

# Evaluation of ABBV-085, an antibody-drug conjugate targeting LRRC15, in Osteosarcoma by the Pediatric Preclinical Testing Consortium

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## Introduction

- Survival rates for patients with metastatic and recurrent osteosarcoma (OS) have remained stagnant at <30% for several decades
- Data from genome sequencing has failed to reveal recurrent genetic aberrations that are therapeutically targetable in a large proportion of patients
- Identification of cell-surface proteins that are strongly expressed in a majority of tumors and can be targeted directly or indirectly provides a novel therapeutic avenue
- Antibody-drug conjugates (ADC) are novel therapeutic agents with a monoclonal antibody against a cell surface protein linked to a cytotoxic payload via a linker that releases the payload inside the cell
- ABBV-085 is an ADC against LRRC15, a highly expressed cell surface protein in OS, linked to a tubulin inhibitor MMAE.
- The PPTC sought to evaluate the potential anti-cancer efficacy of ABBV-085 against *in vivo* OS models

## Methods

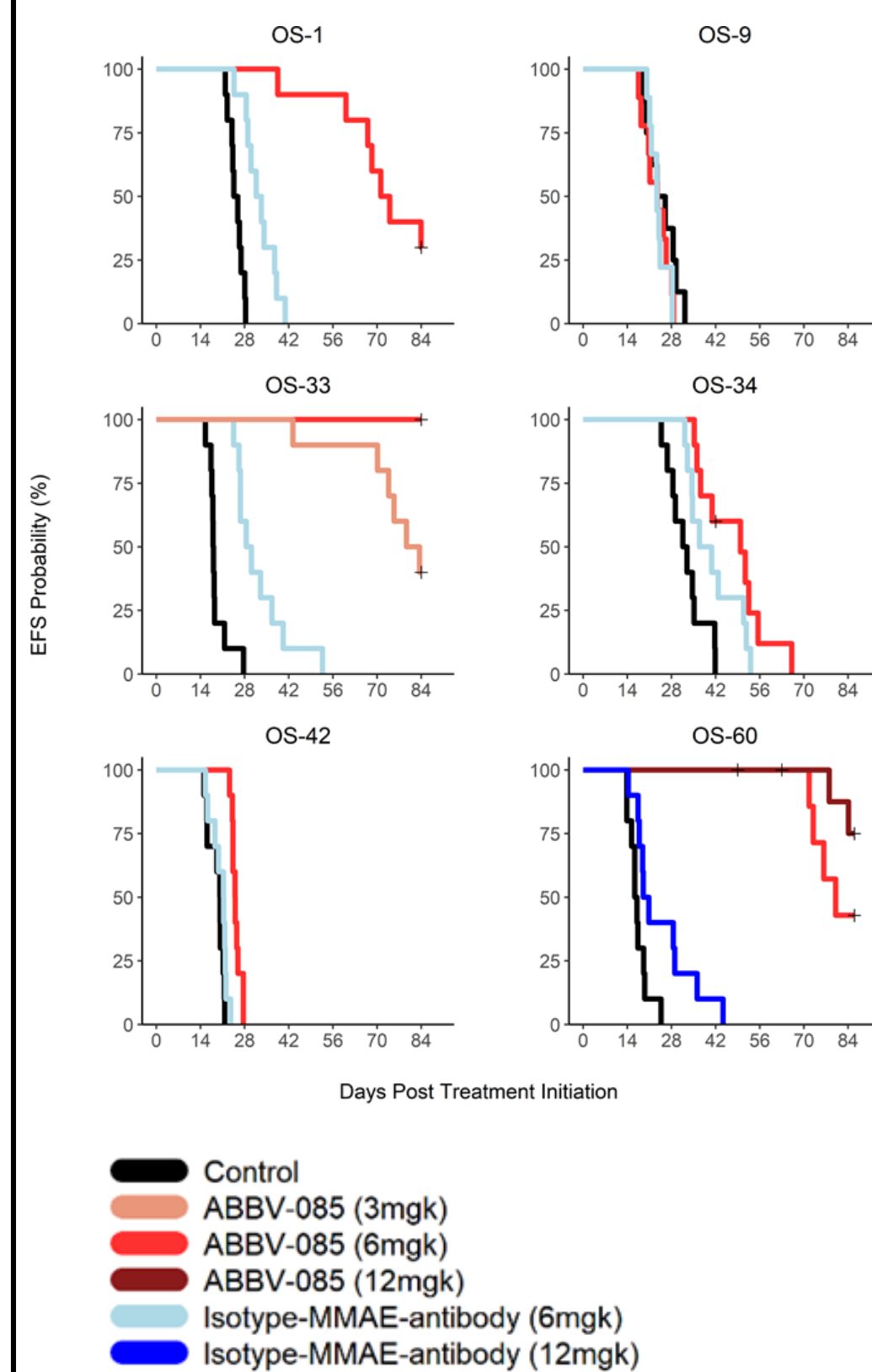
### ABBV-085 Administration:

- Two doses, 6 mg/kg and 12mg/kg, once a week for 4 weeks via intraperitoneal injection were tested in 2 patient derived xenografts (PDX) models; remaining models were tested at 6mg/kg dose with a single model (OS-33) also tested at 3 mg/kg.

