

Phase I Trial of Seneca Valley Virus (NTX-010), a Newly Discovered Systemically Deliverable Oncolytic Picornavirus, in Patients with Solid Tumors with Neuroendocrine Features

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ABSTRACT

Background
NTX-010 is a novel replication-competent picornavirus with selective tropism for cancers with neuroendocrine features. Antitumor efficacy from intravenous administration of NTX-010 was demonstrated in 15/15 murine models and no dose limiting toxicity in animals was seen at doses up to 10¹¹ vp/kg.

Methods
Neotropix is conducting a Phase I intravenous delivery, dose-escalation study in patients with advanced solid tumors expressing neuroendocrine markers. Dose escalation was planned in log increments from 10⁷ vector particles/kg to 10¹¹.

Results
Dose escalation progressed such that 3 patients were treated at dose level 4 (10¹⁰) without dose limiting toxicity. No therapy-related AEs above grade 2 were observed. Six patients that had recurrent and widely metastatic small cell carcinoma and life expectancy of \geq 3 months were treated at 10⁷ vector particles/kg. Three/six small cell patients died in 120 days or less with far-advanced disease as documented at autopsy while one patient is stable 6 months after treatment. Twelve patients that had carcinoid or neuroendocrine-marker-positive tumors other than small cell and had life expectancy of \geq 6 months were treated from doses ranging from 10⁷ vector particles/kg to 10¹⁰. The non-small cell patients tolerated therapy well. While no patients had objective evidence of tumor response by the standard criteria 6/12 had signs of clinical benefit including improved symptoms, prolonged stability of good performance status or work status, or improvement in biochemical markers.

Conclusions
NTX-010 is a novel first-in-class anticancer virus with selective tropism for tumors with neuroendocrine features. Safety and signs of clinical benefit in the non-small cell group encourage further investigation of the possibility that objective response will occur at the higher dose levels. Small cell patients may have to be treated at an earlier time in their course and as anticipated higher doses are likely required to elicit objective responses.

BACKGROUND

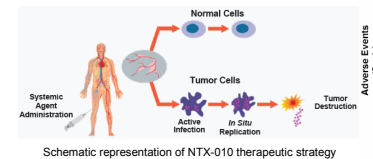
Several prior clinical trials have demonstrated that oncolytic viruses can elicit anti-tumor responses when administered directly into localized tumors. However, systemic treatment of advanced or metastatic cancer had been limited due to inadequate tumor selectivity or rapid inactivation of virus in blood.

Oncolytic viruses can kill cancer cells directly, by tumor cell lysis, or indirectly, by induction of tumor cell apoptotic pathways or stimulation of inflammatory/immune responses. Oncolytic viruses can also increase the efficacy of standard cytotoxic chemotherapy or radiation.

NTX-010 (SVV-001 or Seneca Valley Virus) is a novel replication-competent picornavirus with selective tropism for human cancers with neuroendocrine features (1). Common tumors with neuroendocrine features include carcinoid, small cell lung cancer, and pediatric malignancies including neuroblastoma. Development of more effective therapies for each of these cancers is a critical need.

Intravenous administration of NTX-010 in multiple relevant preclinical xenograft models demonstrates remarkable anti-tumor efficacy, including durable complete remissions with high-dose (10¹² – 10¹⁴ vp/kg) single administration (1). Animal toxicity was minimal at doses up to 10¹⁴ vp/kg.

NTX-010 was prepared for human administration under GMP conditions. We initiated a first-in-human, first-in-class phase I clinical trial to assess the safety and feasibility of NTX-010 as an oncolytic virus for the treatment of metastatic cancers with neuroendocrine features.



METHODS

Objectives

Primary

To evaluate safety and tolerability and to define the recommended phase II dose of NTX-010 in patients with advanced solid tumors with neuroendocrine features.

Secondary

To characterize changes in viral titers, viral distribution and viral elimination in blood, urine, stool, sputum, and nasal swab following IV administration of NTX-010.

To evaluate development of neutralizing antibodies to NTX-010 following IV administration of NTX-010.

To document intratumoral viral replication of NTX-010 in vivo.

To obtain preliminary information regarding the anti-tumor activity of NTX-010 in this patient population.

Eligibility

Two primary cohorts of patients have been studied to date: a dose-escalation cohort in patients with any NE cancer with estimated survival \geq 6 months, and an expansion cohort of advanced SCLC treated at 10⁷ vp/kg.

Solid tumor with NE features
synaptophysin
chromogranin A
CD56

Age \geq 18, ECOG 0 - 1
 \geq 1 week since prior XRT
No chemo or RT within 4 weeks
No CNS metastases

Required laboratory values
Granulocytes \geq 1,500/ μ l
Platelets \geq 100,000/ μ l
Bilirubin \leq 1.5 \times ULN
AST/ALT \leq 2.5 \times ULN
Creatinine \leq 1.5 \times ULN
OR
Creat. Cl. \geq 60 ml/min/1.73m²

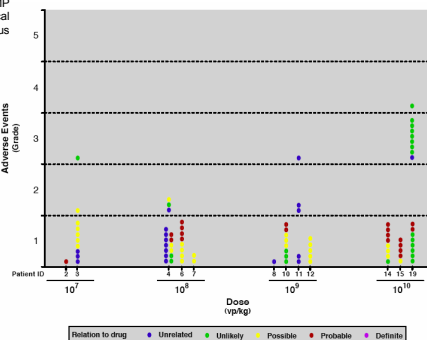
Dose escalation cohorts

Cohort	NTX-010 (vp/kg)	N (to date; 18 total)
1	10 ⁷ \times 1 dose only	2
2	10 ⁸ \times 1 dose only	3
3	10 ⁹ \times 1 dose only	4
4	10 ¹⁰ \times 1 dose only	3
5	10 ¹¹ \times 1 dose only	0
SCLC expansion 10⁷ \times 1 dose only 6		

Eight of the 12 patients in the dose-escalation cohort had carcinoid.

