# ABBV-085, Antibody–Drug Conjugate Targeting LRRC15, Is Effective in Osteosarcoma: A Report by the Pediatric Preclinical Testing Consortium

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## ABSTRACT

Membrane protein leucine–rich repeat containing 15 (LRRC15) is known to be expressed in several solid tumors including osteosarcoma. ABBV-085, an antibody–drug conjugate against LRRC15, conjugated to monomethyl auristatin E (MMAE), was studied in osteosarcoma patient-derived xenografts (PDXs) by the Pediatric Preclinical Testing Consortium (PPTC). *LRRC15* expression data were obtained from PPTC RNA-sequencing data for the PDX models. The TARGET database was mined for *LRRC15* expression in human osteosarcoma. Protein expression was confirmed via IHC in three PDX models. Seven osteosarcoma PDX models (OS1, OS9, OS33, OS34, OS42, OS55, and OS60) with varying *LRRC15* gene expression were studied. ABBV-085 was administered at 3 mg/kg (OS33), 6 mg/kg (all seven PDXs), and 12 mg/kg (OS60) weekly for 4 consecutive weeks via intraperitoneal injection. Control cohorts included vehicle and an isotype MMAE-linked antibody. Tumor volumes and responses were reported using PPTC statistical analysis. OS1, OS33, OS42, OS55, and OS60 had high *LRRC15* expression while OS9 and OS34 had low *LRRC15* expression. ABBV-085 inhibited tumor growth in six of seven PDX models as compared with vehicle control and significantly improved event-free survival in five of seven models as compared with isotype controls. Two models showed maintained complete responses while all others showed progressive disease. Response correlated with LRRC15 expression. ABBV-085's antitumor activity against osteosarcoma PDX suggests LRRC15 may be a rational target for pursuing clinical trials in patients with this disease.

## Introduction

The outcome of patients with osteosarcoma, both localized and metastatic, has not changed for several decades since the advent of adjuvant chemotherapy (1). This is especially frustrating given the tremendous advances that have occurred in the ability to analyze and understand its very complex genome (2–4). Because of the lack of identification of recurrent targetable genetic alterations in a large proportion of patients, these biologic discoveries have thus far not led to significant therapeutic advancements. Thus, other strategies that are broadly applicable in OS are needed to target this disease.

Membrane protein leucine-rich repeat containing 15 (LRRC15), a 581 amino acid type 1 membrane protein with no obvious intracellular signaling domains, is highly expressed on cancer-associated fibroblasts in the stromal microenvironment of many solid tumors. In some tumors such as sarcomas including OS, melanoma, and glioblastoma, it is expressed both on stromal fibroblasts as well as tumor cells (5). LRRC15 has limited expression in normal tissue and thus may be an attractive target for drug therapy.

Antibody–drug conjugates (ADCs) are a therapeutic strategy in which a cytotoxic payload is attached to an antibody against a surface protein expressed on cancer and/or cancer-associated stromal cells via a linker, with the goal of delivering the payload to these cells via antigen–antibody interaction and internalization. The antibody, by targeting a specific cell population, enhances the therapeutic index and permits the delivery of drug doses that would otherwise be too toxic with systemic administration (6).

ABBV-085 is an ADC directed against LRRC15 that contains the tubulin inhibitor monomethyl auristatin E (MMAE) (7, 8). Preclinical testing of ABBV-085 in rats and cynomolgus monkeys have not shown any significant targeted toxicities at sites of normal expression such as skin (5). ABBV-085 has also been shown to be active against several adult tumor xenografts such as non–small cell lung cancer, breast, and glioblastoma multiforme as well as against a multidrug-resistant OS xenograft when administered at dose of 6 mg/kg every 4 days (5). A recent phase I study of ABBV-085 in patients with advanced sarcoma demonstrated the agent is well-tolerated, and more than 50% of patients had a partial response (PR) or stable disease. Two of the 10 OS patients enrolled on study had a PR (9).

In this study, the *in vivo* activity of ABBV-085 was assessed in a panel of OS PDX models with high and low LRRC15 expression, as part of Pediatric Preclinical Testing Consortium (PPTC).

