 ng/mL and an AUC of 850 ng × h/mL. The C_{max} was achieved at 3.25 hours for conjugate and total antibody, and at approximately 2 days for unconjugated MMAE. ABBV-085 exhibited approximately dose-proportional PK across 0.3 to 4.8 mg/kg every 2 weeks doses; the $t_{1/2}$ of the conjugate and total antibody was similar (3 days), while MMAE had a $t_{1/2}$ of 4.3 days (13).

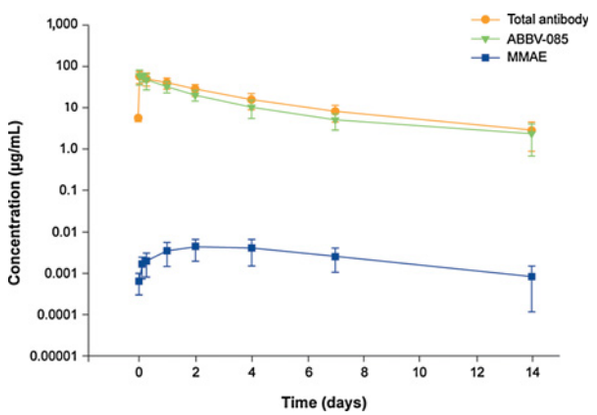

Figure 1.
Preliminary PK profiles (mean ± SD) for ABBV-085, total antibody, and unconjugated MMAE following the first dose of 3.6 mg/kg every 2 weeks in cycle 1.

Antitumor activity

The best overall response data are summarized in **Table 2** for patients with osteosarcoma or UPS treated at the 3.6 mg/kg dose, all patients with any sarcoma treated at all doses, and all nonsarcoma patients at all doses. In the "all sarcomas at all doses" population the ORR was 10.8% (**Fig. 2A**). In the patients with osteosarcoma or UPS treated at the 3.6 mg/kg dose the ORR was 20%. Among patients with UPS treated at 3.6 mg/kg, four patients had PR with tumor shrinkage of >30% (**Fig. 2B** and **C**); of these, two patients had a confirmed PR and two an unconfirmed PR. PR could not be confirmed in these two patients due to target lesion growth in the next scan following a 31% tumor shrinkage ($n = 1$), and the occurrence of a new lesion at the second scan while target lesion reduction was 66% ($n = 1$). Among patients with osteosarcoma treated at the 3.6 mg/kg dose, two had a confirmed PR (**Fig. 2B** and **D**). In the "nonsarcoma at all doses" population, only a single PR was observed in a patient with colon/rectum cancer receiving ABBV-085 plus gemcitabine (ORR 2.1%). No responses were observed in 18 nonsarcoma patients treated with ABBV-085 monotherapy at 3.6 mg/kg.

In the cohort of patients with osteosarcoma or UPS treated at the 3.6 mg/kg dose, five patients (25%) had stable disease, and nine (45%) had progressive disease. In all patients with sarcoma at all doses, stable disease was seen in 13 (35.1%) and progressive disease in 17 (45.9%) patients. In the nonsarcoma population treated at all doses, 13 (27.1%) patients had stable disease and 24 (50%) had progressive disease.

The median DOR for the four sarcoma patients with a confirmed response was 7.8 months (range, 3.7–14.8), with a median reduction in tumor diameter from baseline of 60.6% (range, 44.2%–82.0%; **Table 3**). The patient with colon/rectum cancer who had a PR had a 50% reduction in tumor diameter from baseline, and DOR of 5.7 months.

Pretreatment LRRC15 expression

LRRC15 expression on baseline tissue samples was determined by IHC and NanoString gene expression. Clinical characteristics and available LRRC15 IHC data from sarcoma patients treated with 3.6 and 4.2 mg/kg ABBV-085 as monotherapy ($n = 29$) are summarized in Supplementary Table S2, including both cancer cell staining and stroma staining LRRC15 H-scores. The tumor tissues were from a mixed source of primary or metastatic sites and were obtained at different collection times, including archival samples. Low expression of LRRC15 was defined as an H-score <100. Overall, the median cancer cell H-score was 100, and the median stroma H-score was 15. Of the six patients with a response (either confirmed or unconfirmed PR), three responders (two UPS, one osteosarcoma) had cancer cell H-scores of 180, 270, and 280 and stroma H-scores of 0, 0, and 300. The remaining

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Table 2. Best overall response.

