



NTX-010
A Novel Mechanism Anti-Cancer
Agent In Phase I/II Clinical
Development

Non-Confidential Summary

Neotropix, Inc.

EXECUTIVE SUMMARY

- Lung cancer represents the leading cause of death among cancer patients worldwide. Small cell lung cancer (SCLC) is a particularly aggressive form of lung cancer with an annual new case incidence of 35-40,000 cases in the US and an estimated 200,000 new annual cases worldwide.
- Current first line standard-of-care treatment for SCLC is highly toxic and of marginal efficacy producing a median survival extension of 12 months, and a therapy-induced mortality rate of up to 5%. There are currently no approved products for treatment of first line non-responders and only one product for patients who become refractory to first line treatment.
- As a result, there is a continuing need for breakthrough therapies to effectively treat SCLC with new mechanisms of action, improved clinical outcomes, and better tolerability profiles.
- NTX-010 is a first-in-class, naturally occurring (non-engineered) oncolytic virus with excellent selectivity for SCLC cells and other cancer types expressing certain biomarkers associated with tropism. NTX-010 has a selectivity index for its target cancer types of >10,000-fold with respect to non-neoplastic healthy tissues.
- NTX-010 can be systemically administered to patients because (i) it is highly selective for certain cancers over healthy tissues; (ii) humans lack neutralizing antibodies for NTX-010 in blood; (iii) it is not known to be pathogenic to humans or animals; (iv) no NTX-010 transmissibility among humans has been observed.
- NTX-010 is currently undergoing dose escalating Phase I/II clinical trials at leading oncology centers on an out-patient basis underscoring data showing that NTX-010 has a compelling pre-clinical safety profile and displays no evidence of human pathogenicity or transmissibility.
- In xenograft models, NTX-010 exhibits potent anti-tumor activity with a superior pre-clinical safety profile to traditional chemotherapeutic regimens.
- *In vitro*, NTX-010 exerts an oncolytic effect against multiple SCLC cell lines and about 15% of non-small cell lung cancer (NSCLC) cell lines as well as other tumor cell lines expressing biomarkers associated with tropism.
- Neotropix has worldwide patent applications covering the previously undiscovered NTX-010 virus, its methods of use, and pharmaceutical compositions.

COMMERCIAL OPPORTUNITY

High Unmet Need for Effective SCLC Treatments with Improved Clinical Outcomes

There are 35-40,000 new cases of small cell lung cancer (SCLC) annually in the U.S., and an estimated 200,000 new annual cases diagnosed worldwide. Without treatment, this disease has the most aggressive clinical course of any type of pulmonary tumor. Median survival from diagnosis without treatment is 2-4 months; treatment with the standard of care drug regimen results in a median survival of 12 months and an overall 5-year survival of just 5%. SCLC is usually disseminated by the time it is diagnosed, limiting the effectiveness of surgical resection and radiation therapy.

The current first line chemotherapy regimen, consisting of cisplatin and etoposide, is highly toxic; the therapy itself carries a 1-5% mortality rate. Furthermore, 20-25% of patients do not respond to first line therapy and for these non-responders, median survival is only 2-3 months. There is currently no approved product to treat non-responders though other products are used. The best unapproved product offers a response in only 7% of this patient subset, resulting in a relatively low efficacy bar for approval.

The worldwide treatment market for cancers responsive to NTX-010, which includes SCLC, approximately 15% of NSCLC, other small cell cancers, and certain other neuroendocrine cancers expressing biomarkers associated with virus permissivity has been estimated to be at least \$3.0 billion. Neotropix estimates that the U.S. market potential for NTX-010 will be greater than \$850 million at the time of product launch.

