Abstract

NTX-010 is a novel oncolytic picornavirus with selective activity against tumor variants expressing neuroendocrine markers. The activity of NTX-010 was evaluated against the in vitro and in vivo panels of the Pediatric Preclinical Testing Program (PPTP).

Methods: The PPTP includes a molecularly characterized in vitro panel of cell lines (n=53) and in vivo panel of xenografts (n=71) representing most of the common types of childhood cancers. In addition to NTX-010, the PPTP includes a panel of 32 potent anticancer agents from 7 different classes.

Results: NTX-010 was variably active against lines in the in vitro panel with activity focused in the Ewing, neuroblastoma, osteosarcoma, and lymphoid/lymphoblastic histologies, while no activity was observed against mesenchymal histologies. NTX-010 achieved objective responses in 12 of 29 xenografts tested (41%) with objective responses in the Wilms, rhabdoid, glialblastomas, and osteosarcomas panels. Activity was greatest for the neuroendocrine and neuroectodermal tumors including neuroblastoma (4 of 4 neuroblastoma, 2 of 4 rhabdomyosarcoma, and 1 of 4 Ewing sarcoma), glioblastoma (4), osteosarcoma (4), ALL (4). The drug was well tolerated when dosed at or below the Maximum Tolerated Dosage (MTD).

Conclusions: NTX-010 demonstrated activity against the neuroblastoma and alveolar rhabdomyosarcoma panels. Activity was observed against leukemia and lymphoma lines. NTX-010 was provided by Neotropix, and administered intravenously as a single dose via intravenous injection. Three measures of antitumor activity were used: 1) response criteria modeled after those used in the National Cancer Institute’s (NCI) Developmental Therapeutics Program (NCTD) (4), Ewing sarcoma (4), ALL (4), the study was exploratory in nature and was performed with adherence to each institution’s Institutional Review Board (IRB). NTX-010 was provided by Neotropix (Malvern, PA). NTX-010 was diluted in Dulbecco’s phosphate buffer saline (dPBS) (Hanks) and administered intravenously as a single dose at the estimated MTD.

Statistical Methods for PPTP

1) Response rates were calculated and then each treatment group was assigned an overall response according to the Response Evaluation Criteria in Solid Tumor (RECIST) treatment.

2) Event free survival (EFS) distributions of each treatment group were compared using the Log rank test.

3) Expression of selected genes that are markers for Neuroendocrine origin (AR, SMP30, Trp53, 131Pal3) .

4) One-way analysis of variance (ANOVA) was used to determine the molecular characteristics associated with response.

CONCLUSIONS

NTX-010 demonstrated in vitro activity against Ewing sarcoma, alveolar rhabdomyosarcoma and neuroblastomas.

NTX-010 demonstrated high level in vitro activity against models of chondoblast and Wilms tumor of the kidney, alveolar rhabdomyosarcoma, glioblastomas and neuroblastomas.

Ewing sarcoma showed no sensitivity, while no activity was demonstrated against mesenchymal tumors.

Activity was observed against leukemia and lymphoma lines. NTX-010 was provided by Neotropix, and administered intravenously as a single dose at the estimated MTD.

Further work is needed to determine the molecular characteristics associated with response.

Neuroblastoma (in vitro)

Glioblastoma (in vitro)

ALV RMS (in vitro)

Ewing sarcoma (in vitro)

Methods: For PPTP xenografts, a single dose of NTX-010 was administered at 5x the MTD. A single dose was selected based on PK/PD studies using adult mice.

Three of 4 neuroblastoma, 2 of 4 rhabdomyosarcoma, and 1 of 4 Ewing sarcoma xenograft lines at its MTD or at a dose selected based on PK/PD studies using adult mice.

Event-free survival (EFS) distributions of each treatment group were compared using the Log rank test.

Expression of selected genes that are markers for Neuroendocrine origin (AR, SMP30, Trp53, 131Pal3) .

One-way analysis of variance (ANOVA) was used to determine the molecular characteristics associated with response.