Best overall response, n (%)	Non-sarcomas All doses $n = 48$	Sarcomas All doses $n = 37$	Osteosarcoma + UPS 3.6 mg/kg $n = 20$	Osteosarcoma 3.6 mg/kg $n = 10$	UPS 3.6 mg/kg $n = 10$
Complete response	0	0	0	0	0
Partial response	1 (2.1)	4 (10.8)	4 (20.0)	2 (20.0)	2 (20.0)
Stable disease	13 (27.1)	13 (35.1)	5 (25.0)	2 (20.0)	3 (30.0)
Progressive disease	24 (50.0)	17 (45.9)	9 (45.0)	6 (60.0)	3 (30.0)
Unknown	10 (20.8)	3 (8.1)	2 (10.0)	0	2 (20.0)
Objective response rate (CR + PR) 95% CI, %	1 (2.1) 0.1–11.1	4 (10.8) 3.0–25.4	4 (20.0) 5.7–43.7	2 (20.0) 2.5–55.6	2 (20.0) 2.5–55.6

50% of responders (two UPS, one osteosarcoma) had a low H-score (<100) both in the cancer cells and the stroma (**Fig. 2B**).

The NanoString gene expression analysis of tumor tissue samples from patients with sarcoma compared LRRC15 levels in responders ($n = 5$) and nonresponders ($n = 19$). No direct correlation was observed between the gene expression level of LRRC15 and clinical response (Supplementary Fig. S2).

Pretreatment TME gene signatures

Using NanoString, gene expression profiles were determined in pretreatment tumor tissues and compared between responder and nonresponder patients with sarcoma ($n = 24$). The immune TME was first characterized by profiling the immunologic constant of rejection (ICR) gene signature, which is a surrogate predictive marker for responsiveness to anticancer immunotherapies (14). A trend for increased ICR scores was seen in responders compared with nonresponders (**Fig. 3A** and **B**). Additional over- and underexpressed gene signatures in the responder population are presented in **Fig. 3C** and **D**, respectively. Gene Ontology analysis showed that the top involved pathways were increased inflammatory response, defense response, and response to wounding in overexpressed genes, and decreased intracellular organelle in underexpressed genes in responders.

Immune cell infiltration after treatment initiation

To explore pharmacodynamic effects of ABBV-085 treatment, a limited amount of paired pre- and posttreatment tissues was available for study. The infiltration of immune cells was investigated by IHC and multiplex immunofluorescence in samples from four patients with breast cancer before (cycle 1, day 1) and after (cycle 2, day 1) treatment with ABBV-085. Tissue regions were selected for analysis that had >70% tumor cells. In half (two of four) of the patients, a clear increase in absolute numbers of $CD3^+$ and $CD8^+$ T cells was observed posttreatment (Supplementary Fig. S3A and S3B). For one patient, the levels of $CD3^+$ and $CD8^+$ T cells remained stable and were seemingly not affected by ABBV-085 treatment. The fourth patient appeared to have an increased presence of T cells at baseline compared with the other patients, and the number of $CD3^+$ and $CD8^+$ T cells present in the tissue decreased after treatment initiation. The patient with the largest increase in $CD3^+$ and $CD8^+$ T cells posttreatment also had upregulation of macrophages (CD68).