## Materials and Methods

### Pediatric preclinical testing consortium models

PPTC is an NCI-funded collaborative initiative that includes researchers within and outside United States that contribute preclinical models and help evaluate new agents across a variety of pediatric cancers. All of these models have been well validated through multiple

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**Note:** Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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different technologies over the years and all of the current available data on these models including their molecular and histologic characterization is in the public domain at PedcBioPortal (https://pedcbioportal.kidsfirstdrc.org/study/summary?id=pptc) (10–13). Supplementary Table S1 lists the passage number and growth characteristics of each of the tested xenografts.

### LRRC15 expression analysis

The *in vivo* anticancer effects of ABBV-085 were assessed in a panel of seven OS models (OS1, OS9, OS33, OS34, OS42, OS55, and OS60). PPTC xenograft RNA-sequencing data (RNA-seq; www.cBioPortal.org) was mined for *LRRC15* mRNA expression. The panel of OS xenografts selected for the study was based on the RNA expression data with the goal of including both high- and low- expression models. In addition, LRRC15 protein expression was assessed in three of the PDX models (OS9, OS33, OS60) via IHC by Abbvie Inc. using the LRRC15 antibody-Biotin: ABR, MouseIgG2a, lot No. 17S56. Isotype antibody was used for negative control. Staining was assessed by determining the intensity (0–3) as well as percentage of positive cells and calculating an H score as described previously (14).

*LRRC15* gene expression was also evaluated in human OS samples. RNA-seq data from 101 OS patients was mined from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) database (https://ocg.cancer.gov/programs/target). Furthermore, OS tumor *LRRC15* expression data were compared with normal tissue RNA-sequencing data from the NIH Genotype-Tissue Expression database (GTEx; https://www.gtexportal.org)

### *In vivo* testing

ABBV-085 was provided by Abbvie Inc. C.B.17SC *scid*$^{-/-}$ female mice were used to propagate subcutaneous flank tumors. Ten mice were used in each control or treatment group. First, ABBV-085 was tested at two doses of 6 mg/kg and 12 mg/kg administered via intraperitoneal injection once per week for 4 consecutive weeks in two models with the highest LRRC15 expression (OS33 and OS60) to select appropriate dose for testing in all models. Then all the remaining models were tested at 6 mg/kg once per week for 4 weeks. OS33 underwent two sets of experiments – OS33–1 (initial dose finding) and OS33–2 (repeat 6 mg/kg and a lower dose of 3 mg/kg) to determine dose sensitivity. A control cohort that received vehicle and an additional control cohort that received an isotype MMAE-linked antibody were included in all PDX models assessed. Tumor volumes were measured biweekly as described previously (10). All mice were maintained under barrier conditions and experiments were conducted using protocols and conditions in accordance with the Institutional Animal Care and Use Committee at MD Anderson Cancer Center (ACUF Study No. 00001656-RN00).

The *in vivo* activity of ABBV-085 was evaluated using standard PPTC measures. Briefly, for solid tumor experiments, an event is defined as a quadrupling of tumor volume from day 0. The median time to event was assessed between the experimental and control cohorts. Differences in event-free survival (EFS) between experimental groups (e.g., treated vs. controls) were tested with $\alpha = 0.05$, two-sided alternative with $\rho = 1$, which is equivalent to the Peto & Peto modification of Gehan–Wilcoxon. Objective responses reported as maintained complete response (MCR), complete response (CR), PR, and stable disease were described for each model as defined previously (10). Details of the statistical analysis methods are provided Appendix 1.

## Results

### LRRC15 expression in OS PDX models

We reviewed PPTC Agilent microarray gene expression data which showed overexpression of *LRRC15* for OS xenografts. The average *LRRC15* gene expression value for non-OS/non-glioblastoma multiforme xenograft lines was 35, whereas the OS xenograft expression values ranged from 232 to 12,582 (Supplementary Table S2). Review of

