Preclinical Evaluation of Trastuzumab Deruxtecan (T-DXd; DS-8201a), a HER2 Antibody Drug Conjugate, in Pediatric Solid Tumors by the Pediatric Preclinical Testing Consortium (PPTC)

Abstract ID: 10446

Pediatric Preclinical Testing Consortium
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1. Introduction

HER2, also known as ErbB2, is a receptor tyrosine kinase known to be expressed on the cell surface and cytoplasm of many adult and pediatric solid tumors. HER2 is widely expressed during fetal development and lower levels of expression are also seen in adult tissues: kidney, liver, skin, lung, jejunum, uterus, stomach, and colon.

Several HER2-directed therapies such as monoclonal antibody and CAR-T cell therapy have been investigated in pediatric sarcomas. DS-8201a is an antibody-drug conjugate in which the HER2-directed monoclonal antibody with the same amino acid sequence as trastuzumab is linked to a topoisomerase I inhibitor payload, DXd via a linker.

Here we report the antitumor activity of DS-8201a against xenograft models of pediatric solid tumors.

2. Study Methods

HER2b mRNA expression was determined across the PDX tumor models. Trastuzumab deruxtecan was administered by intravenous injection at a dose of 5 mg/kg, once on day 1.

3. ERBB2 Expression in PPTC models

- HER2b mRNA expression was measured during the PDX tumor models.
- Trastuzumab deruxtecan was administered by intravenous injection at a dose of 5 mg/kg, once on day 1.
- Solid tumor testing used subcutaneous xenografts. Events were defined as a 4-fold 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 described by Houghton, et al., 2007.
- The Kaplan-Meier method was used to compare time-to-event between treated and control groups.

4. Results

Table 1: Testing Summary for Standard Experiments

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Treatment</th>
<th>Tumor Volume</th>
<th>Effect</th>
<th>SD/PR</th>
<th>CR/MCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS ATRT</td>
<td>DS8201a</td>
<td>0.757</td>
<td>0.486</td>
<td>0.398</td>
<td>0.232</td>
</tr>
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<td>Extracranial rhabdoid tumors</td>
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<td>Osteosarcoma</td>
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<td>0.757</td>
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<tr>
<td>Rhabdomyosarcoma (fusion positive)</td>
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<td>0.398</td>
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<td>Wilms tumor</td>
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Figure 1: Osteosarcoma Tumor Growth

Table 2: Overall Summary of Response for Standard and Single Mouse Experiments

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Figure 2: Rhabdoid Tumor and Wilms Tumor Growth

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Figure 3: Osteosarcoma Event-Free Survival

Figure 4: Rhabdoid and Wilms Tumor Event-Free Survival

Figure 5: Waterfall and Swimmer’s Plot of Tumor Response Across Histologies

5. Results (continued)

6. Discussion and Conclusions

- Trastuzumab deruxtecan was tested in both conventional (5-10 mice) and single mouse testing experiments.
- Trastuzumab deruxtecan was well tolerated, with no treatment-related deaths and minimal weight loss.
- Trastuzumab deruxtecan showed high levels of activity when tested against PPTC pediatric solid tumor preclinical models at 5 mg/kg administered x 5.
- Objective responses (PR or MCR) were observed in 5 of 13 models (38%) in conventional testing: 1/2 extrarenal rhabdoid, 2/3 Wilms tumor. 1/7 OS models (OS33) showed SD.
- Single mouse testing extended the observation of high level activity for rhabdoid tumors, and it showed additional objective responses in medulloblastoma, glioblastoma, Ewing sarcoma and neuroblastoma.
- Single mouse experiments showed results concordant with conventional testing for models tested in both experiments, providing proof of principle for use of this methodology to enhance capability for testing a broader range of models more rapidly.
- RNAseq data for PPTC models show elevated ERBB2 expression levels for a wide range of pediatric solid tumors.
- Tumor panels showing most consistent responses (ATRT, rhabdoid tumor and Wilms tumor) had ERBB2 b mRNA expression level between 11-40 FPKM.
- A few low expressing tumors (Rh-30, Rh-30R and OS33) also demonstrated activity with DS8201a.
- Evaluation of HER2 expression by IHC and response is pending.
- A clinical trial with trastuzumab deruxtecan in recurrent HER2+ osteosarcoma is under development.

Conclusion: Our results confirm HER2 as a high priority target for selected pediatric solid tumors and support further evaluation of HER2 targeting ADCs.

7. References

- Phase I trial of trastuzumab in combination with cytotoxic chemotherapy for treatment of metastatic osteosarcoma with human epidermal growth factor receptor 2 overexpression: a report from the Children’s Oncology Group.

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