Discussion

ABBV-085 monotherapy was reasonably tolerated in most patients with solid tumors treated at 3.6 mg/kg every 2 weeks, with an overall manageable safety profile. Safety data for the combination cohorts were difficult to interpret due to the small sample sizes, and no clear conclusion could be drawn. The most common ABBV-085–related AEs were fatigue, nausea, and decreased appetite. While the occurrence of AEs increased with doses of 4.2 mg/kg and higher, no clear dose dependency was observed at lower doses. The frequencies of ocular toxicity and peripheral neuropathy were around 25% to 30%. Peripheral neuropathy has been found with other MMAE-containing ADCs, including brentuximab vedotin; the peripheral neuropathy seen after treatment with brentuximab vedotin was dose dependent and cumulative (15). Similarly, polatuzumab vedotin was associated with incidence of grade ≥2 peripheral neuropathy in 55% of patients treated with 1.8 mg/kg and 72% of patients treated with 2.4 mg/kg in a phase II study (16). ABBV-085 can be given at a higher dose (3.6 mg/kg) and frequency (every 2 weeks) than brentuximab vedotin (1.8 kg/mg, every 3 weeks) and polatuzumab vedotin (1.8–2.4 mg/kg, every 3 weeks). This could be the result of the lower number of MMAE molecules loaded per antibody (two vs. four for typical MMAE-containing ADCs; ref. 9). The PK of ABBV-085 was dose-proportional, with a half-life of 3 days. Unconjugated MMAE had a $t_{1/2}$ of 4.3 days, which likely reflected a slow release from the conjugate.

There was a very intriguing signal of antitumor activity noted in patients with advanced osteosarcoma or UPS who were treated at the 3.6 mg/kg dose, with an ORR of 20%, including four patients achieving a confirmed PR and an additional two patients with unconfirmed PR in the UPS population. The median DOR was 8 months (range, 4–15) in patients with a confirmed PR. Any objective responses in these sarcomas are compelling, as these malignancies are often highly resistant to most cytotoxic chemotherapies. Currently, patients with sarcoma are generally treated with intense regimens of cytotoxic therapy that include the topoisomerase II inhibitor doxorubicin, the DNA alkylator ifosfamide, or other cytotoxic medications that bring substantial toxicity. In the setting of locally advanced or metastatic sarcoma, these aggressive regimens achieve response rates of only 12% for doxorubicin and 6% to 8% for ifosfamide as single agents (17). For ifosfamide treatment in osteosarcoma, one retrospective study yielded a single case of improvement among 13 patients (18). A second study reported an ORR of 20% after high-dose ifosfamide treatment in patients with relapsed osteosarcoma; the median DOR was 7 months, similar to that seen in the presented study (8 months; ref. 19). Thus, while the current study is small, the 20% response rate seen may be clinically significant in this rare disease population and should be studied further.

In the nonsarcoma population, only a single PR was observed out of seven patients treated with the combination of ABBV-085 and either nivolumab or gemcitabine (in a patient with colon/rectum cancer), and no responses were observed in 18 monotherapy patients treated at the 3.6 mg/kg dose. A reason for the higher response rate seen in patients with sarcoma could be that LRRC15 is expressed on cancer cells in some sarcomas, in addition to being expressed in the tumor stroma (4),