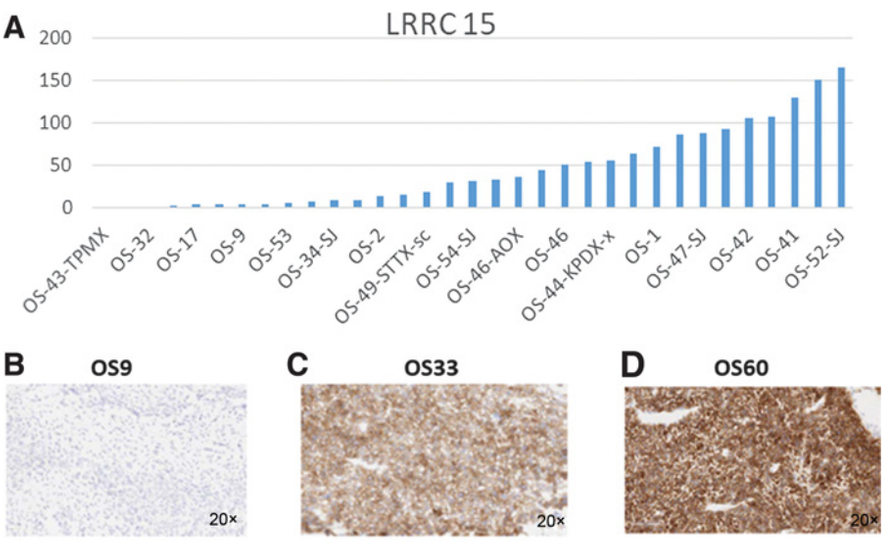


**Figure 1.**

*LRRC15* expression across OS PDX models. **A,** Relative mRNA expression of LRRC15 assessed by RNA-seq in 33 OS PDX models. LRRC15 protein expression assessed by IHC in OS models OS9 (**B**), OS33 (**C**), and OS60 (**D**). **E,** H-score for the three models tested.

**E**

| PDX model | Intensity | % Positive tumor cells | H-score |
|---|---|---|---|
| OS9 | 0 | 0 | 0 |
| OS33 | 2 | 90 | 180 |
| OS60 | 3 | 100 | 300 |