PRODUCT DESCRIPTION

NTX-010 is the First in a New Class of Highly Targeted, Naturally Occurring, Systemically Administered Oncolytic Viruses

NTX-010 is a newly discovered oncolytic virus, which is highly selective for certain tumor cell types expressing the required permissivity biomarkers. Unlike previous oncolytic virus product candidates, NTX-010 is a stable naturally occurring virus which has not been observed to be pathogenic to humans, and therefore, has not had to be artificially engineered to remove pathogenic properties and enhance tumor specificity. Based on extensive *in vitro* testing of NTX-010, Neotropix believes that the product will have enhanced efficacy and less toxicity than any currently approved therapy for SCLC and other permissive cancers.

NTX-010 demonstrates the following critical properties for commercial success:

High Selectivity for Tumor Cells Over Normal Cells. NTX-010 has an extremely high selectivity index of >10,000, which is the ratio of the dose of agent required to kill tumor cells versus normal cells. In pre-clinical xenograft models, the selectivity index is as high as one million-fold when used as a monotherapy. NTX-010's selectivity index is 10,000-fold greater than that of most chemotherapies and 100-fold greater than that of other genetically modified oncolytic viruses.

Systemically Administered Dose Will Reach All Cancerous Sites. The virus is only 27nm enabling excellent initial penetration of solid tumors as well as better distribution to distal sites of metastatic tumor masses. Based on animal models and initial human data, it is believed that systemic administration results in penetration into permissive tumor masses followed by potent self-amplification of the tumor killing effect resulting from rapid replication of the NTX-010 virus within permissive tumor cells.

Anti-Tumor Efficacy Despite Host Defenses. Unlike other oncolytic viruses, NTX-010 is not inhibited by any component of human blood. Pre-existing antibodies are not found in humans, and as such NTX-010 can be delivered systemically. Upon initial administration, neutralizing antibodies are generated against the virus 7 - 25 days post-treatment, however the host immune response does not eliminate ongoing replication or active therapy within the tumor itself. Once tumor cells receptive to the virus are destroyed, the virus is eliminated by the body's natural immune system.

Minimum Toxicity to Normal Tissue and High Therapeutic Index. NTX-010 is not known to be pathogenic to adult humans or animals, and has not shown toxicity in animal models. The drug has exhibited no dose-limiting toxicity to date in the company's Phase I/II clinical trial and exhibits no overt toxicity in 13 out of 13 normal human primary cell culture lines tested *in vitro*. Additionally, in the company's IND-enabling studies, no dose limiting toxicity was observed following systemic administration of 1×10^{14} viral particles/kg. This dose is a one million-fold higher dose than that required to eradicate pre-established SCLC xenograft tumors in mice. Safety has also been demonstrated in swine and primates up to 3×10^{11} and 5×10^{11} viral particles/kg respectively.

Potent Efficacy Against Pre-Established Tumors. NTX-010 elicits complete long-term eradications in several tumor models following a single systemic delivery at doses as low as 1×10^7 vp/kg. Further, NTX-010 has been shown to eliminate pre-existing metastases in other models. Efficacy has been demonstrated in 11 out of 11 *in vivo* models tested with systemically delivered NTX-010.

Excellent Viral Safety Against Mutation and Transmission. Unlike rapidly changing viruses, such as the flu virus, picornaviruses (the family to which NTX-010 belongs) cannot undergo genetic reassortment, so picornaviruses rarely change their tropism over time. Neotropix has tested

this premise by attempting to generate viral mutations with selective pressure by sequentially passing NTX-010 on multiple non-permissive host cell lines. These experiments produced no mutants that were capable of replicating in non-permissive cells. To further examine viral safety, Neotropix has tested caregivers involved in the clinical trial as well as Neotropix employees with no evidence of transmission having been found to date. In 2007, the company will expand its clinical trial screening activities to include both caregivers and family members.

Feasible Manufacturing and Distribution. Unlike most oncolytic viral therapies that have been developed, NTX-010 is a naturally occurring, non-pathogenic virus. As a result, it does not require re-engineering or genetic modification prior to use to avoid infection of normal cells or to circumvent pre-existing immunity. NTX-010 can be produced to high levels in serum-free FDA-approved host cell lines (yield >50,000 viral particles/per host cell). CMC testing to date has been successfully completed for the toxicology lot, the master virus bank, and the Phase I/II clinical trial lot. In addition, NTX-010 has a rapid life cycle and is easily purified. These properties confer significant advantages in manufacturing.