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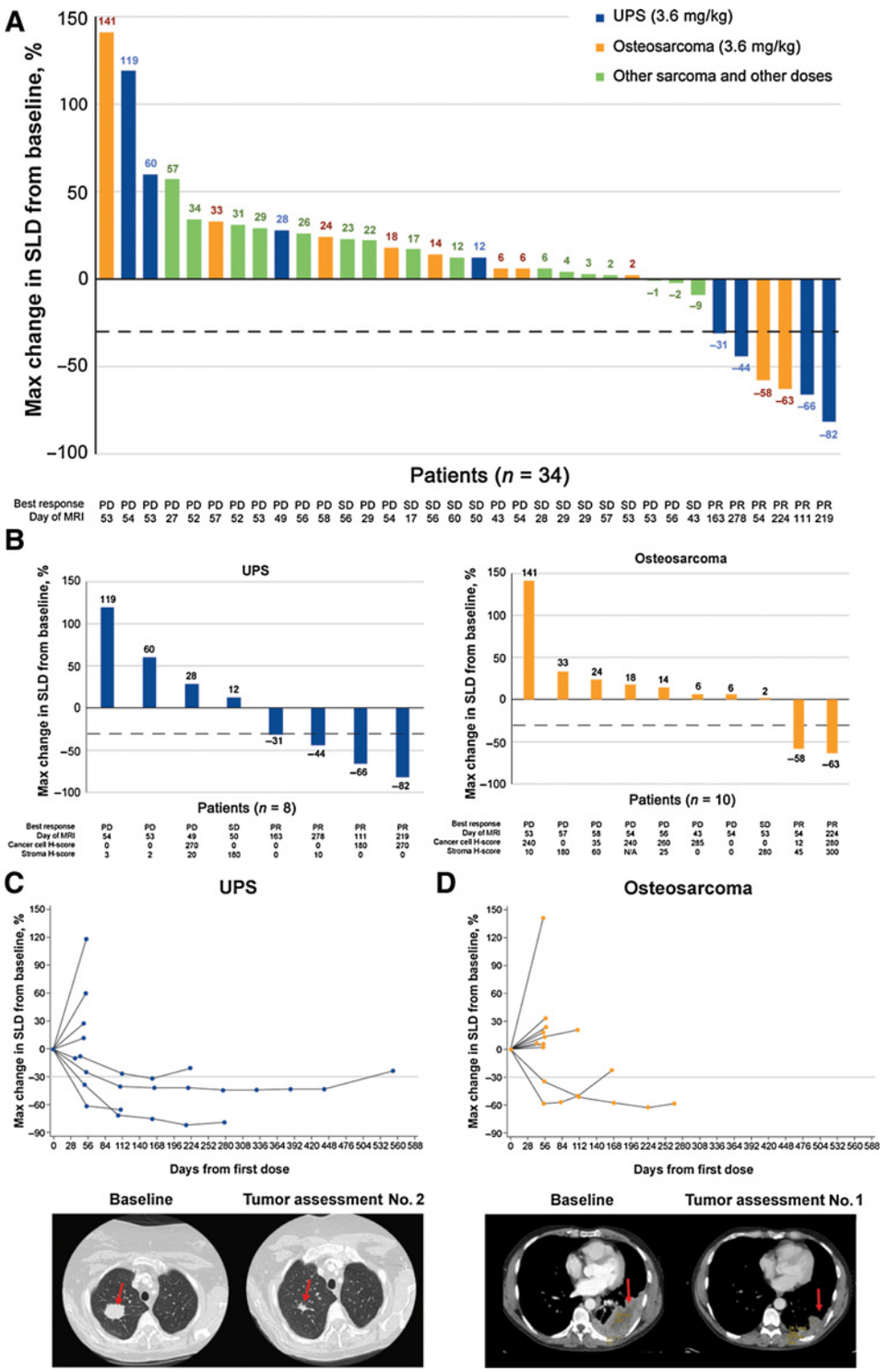

Figure 2.

Individual patient responses. **A,** Best response for all individual patients with sarcoma. The dashed line represents a 30% decrease from baseline, which is indicative of partial response level. **B,** Best response for individual patients with UPS and osteosarcoma treated with 3.6 mg/kg ABBV-085 monotherapy with corresponding LRRC15 H-scores. **C,** All individual responses for patients with UPS (top) and an example response of a patient with a 40% change from baseline (bottom). **D,** All individual responses for patients with osteosarcoma (top) and an example response of a patient with a 58% change from baseline (bottom). N/A, not available; SLD, sum of longest diameter.

which may result in greater delivery of the cytotoxic MMAE payload directly to the cancer cell, compared with tumor types where LRRC15 is only expressed on stromal cells. This observation is consistent with a previous study showing stromal cells were less affected by treatment with ABBV-085 compared with cancer cells (4). However, a strict correlation with response and LRRC15 cancer cell expression was not observed. In the current study, one of the six responder patients with sarcoma had a positive LRRC15 expression H-score in both stroma and cancer cells, while two additional patients had positive LRRC15 expression scores on cancer cells only. The remaining three responders

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Table 3. Duration of response.

Tumor type	Age	Sex	Nadir sum of diameters	Change from baseline, %	Duration of confirmed response, months
UPS	56	F	24	−82.0	8.6
UPS	55	F	43	−44.2	14.8
Osteosarcoma	63	M	23	−62.8	7.0
Osteosarcoma	51	M	67	−58.4	3.7
Colon/rectum cancer[a]	47	F	6	−50.0	5.7

[a]Treated with ABBV-085 (1.8 mg/kg) and gemcitabine; other responders were treated with ABBV-085 monotherapy at 3.6 mg/kg.