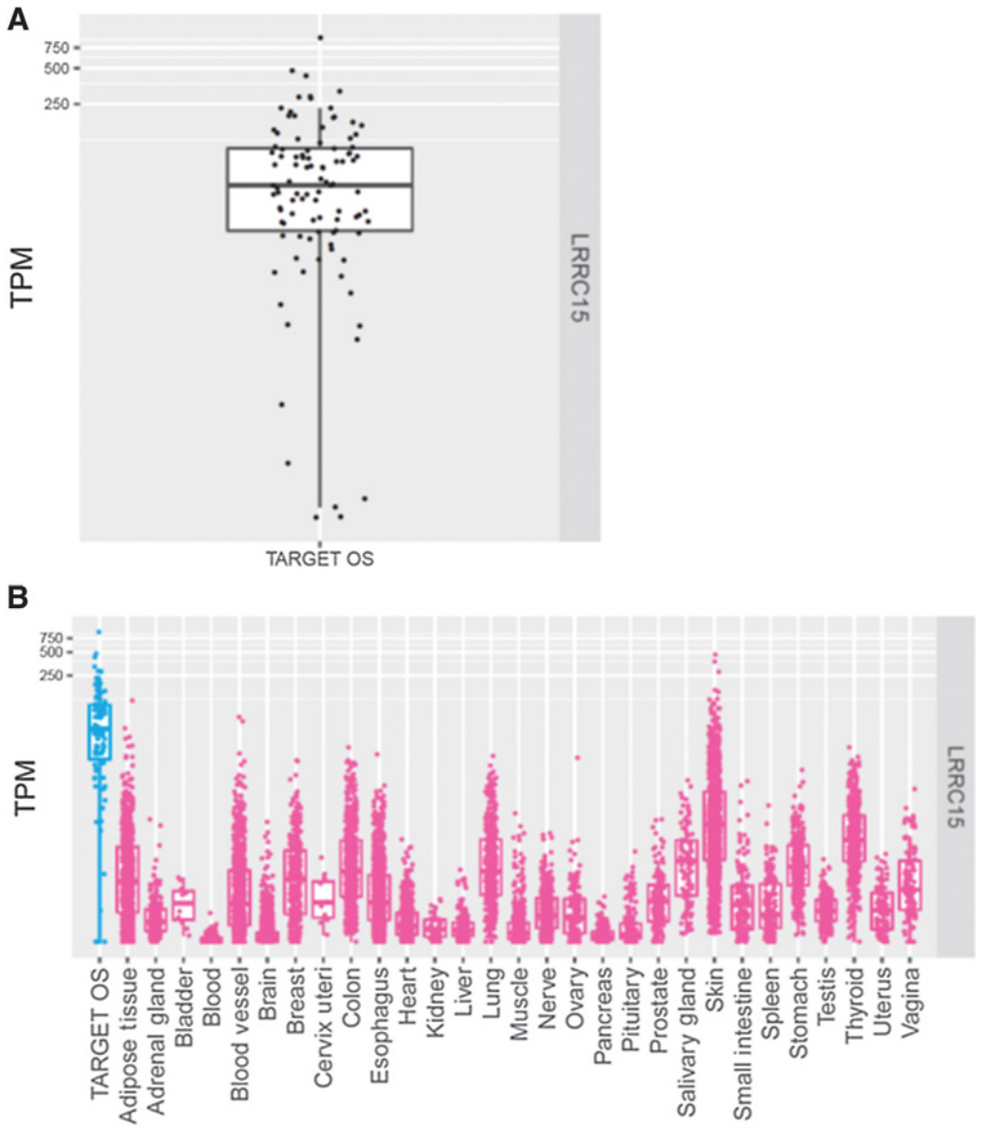


**Figure 2.**

*LRRC15* expression across human osteosarcoma tumors from TARGET database (**A**) and in comparison with normal tissues (**B**).

the RNA-sequencing data for PDX models showed that OS1, OS33, OS42, OS55, and OS60 demonstrated high relative mRNA expression compared with PDX models OS9 and OS42, with OS9 demonstrating the lowest expression (**Fig. 1A**). LRRC15 protein expression was assessed in OS9, OS33, and OS60 and mirrored the mRNA findings with minimal expression in OS9 and strong expression in OS33 and OS60. OS60 demonstrated the highest intensity (3/3) and greatest proportion of cells staining positive (100%), whereas OS9 did not demonstrate any positive staining (**Fig. 1B–D**). H scores were calculated for these three models (**Fig. 1E**).

## LRRC15 expression in human OS tumors

*LRRC15* gene expression on human OS samples from TARGET database showed variable expression levels in >90% of the samples with a median of 51.92 TPM (**Fig. 2A**). Comparison with normal human tissues showed significantly higher expression level in OS (median normal tissue expression = 0.184 TPM; log fold change tumor versus normal = 4.36; $P < 0.01$; **Fig. 2B**).

## *In vivo* efficacy of ABBV-085

ABBV-085 was initially tested in two PDX models (OS33 and OS60) predicted to be responsive due to high LRRC15 expression at doses 6 mg/kg and 12 mg/kg once per week for 4 weeks to determine the optimal dose for testing in additional models. In addition, OS33 was also tested at the lower dose of 3 mg/kg. ABBV-085 at both 6 mg/kg and 12 mg/kg significantly inhibited tumor growth and prolonged EFS in the OS60 model compared with both the vehicle control animals, with EFS T/C values > 4.0 and with PD2 objective responses. The isotype MMAE control at 12 mg/kg did not significantly extend EFS compared with vehicle controls. In OS33, ABBV-085 at both 6 mg/kg and 12 mg/kg was highly active with EFS T/C > 5.0, and with PR and maintained complete response (MCR) objective responses,

**Table 1.** Response to ABBV-085 at varying doses in two OS PDX models for dose finding.

| Model | Agent | Dose (mg/k) | KM med (days) | EFS T-C (days) | EFS T/C | *P* value Gehan–Wilcoxon | minRTV mean ± SD | minRTV *P* value | Objective response measure[a] |
|---|---|---|---|---|---|---|---|---|---|
| **OS-60** | Vehicle control | | 16.7 | | | | 1.997 ± 0.228 | | PD |
| | ABBV-085 | 6 | 80.1 | 63.4 | 4.79 | $P < 0.001$ | 1.022 ± 0.167 | $P < 0.001$ | PD2 |
| | ABBV-085 | 12 | >86 | >69.3 | >5.14 | $P < 0.001$ | 0.977 ± 0.213 | $P < 0.001$ | PD2 |
| | MMAE-antibody | 12 | 19.9 | 3.2 | 1.19 | $P = 0.024$ | 1.634 ± 0.347 | $P = 0.023$ | PD1 |
| **OS-33** | Vehicle control | | 15.6 | | | | 1.990 ± 0.264 | | PD |
| | ABBV-085 | 6 | >86 | >70.4 | >5.53 | $P < 0.001$ | 0.117 ± 0.138 | $P = 0.001$ | PR |
| | ABBV-085 | 12 | >86 | >70.4 | >5.53 | $P < 0.001$ | 0.080 ± 0.148 | $P = 0.001$ | MCR |
| | MMAE-antibody | 12 | >86 | >70.4 | >5.53 | $P < 0.001$ | 0.065 ± 0.116 | $P = 0.002$ | MCR |

