Evaluation of the in vivo efficacy of the B7-H3 targeting antibody-drug conjugate (ADC) DS-7300a: A report from the Pediatric Preclinical In Vivo Testing (PIVOT) program

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ABSTRACT

B7-H3 (encoded by the CD277 gene) is suggested to act as an immune checkpoint molecule and is highly expressed in some pediatric solid tumors. Monoclonal antibodies targeting B7-H3 (IH9 and MGA271) are well-tolerated but have demonstrated limited success in clinical trials. DS-7300a is a B7-H3 targeting antibody-drug conjugate (ADC) with a payload of DXL (an oxetane derivative that inhibits DNA topoisomerase I). DS-7300a has an average drug-to-antibody ratio of 4 and it has shown promising early clinical activity in adults with advanced solid cancers (Johnson, Annals of Oncology 2021; 32:5883-5889, Patel, Journal of Clinical Oncology 2022; 40(7)). We report here the results of single agent testing of DS-7300a in pediatric cancer models.

STUDY METHODS

Patient derived in vivo models for several pediatric cancer types were selected for preclinical testing of DS-7300a based on the high rates of B7-H3 (CD277) expression.

CD277 expression in PIVOT pediatric models

https://pediatriccanceratwork.org

MODELS

Models were dosed at 10 mg/kg administered intravenously every other week for 14 consecutive weekly readings for at least 6 weeks. Each model was treated with isotype control or drug and scored as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The objective response is defined as the sum of CR and PR. The median of the group determines the overall response.

RESULTS

Table: Objective Response

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<th>Model</th>
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DISCUSSION

DS-7300a showed single agent activity across a broad range of tested models:

- DS-7300a demonstrated high efficacy (maintained complete response, complete response, and partial response) in most non-CNS models tested:
  - 5 of 7 osteosarcomas
  - 7 of 10 neuroblastomas,
  - 17 of 21 rhabdomyosarcomas,
  - 6 of 15 Ewing sarcomas
  - 2 of 2 Wilms tumors.

For Ewing sarcoma, most models were classified as progressive disease (9 of 15).

For osteosarcoma models, the log cell kill per dose values ranged from 0.95 to 2.76, demonstrating the high activity of the agent in these models.

DS-7300a induced a statistically significant prolongation of survival in 1 of 3 osteosarcoma and 2 of 3 glioblastoma orthotopic tumor models.

The activity for DS-7300a followed the general pattern of protein and RNA expression levels for B7-H3/CD277 in the models, with Ewing sarcoma models showing lower expression and less robust DS-7300a activity compared to the other models.

CONCLUSIONS

- DS-7300a showed robust tumor-regressing antitumor activity across a wide range of pediatric solid tumor models.
- The maintained complete remission (MCR) classification for osteosarcoma models are noteworthy, as this level of response is uncommon for these models. Osteosarcoma models show the highest B7-H3 expression among PIVOT preclinical models.
- The high level of preclinical activity observed for DS-7300a combined with the promising early clinical activity observed for adult patients provide strong rationale for studying DS-7300a in children with B7-H3 expressing solid tumors.

REFERENCES

Clark, Breast Cancer Research and Treatment 1997; 46:255-278
Houghton, Pediatric Blood Cancer 2007;49:928-940
Johnson, Annals of Oncology 2021; 32:5883-5889

MORE INFORMATION

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Leg call kill (OCR) per dose (Clark et al. 1997) was estimated from LCR/dose = (T-C)/(T0-C)/(Tn-CN)tn, where Tn is tumor doubling time and n is number of treatments. The equation simplifies to LCR/dose = 0.301 * (TC - T1)