were considered negative for either stroma or cancer cells, albeit with some detectable signals in two responders. In addition, LRRC15 gene expression level in five patients with sarcoma who responded to ABBV-085 treatment did not appear to be higher compared with nonresponders, although the number of responders included in this analysis was low. Regarding the lack of association between H-score and response, it is notable that almost all tissues used to determine LRRC15 expression in the study were archival in origin, rather than having been obtained at the time of initiation of study treatment. As LRRC15 expression is dynamic and can be upregulated (e.g., in response to transforming growth factor beta; ref. 4), it is possible that archived tumor tissue may not be representative of LRRC15 expression in the tumor and stroma just prior to treatment with ABBV-085. In addition, it is possible that the sensitivity and specificity of the IHC assay used to determine LRRC15 expression was insufficient for the desired purpose. At the present time, this assay cannot be used to

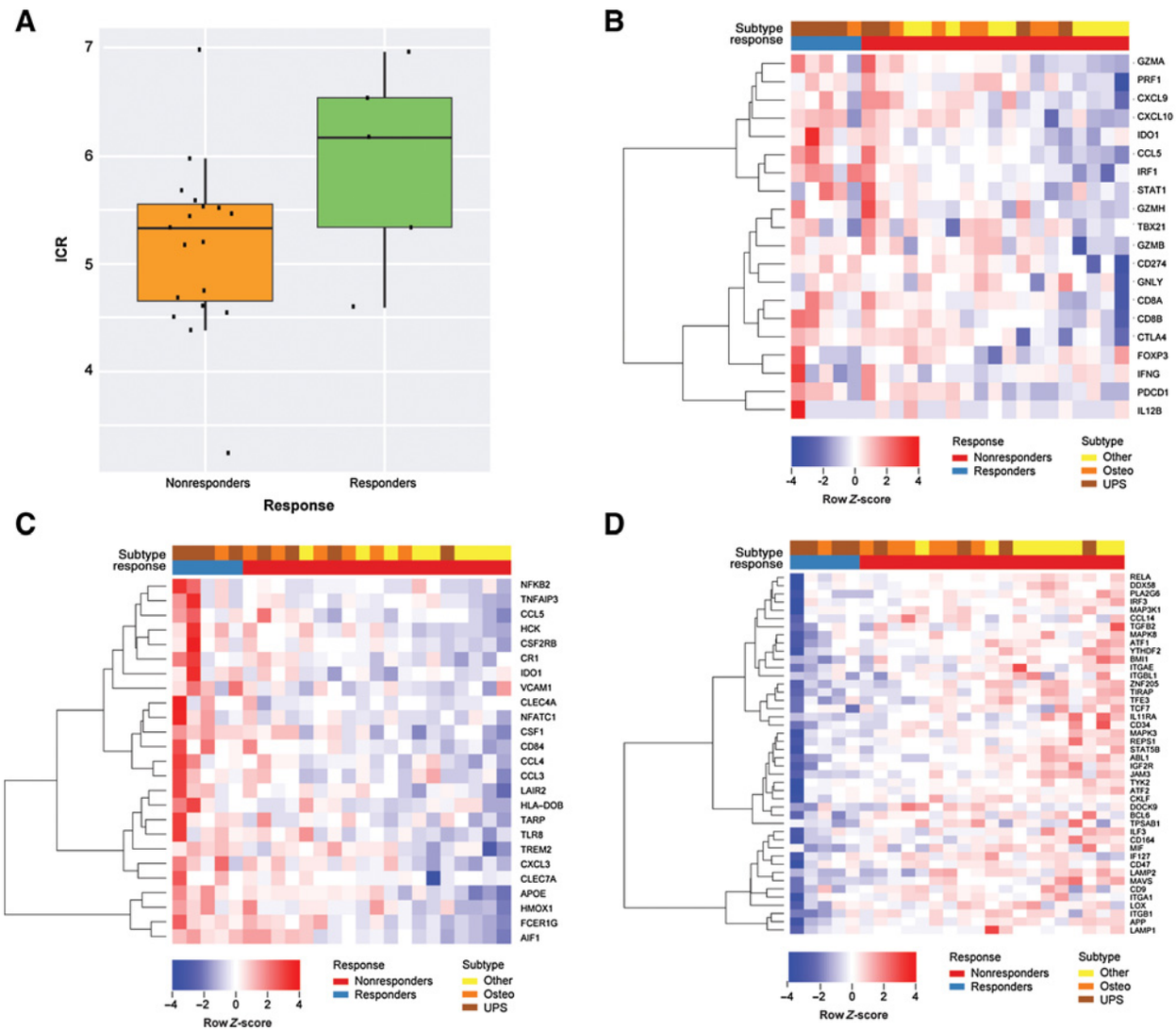

Figure 3.
Gene expression in patients with sarcoma. **A** and **B,** Immunologic constant of rejection gene expression set compared between patients with and without a response. **C** and **D,** All over- or underexpressed genes in responders compared with nonresponders.

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identify patients who would benefit from ABBV-085 treatment. It is unclear if further optimization of the IHC assay might identify a relationship to response after ABBV-085 treatment. Another potential confounding factor is the heterogeneity of tumor biopsy tissues, as there might be different expression levels of LRRC15 at different tumor locations. However, a general lack of available tissue precluded repeated testing. Therefore, an association between ABBV-085 response and LRRC15 expression in the tumor stroma or cancer cells might not have been detected due to variable expression over time, assay insensitivity, or tumor heterogeneity. Future research could benefit from addressing these limitations, for example by improving assay analytic specifics to obtain more-accurate LRRC15 expression levels and by testing tumor biopsy tissues procured just prior to treatment.

While a previous mouse model study indicated that ABBV-085 may have increased efficacy when combined with other anticancer therapies (4), in the current study the majority of patients received monotherapy, and no conclusions could be made about combination treatment due to the small sample size of these exploratory pilot cohorts ($n = 3$ for nivolumab and $n = 4$ for gemcitabine with or without *nab*-paclitaxel). However, it is notable that one of the nonsarcoma gemcitabine-combination patients had a confirmed PR.