[a]All the response measures are defined in Appendix 1.

respectively. The isotype MMAE control at 12 mg/kg showed comparable levels of activity as ABBV-085 with an MCR suggesting nonspecific activity of payload in this model unrelated to LRRC15 at high doses. No significant weight loss was observed in the treated mice and no mice experienced death due to toxicity. Details of these testing results are provided in **Table 1**. On the basis of these studies, dose of 6 mg/kg was selected for testing in remaining models.

ABBV-085 significantly inhibited tumor growth at 6 mg/kg in six of seven of the models tested compared with the vehicle control cohorts (**Table 1**; **Fig. 3A**). OS9 was the only model that did not demonstrate significantly delayed tumor growth compared with the vehicle control. We also compared the response of ABBV-085 cohort to isotype MMAE antibody cohort. A difference in tumor growth inhibition was seen in three of seven models (OS1, OS33, and OS60) suggesting some nonspecific activity of isotype antibody in some of the OS models (**Fig. 3A**). ABBV-085 treatment resulted in an objective response in two of seven of models at 6 mg/kg, with OS33 and OS55 experiencing an MCR (**Fig. 3A**). All other models experienced progressive disease

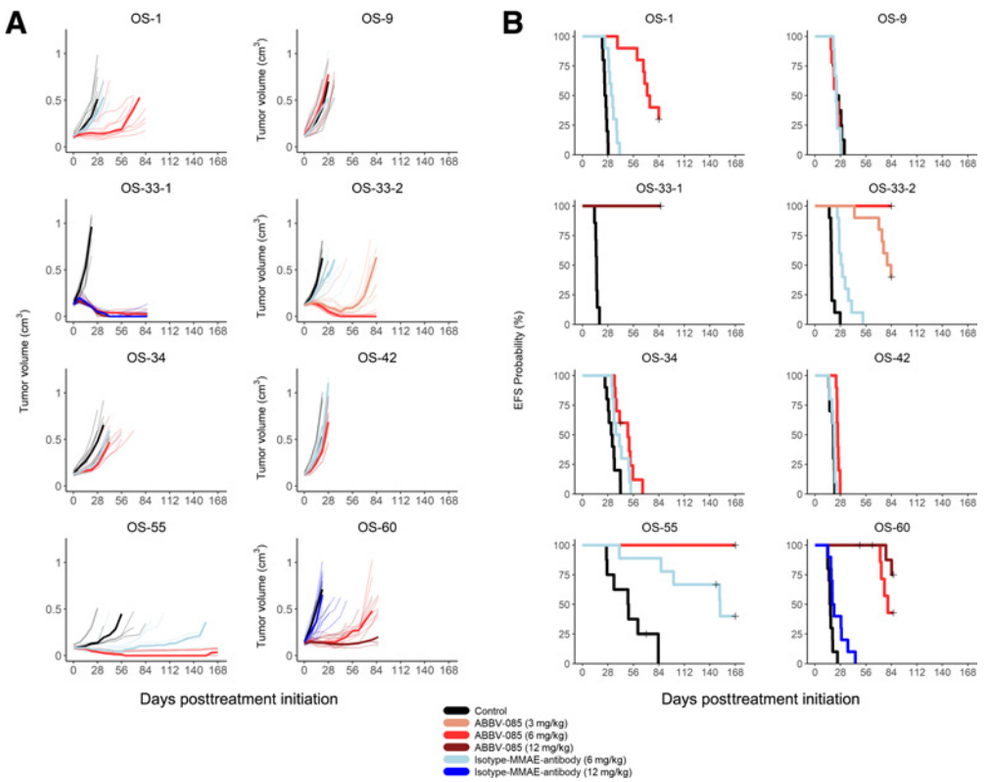


**Figure 3.**

**A,** Tumor growth inhibition with ABBV-085 across OS PDX models: ABBV-085 induced significant inhibition in tumor growth in six of seven of the osteosarcoma models (except OS9) as compared with vehicle control and three of seven models (OS1, 33 and 60) as compared with isotype MMAE, when given once a week for 4 consecutive weeks. The lighter lines represent individual mice and the bolder lines represent median tumor growth in each group. Two sets of experiments were performed for OS33. OS-33-1 included control, ABBV-085–6 mg/kg and 12 mg/kg and isotype MMAE 12 mg/kg. OS-33-2 included control, ABBV-085-3 mg/kg and 6 mg/kg and isotype MMAE at 6 mg/kg. **B,** Event-free survival to ABBV-085 across OS PDX models. ABBV-085 induced significant improvements in event-free survival (EFS) compared with vehicle (except OS9 and OS42) and isotype MMAE (except OS9 and OS34) control in five of seven of the osteosarcoma models tested.