CLINICAL DEVELOPMENT

NTX-010 is in Phase I/II Clinical Trials in Cancer Patients

Phase Ia/II Program. The initial Phase Ia/II clinical development program in cancer patients with solid tumors possessing at least one permissivity biomarker is designed to assess (i) safety; (ii) tolerability; (iii) potential for *in situ* replicative expansion of the virus in tumor; (iv) clearance of the virus from the patient following administration; and (v) potential for transmissibility to clinical trial caregivers. The choice of carcinoid tumor patients for the Phase Ia/II study was driven by the desire to enroll patients with slightly permissive tumors that are not as clinically aggressive as advanced SCLC so as not to confound the interpretation of the Phase Ia safety and tolerability data by uncontrolled progressive disease. The trial design calls for dose escalation from 1×10^7 to 1×10^{11} viral particles/kg in three-patient cohorts at each decade step in dosing. The drug candidate is delivered in a single one hour IV infusion to patients in an out-patient setting.

The Phase Ia/II IND was opened in 2006, is operating at 10 centers across the US, and is expected to enroll up to 73 patients with enrollment conclusion scheduled for 2008. To date, a total of seven (7) patients have been dosed at the first three dose levels. No dose limiting toxicity (DLT) has been observed in patients, which is consistent with the pre-clinical animal data. Pre-clinical animal safety testing did not identify a maximum tolerated dose (MTD) or lethal dose, and predicts that there will be no severe toxicity in humans.

All patients treated so far have exhibited evidence of *in situ* viral replication in their tumors as well as complete clearance of the NTX-010 virus at the conclusion of treatment. In addition, no clinical trial caregivers have been observed to seroconvert and exhibit circulating antibodies against NTX-010.

Phase Ib/II Program. Given the Phase Ia/II clinical data collected to date, Neotropix plans to expand the NTX-010 clinical program to include a Phase Ib/II study in which an expansion cohort of SCLC patients will be treated with NTX-010 at the dose levels outlined in the Phase Ia/II program. The Phase Ib/II trial expansion is designed (i) to provide a first test of efficacy in patients possessing the highly permissive tumor types described by the Target Product Profile; and (ii) to continue the evaluation of the safety of NTX-010 in a larger patient population. The Phase Ib/II trial also provides an accelerated Phase II-like study activity, and will proceed in parallel with the dose escalation Phase Ia/II trial. The FDA has authorized inception of the Phase Ib/II trial, and the trial is recruiting patients as of 2Q2007.

Phase II and Pivotal Trials. After the determination of a proposed Phase II dose and estimated margin of safety, the Company plans to initiate a Phase II trial in 1H2008 in patients with measurable small cell cancer of the lung. The Company estimates an 80 patient trial designed to estimate the response rate and survival benefit in a population similar to that to be addressed in the pivotal trial.

Neotropix plans to initiate a pivotal trial in 2H2009, which is expected to be a randomized comparison of NTX-010 to a standard topotecan (Hycamtin®) salvage regimen. The target population will have failed to respond to first line therapy or will have progressed within a few weeks of completion of the full course of first line therapy. Topotecan is approved in the U.S. for use in SCLC, but the pivotal study did not address first line therapy failures, and as such the drug is not approved for first line failures. The distinction is important for several reasons. Approval in an indication for which there is an already approved therapy can only be achieved on a full approval basis with two well controlled survival trials. Since there is no approved therapy for first-line failures, conditional approval is available in this setting. Secondly, in the first line failure setting, the response rate of topotecan can be estimated from the literature to be quite low; in the vicinity of 7%, with no proven survival advantage. This provides a relatively low bar for NTX-010, which, given its novel mechanism, should still be effective despite chemotherapeutic failure.

