Abstract ID: 167

Initial Testing of m276-PBD CD276 Antibody Conjugate in Preclinical Models of Pediatric Cancers by the Pediatric Preclinical Testing Consortium (PPTC)

1. Introduction

CD276 (B7-H3) is an immunoregulatory molecule that is reported to be widely expressed in pediatric embryonal tumors, pediatric sarcomas, and tumor infiltrating blood vessels (Majzer et al. 2018).

CD276 protein is expressed at low levels on several normal tissues, including cerebral cortex, liver and genital lymph nodes.

m276 is a fully-human IgG1 that binds with similar affinity to both mouse CD276 (24 nM kD) and human CD276 (29 nM kD) (Seaman et al. 2017).

To generate an antibody-drug conjugate, m276 was site-specifically conjugated to the DNA damaging agent pyrrolobenzodiazepine (PBD) via a cleavable valine-alanine linker, providing m276-PBD conjugated to the DNA damaging agent pyrrolobenzodiazepine (PBD) via a cleavable valine-alanine linker, providing m276-PBD to evaluate for tumor regression and for time to event.

Here we report the antitumor activity of m276-PBD against preclinical xenograft models of pediatric solid tumors.

2. Study Methods

m276-PBD was administered by intraperitoneal injection at a dose of 0.5 mg/kg, once weekly x 3 consecutive weeks.

Solid tumor testing used subcutaneous xenografts. Events were defined as ≥50% increase in tumor volume from the first day of treatment. The Kaplan-Meier method was used to compare time-to-event between treated and control groups.

The objective response categories are as described by Houghton, et al. 2007. CR = complete response, disappearance of measurable tumor mass during study; PR = partial response, ≥50% tumor regression at any point during study but <50% tumor regression throughout study and ≤25% tumor growth; SD = stable disease, <50% tumor regression throughout study and ≤25% tumor growth; PD = progressive disease, <50% tumor regression throughout study and >25% tumor growth.

3. CD276 Expression in PPTC models

CD276 expression was high in most solid tumors (median 41 FPKM) with highest expression in osteosarcoma (median 82 FPKM) and human CD276 expression in osteosarcoma, 3/3 Ewing sarcoma, 2/2 Wilms tumor, and 6/11 neuroblastoma.

Here we report the antitumor activity of m276-PBD against preclinical xenograft models of pediatric solid tumors.

4. Results

Table 1: Testing Summary

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Model</th>
<th>Number of Tumors</th>
<th>Tumor Volume</th>
<th>Tumor Volume Median (FPKM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>Ewing Sarcoma</td>
<td>ES-1</td>
<td>SK-N-E1</td>
<td>0.9</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Rhabdomyosarcoma</td>
<td>RH1</td>
<td>RH3</td>
<td>0.9</td>
</tr>
<tr>
<td>Wilms Tumor</td>
<td>Wilms Tumor</td>
<td>KT-10</td>
<td>KT-11</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Figure 1: Ewing Sarcoma Tumor Growth

Figure 2: Rhabdomyosarcoma Tumor Growth

Figure 3: Wilms Tumor Growth

Figure 4: Osteosarcoma Tumor Growth

Figure 5: Neuroblastoma Tumor Growth

4. Discussion and Conclusions

RNAseq data for PPTC models show elevated CD276 expression levels for a wide range of pediatric solid tumors, which is consistent with protein expression data from clinical specimens (Majzer et al., 2019).

m276-PBD showed very high levels of activity when tested against PPTC pediatric solid tumor preclinical models at 0.5 mg/kg administered weekly x 3.

Objective responses (PR/CR/MCR) were observed in 23 of 25 models that attained CR not showing regrowth by day 56 and with follow-up still ongoing. There was no clear relationship between CD276 expression by RNAseq and response to m276-PBD, with CR and MCR responses observed in models with CD276 expression ranging from 20 to 166 FPKM, and with SD/PR responses observed at expression levels from 14 to 131 FPKM.

m276-PBD was well tolerated, with a toxic death rate < 2% and with mean body weight loss of 9.5%.

The translatability of our results to the clinical setting is dependent upon the extent to which the drug levels achieved in mice can be replicated in humans. Additional experiments to define the dose-response to m276-PBD across a range of histologies will help to define the minimum exposure levels associated with tumor-regressing activity.

Conclusion: Our results confirm m276 as a high priority target for pediatric solid tumors and support further evaluation of CD276-targeted ADCs with direct DNA-damaging payloads for these cancers.

5. References


More Information

Corresponding author: Dr. Peter Houghton
Presentation at: AACR-EMRC International Conference on Molecular Targets and Cancer Therapeutics
Supported by: NCI Grants CA199222, CA199287, CA199221, and CA199297
Poster available at: http://www.nci-pptc.org/publications