**Table 2.** Activity of ABBV-085 and isotype MMAE antibody versus vehicle control for all PDX models.

| Model | Agent | Dose (mg/k) | KM med (days) | EFS T-C (days) | EFS T/C | *P* value Gehan–Wilcoxon | minRTV mean ± SD | minRTV *P* value | Objective response measure[a] |
|---|---|---|---|---|---|---|---|---|---|
| **OS-1** | ABBV-085 | 6 | 72.6 | 47.4 | 2.88 | $P < 0.001$ | 1.162 ± 0.234 | $P < 0.001$ | PD2 |
| | MMAE-antibody | 6 | 32.5 | 7.3 | 1.29 | $P < 0.001$ | 1.383 ± 0.098 | $P = 0.004$ | PD1 |
| **OS-9** | ABBV-085 | 6 | 23.6 | −1.2 | 0.95 | $P = 0.447$ | 1.687 ± 0.389 | $P = 0.673$ | PD1 |
| | MMAE-antibody | 6 | 23.4 | −1.4 | 0.94 | $P = 0.631$ | 1.684 ± 0.268 | $P = 0.370$ | PD1 |
| **OS-33** | ABBV-085 | 6 | >84 | >65.9 | >4.65 | $P < 0.001$ | 0.026 ± 0.056 | $P < 0.001$ | MCR |
| | ABBV-085 | 3 | 81.4 | 63.4 | 4.51 | $P < 0.001$ | 0.520 ± 0.330 | $P < 0.001$ | PR |
| | MMAE-antibody | 6 | 29.4 | 11.3 | 1.62 | $P < 0.001$ | 1.269 ± 0.150 | $P = 0.002$ | PD1 |
| **OS-34** | ABBV-085 | 6 | 49.9 | 17.6 | 1.54 | $P < 0.001$ | 1.136 ± 0.113 | $P = 0.001$ | PD1 |
| | MMAE-antibody | 6 | 38.8 | 6.5 | 1.2 | $P = 0.025$ | 1.233 ± 0.121 | $P = 0.052$ | PD1 |
| **OS-42** | ABBV-085 | 6 | 25 | 4.8 | 1.24 | $P < 0.001$ | 1.251 ± 0.194 | $P = 0.035$ | PD1 |
| | MMAE-antibody | 6 | 21.3 | 1.1 | 1.06 | $P = 0.226$ | 1.430 ± 0.223 | $P = 0.393$ | PD1 |
| **OS-55** | ABBV-085 | 6 | >168 | >117.6 | >3.34 | $P < 0.001$ | 0.176 ± 0.211 | $P < 0.001$ | MCR |
| | MMAE-antibody | 6 | 151 | 101.1 | 3.01 | $P = 0.003$ | 0.499 ± 0.369 | $P < 0.001$ | PR |
| **OS-60** | ABBV-085 | 6 | 80.1 | 63.4 | 4.79 | $P < 0.001$ | 1.022 ± 0.167 | $P < 0.001$ | PD2 |
| | MMAE-antibody | 12 | 19.9 | 3.2 | 1.19 | $P = 0.024$ | 1.634 ± 0.347 | $P = 0.023$ | PD1 |

[a]All the response measures are defined in Appendix 1.

with median time to event for treated versus control animals (EFS T/C) ranging from 0.95 for OS9 to >4.65 for OS33. At 3 mg/kg, ABBV-085 showed a PR in OS33 (**Table 2**).

OS33 was tested again at 6 mg/kg (OS 33–2), whereas results for OS-60 are from the initial dose-finding experiments. In this second set of experiments with OS33 at 6 mg/kg dose, an MCR was observed. The discrepancy between the two sets of experiments is explained by the fact that in the first experiment, half of the mice in the test group achieved a CR and the other achieved PR, therefore, by PPTC convention, the response was reported as a PR. In the second experiment, two of 10 mice had a PR and eight had an MCR, so the response was reported as MCR.