PHARMACOLOGICAL PROFILE

Potent and Selective Oncolytic Activity in Biomarker Positive Cells

NTX-010 is highly selective for certain cancer cells, and shows no evidence of infecting or adversely affecting normal dividing primary cell lines (Figure 1). Selectivity is conferred on the basis of a mechanism of viral tropism involving

specific cell surface receptors, which are under investigation as candidate biomarkers (Figure 2).

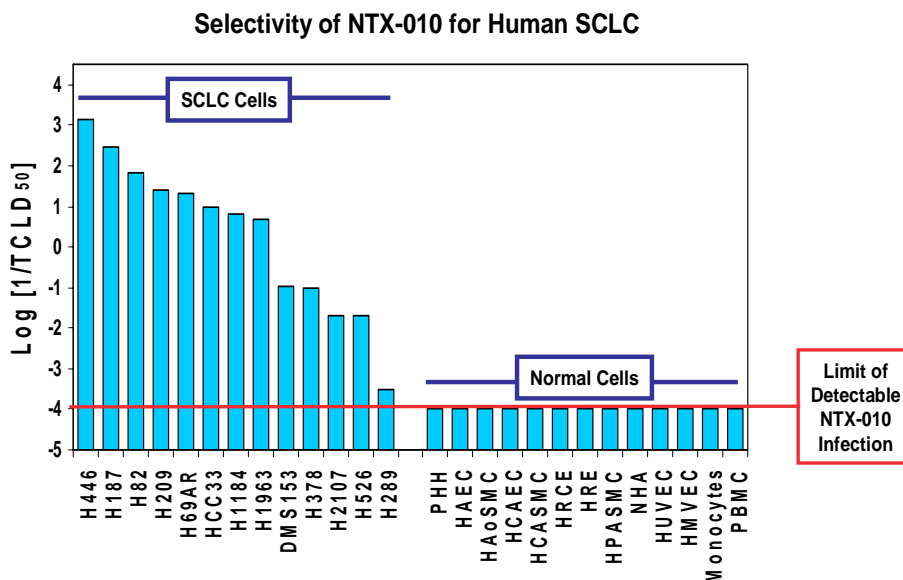


Figure 1. NTX-010 is highly selective for human SCLC. Tissue cultures of both human SCLC cell lines and normal human cell lines were established, and then treated with escalating doses of NTX-010 ranging from 0 to 1×10^4 viral particles per cell. The cytolytic action of NTX-010 on each cell line was observed as a function of dose and reported as a TCLD₅₀ value for each cell line (TCLD₅₀ = tissue culture dose of NTX-010 at which half of the cells are killed by the action of NTX-010).

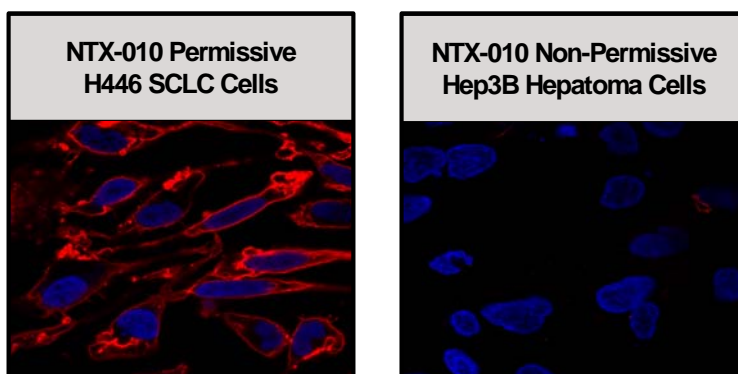


Figure 2. NTX-010 targets cells that express selected biomarkers associated with viral tropism. Immunofluorescence staining of permissive human SCLC cells (H446) and non-permissive human hepatoma cells (Hep3B) was performed using fluorescently-labeled 8G10 (red signal), a proprietary monoclonal antibody directed against a cell surface biomarker discovered by Neotropix and associated with the ability of NTX-010 to infect cancer cells and kill the cells via *in situ* oncolytic action. Cell cytoplasmic material is counterstained blue.