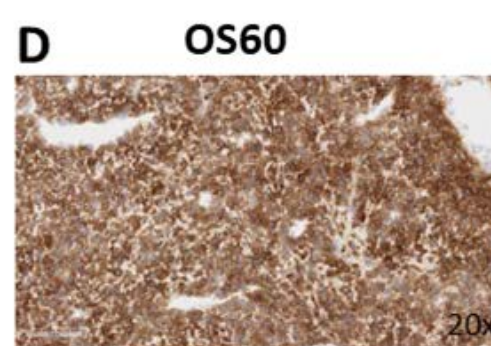
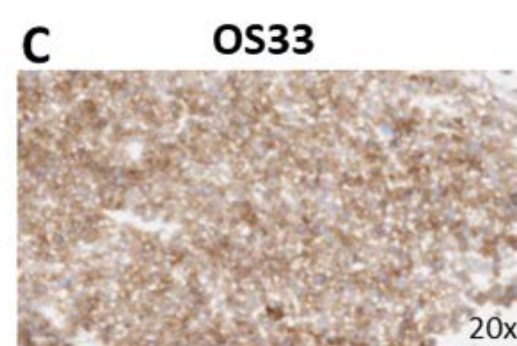
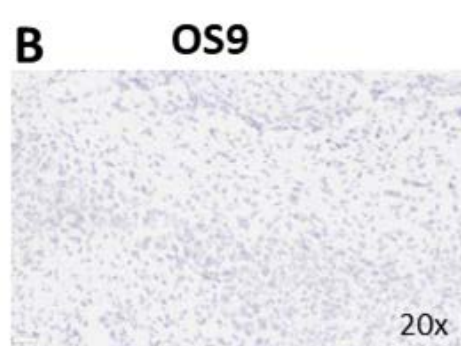
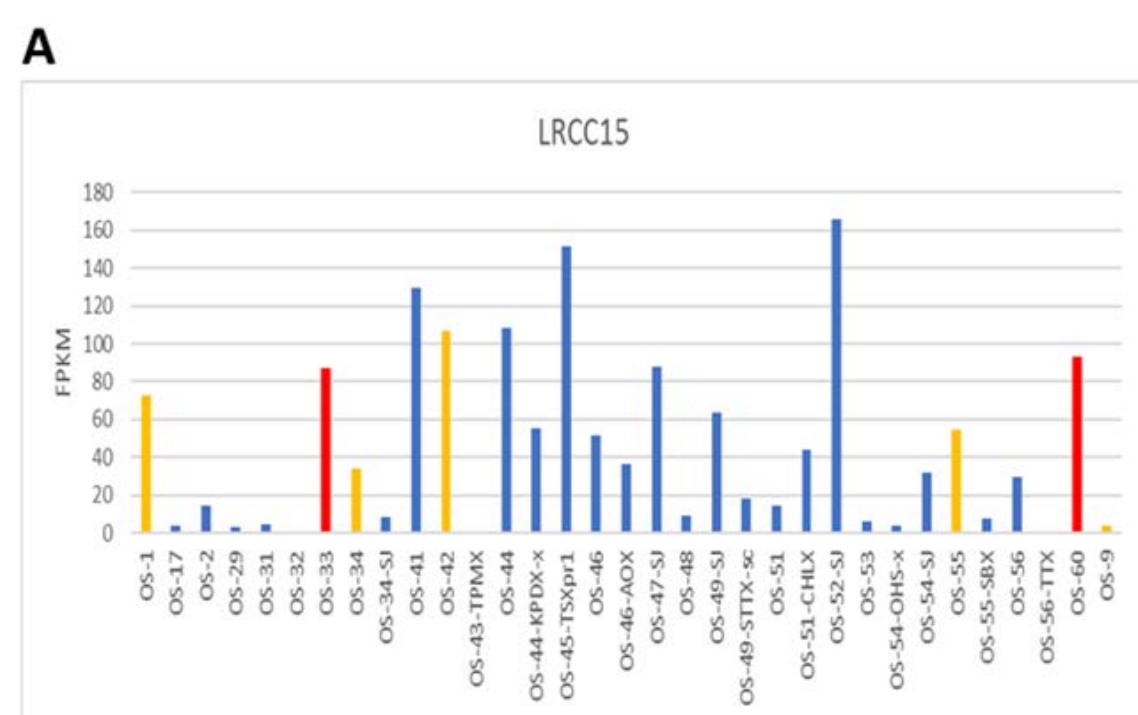
### Study Design and Analysis:

- Four high LRRC15 expressing (OS1, OS33, OS42-SJ and OS60) and two low LRRC15 expressing PDX (OS9, OS34-SJ) were heterotopically injected into the flanks of CB17SC *scid*<sup>-/-</sup> mice
- Two control cohorts that received vehicle and isotype MMAE-linked antibody were included for each PDX model
- Tumor volume was monitored in all cohorts with event defined as 4x initial tumor growth
- Tumor growth, Event Free Survival (EFS) compared between treatment and control groups
- P-values were two-sided and considered statistically significant if  $p < 0.05$

## Event-Free Survival to ABBV-085



## RNA and Protein Expression of LRRC15 in OS



## ABBV-085 vs. Control in 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* |
|-------|---------------|-------------|---------------|----------------|---------|------------------------|----------------|----------------|-----------------------------|
| 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                         |
|       | 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-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                         |

## Discussion and Conclusions

- ABBV-085 demonstrated significant anti-tumor activity in OS with significant prolongation of EFS in 3/5 PDX
- OS33 demonstrated a maintained complete response
- Response was related to tumor LRRC15 expression
- ABBV-085 should be further studied in a clinical trial of patients with OS

## References

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- Demetri GD, Luke JJ, Hollebecque A, Powderly JD, Spira AI, Subbiah V, et al. First-in-human phase 1 study of ABBV-085, an antibody-drug conjugate (ADC) targeting LRRC15, in sarcomas and other advanced solid tumors. *American Society of Clinical Oncology*; 2019