ABBV-085 treatment led to significantly prolonged EFS in five of seven of these models compared with the isotype control (**Table 2**; **Fig. 3B**). OS9 and OS34, the two models with the lowest LRRC15 expression, were the only models that did not demonstrate significantly prolonged EFS compared with the isotype control (**Table 2**; **Fig. 3B**).

## Discussion

ABBV-085 exhibited significant antitumor activity against the PPTC OS PDX models with high expression of LRRC15, demonstrated by prolonged EFS and objective responses. LRRC15 is highly expressed on both cancer cells as well as tumor stroma of mesenchymal origin. High LRRC15 expression is also seen in breast cancer, head and neck cancer, nonsquamous cell lung cancer, and pancreatic cancer making it a potential target in a wide variety of solid tumors. The mRNA expression is generally highly concordant with protein expression via IHC. Data suggest that LRRC15 is a regulator of osteogenesis of mesenchymal stem cells (15). Furthermore, presence of LRRC15 expressing fibroblasts in tumor microenvironment portend a poor response to immune checkpoint blockade (16). Although *LRRC15* mRNA expression in a large cohort of human OS patients from the TARGET database is suggestive of strong expression in majority of the tumors, additional studies establishing the prevalence of LRRC15 protein expression in OS patient samples may be warranted. Our data provide proof of principle that LRRC15 may be a potential target for antibody delivered cytotoxic payloads and worthy of further clinical trials.

ABBV-085 has entered clinical testing with a focus on patients with sarcomas (10). Following dose escalation, an expansion cohort was evaluated using a dose of 3.6 mg/kg administered every 2 weeks. Anticipated auristatin safety findings of ocular toxicity (may be related to the linker) and peripheral neuropathy were observed. Other toxicities included fatigue and neutropenia. No targeted toxicities at sites of normal LRRC15 expression such as skin were observed. Durable responses were observed for relapsed refractory undifferentiated pleomorphic sarcoma (two confirmed partial responses in 10 patients) and for OS (two confirmed partial responses in 10 patients) providing essential human activity data for further OS-specific trials.

ADCs are a relatively newer therapeutic approach in cancer therapy. ADCs comprise of an antibody to a surface protein of interest such as LRRRC15, a linker and a payload cytotoxic agent. The goal of an ADC is to be able to deliver large doses of the cytotoxic agent specifically to the malignant cells that express the antigen without exposure to normal tissues. The prerequisite characteristic for an effective ADC would not require the surface antigen to be oncogenic although a dependency on the protein is preferable. ADC against oncogenic antigens such as HER2 are being explored in OS (17). However, the antigen against which the ADC is developed has to be present in a large proportion of OS tumors along with minimal expression in normal tissues. If further study of LRRC15 expression in OS tumors confirms a strong ubiquitous expression in majority of patient samples, it would make this protein an attractive strategy for using the ADC approach to treat OS.

It is also important to consider what payload or cytotoxic agent the ADC is delivering and its activity towards the tumor cells. Cytotoxic agents used as payloads include microtubule inhibitors, topoisomerase inhibitors, and DNA damaging agents (6). The role of tubulin-targeted drug conjugates is not yet clear in OS, although there is preclinical evidence of target-specific effects. However, other classes of cytotoxic agents such as DNA-damaging agents may be more relevant in the case of OS (18). One potential issue with using the ADC approach may be development of resistance by downregulation of cell surface protein on the tumor cells, and this would need to be monitored in preclinical and clinical studies. Nonetheless, identification of novel surface proteins expressed on a majority of OS tumor cells and samples and developing specific ADCs against them provides an exciting new therapeutic avenue in this disease.

## Authors' Disclosures

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## Authors' Contributions

**P. Hingorani:** Data curation, writing–original draft. **M.E. Roth:** Data curation, writing–original draft. **Y. Wang:** Data curation. **W. Zhang:** Data curation. **J.B. Gill:** Data curation. **D.J. Harrison:** Data curation. **B. Teicher:** Writing–review and editing. **S. Erickson:** Data curation. **G. Gatto:** Resources. **M.A. Smith:** Writing–review and editing. **E.A. Kolb:** Data curation, writing–review and editing. **R. Gorlick:** Writing–review and editing.

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