RESULTS

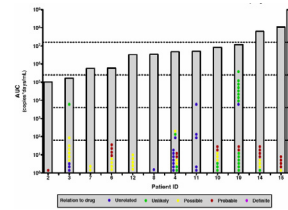
Toxicity: Escalation cohorts



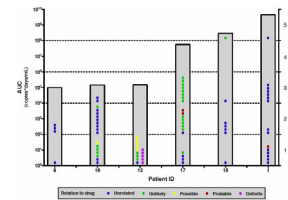
RESULTS

Toxicity vs. viral exposure

Dose Escalation Cohort

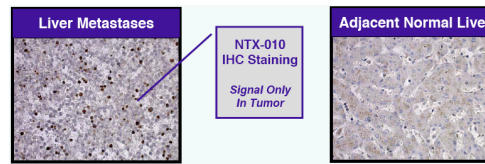


SCLC Cohort



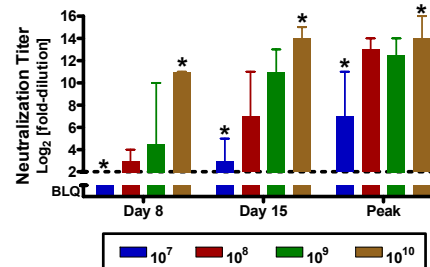
Note: 2 grade 5 (fatal) AEs were observed, both in the SCLC cohort. Both were confirmed progressive disease on autopsy, and are not considered therapy-related.

Intratumoral viral replication: tumor specificity



From autopsy following death on day 28 in Subject #1; dose 10⁷ vp/kg. No viral particles were detected in multiple other non-malignant tissues

Viral immune response



Neutralizing anti-viral immune response was seen in all subjects, and was associated with viral clearance from blood, sputum, nasal mucus, urine, and stool.

Anti-tumor activity

Response assessment is not a primary endpoint of this study. Findings suggestive of clinical benefit have been observed.

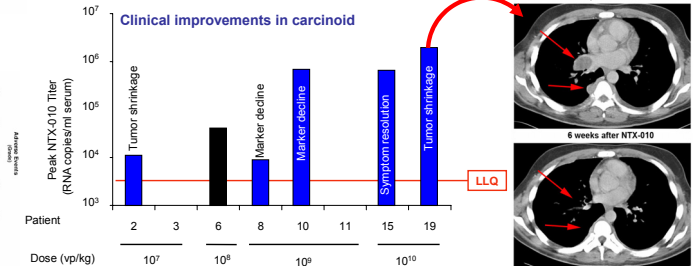
Tumor reduction and disease stabilization

No objective responses by RECIST criteria have been observed to date. One patient with carcinoid had major reduction in a primary mass (shown below) but no evident reduction in other target lesions. Disease stabilization of at least 4 months (and up to over 11 months) has been observed in at least 4 patients with carcinoid in the dose escalation cohort

Tumor marker reduction and symptomatic improvement

A patient with carcinoid experienced reduction in tumor-associated symptoms including flushing and hypoglycemic episodes, was noted to have a decline in blood serotonin (a tumor marker) from 1208 to 713 on therapy. Although her liver lesions remained stable in size by CT scan, tumors were noted to change from hypervascular pretreatment to hypovascular. Another carcinoid patient was noted to have a similar decline in blood chromogranin A from 142 to 35 on therapy.

Two carcinoid patients with no detectable circulating virus had no evident clinical benefit. In contrast, five of the six carcinoid patients with detectable circulating virus post-infusion had some findings suggestive of clinical benefit. These findings include reductions in tumor mass not meeting response criteria, reduction in surrogate markers, and/or amelioration of symptoms (shown graphically below).



Based on these encouraging clinical observations in the initial patient cohorts, a protocol amendment has been prepared, including prospective marker evaluation and additional imaging studies including PET and octreotide scans in carcinoid patients, to further characterize viral anti-tumor activity in subsequent dose cohorts.

CONCLUSIONS

Safety and tolerability

NTX-010 was well tolerated by most subjects. No evident dose limiting toxicities have been observed to date. Common toxicities include low grade fever, myalgias and arthralgias within 3 – 5 days of virus administration.

Viral replication in vivo

Intravenous administration of NTX-010 was associated with selective intratumoral viral replication. Viral amplification in vivo was observed in multiple subjects from the dose escalation cohort. Intratumoral virus was persistent 4 weeks after intravenous dosing.

Immune response and viral clearance

All patients developed neutralizing antibodies, and all patients cleared virus from detection in multiple bodily fluids. Early development of high level titers of neutralizing antibody appears to correlate with dose level.

Preliminary evidence of anti-tumor activity

No objective responses have been observed at dose levels tested to date. Several patients have experienced prolonged stable disease, symptomatic improvements, decline in tumor markers, and reduction in tumor size. Suggestive clinical benefit has been particularly notable in carcinoid patients.

Future directions

We plan to continue dose escalation to 10¹¹ vp/kg, with a focus on subjects with carcinoid tumors. Combination strategies, including viral administration together with therapy directed at suppressing the humoral immune response, is being evaluated in relevant preclinical models.

REFERENCES

(1) Reddy PS, Burroughs KD, Hales LM, Ganesh S, Jones BH, Idamakanti N, Hay C, Li SS, Sikeele KL, Vasko A-J, Yang J, Watkins DN, Rudin DM, Hallenbeck PL. Seneca Valley Virus, a systemically deliverable oncolytic picornavirus, and the treatment of neuroendocrine cancers. *J Natl Cancer Inst* 99:1623-33, 2007.