Preliminary results from a limited biomarker data set suggest that administration of ABBV-085 may result in increased T-cell infiltration into tumors of some patients. These analyses were done in a small subset of patients with breast cancer, and it should be noted that these patients did not respond to treatment with ABBV-085. We observed that two of four patients with breast cancer showed a clear increase in the presence of $CD3^+$ and $CD8^+$ T cells after treatment initiation. It is known that one method used by tumors to avoid antitumor activity is to reduce T-cell homing, and enhancing T-cell infiltration in the tumor can improve efficacy of therapies (20). Furthermore, other MMAE-linked ADCs have been hypothesized to increase immunogenic cell death and have shown evidence of increased response rates when combined with immunomodulatory anti–PD-1 antibody therapy (21, 22). Collection of paired pre- and posttreatment samples was scheduled for patients with sarcoma as well; however, tissue was available for only two patients (one with stable disease and one with progressive disease), and no increase in immune cells was seen in these patients. It should also be emphasized that the small dataset explored in these T-cell studies limits the analysis to hypothesis generation. Thus, a potential hypothesis for future study is to combine ABBV-085 with anti–PD-1 treatment to enhance tumor responses.

In addition, there are hints that those patients who responded to treatment with ABBV-085 may have a high ICR gene signature. The ICR signature contains 20 transcripts in different categories involved in T-cell immune responses; these pathways are also activated during other forms of immune-mediated tissue-specific destruction (23, 24). High expression of components of the ICR has been associated with responsiveness to immunotherapy approaches and favorable outcomes. For example, expression of the chemokines CXCL9, CXCL10, and CCL5 in metastatic melanoma tumor pretreatment was associated with treatment response (25), and increased baseline expression of several immune-related genes, including CD8, granzyme B, and perforin, was predictive of clinical response to ipilimumab (26). The trend for increased ICR scores seen in responders compared with nonresponders could point to increased inflammation and T-cell signaling at baseline in responders.

In conclusion, ABBV-085 dosing was associated with an acceptable safety profile, and preliminary antitumor activity was seen in patients with osteosarcoma and UPS, classes of tumor types where LRRC15 can be expressed both on the cancer cell surface and in the stroma. As this patient group has a high unmet need, further investigation into targeting LRRC15 in these patients may be warranted.

Data-sharing statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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