In contrast to conventional chemotherapeutic regimens, the pharmacodynamic action of NTX-010 involves self-amplification via *in situ* viral replication in the tumor tissue once the therapeutic virus has infected a target cell. Viral replication in the target cells results in apoptosis and killing of the cancer cells as opposed

to mere inhibition of cell growth as is frequently observed with chemotherapeutic agents.

Potent *In Vivo* Anti-Tumor Activity

In xenograft studies, NTX-010 exhibits excellent oncolytic activity against established permissive tumors. Figure 3 illustrates the activity of NTX-010 against a permissive SCLC (H446) xenograft model. At doses of 1×10^8 vp/kg and above, the tumor was eradicated by day 15 following treatment with a single intravenous injection of NTX-010.

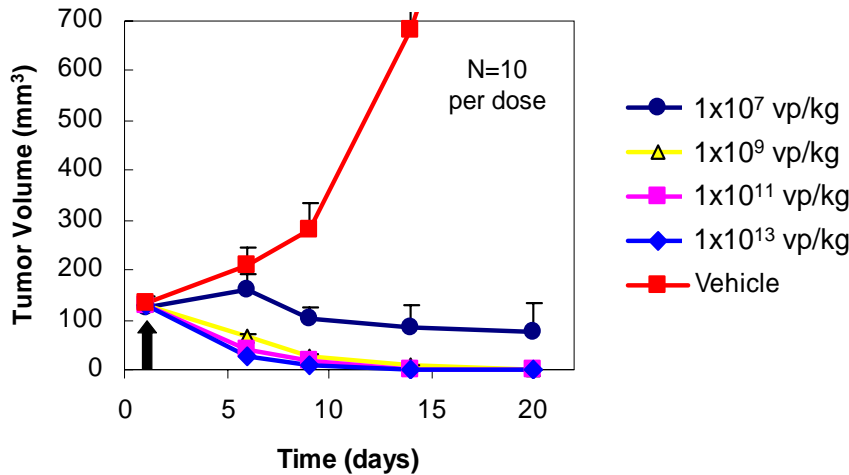


Figure 3. A single injection of NTX-010 is effective against SCLC tumors in a xenograft model. Human H446 SCLC tumor were established in nude mice (mean initial tumor volume = 130 mm³). At each dose, a single injection of NTX-010 was administered via the tail vein to start the experiment (filled arrow). For clarity of dynamic range, the Day 20 tumor volume for the Vehicle treatment (mean volume = 1405 mm³) was omitted from this figure.

A single administration of NTX-010 was also found to be capable of eradicating large, established xenografted tumors in a murine model (Figure 4).

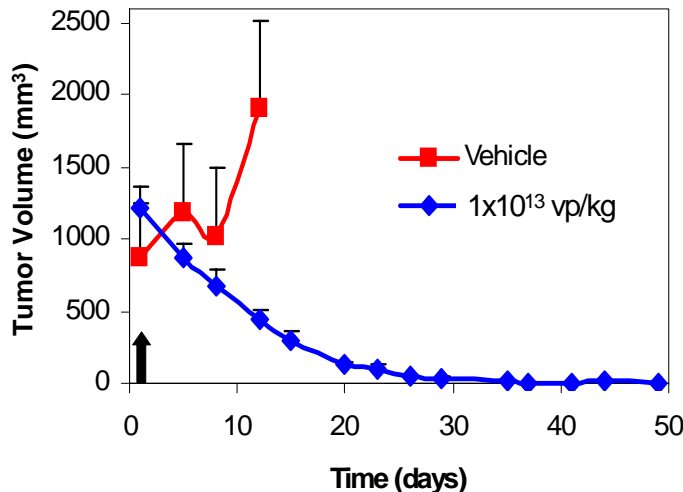


Figure 4. A single injection of NTX-010 can eradicate large xenografted human SCLC (H446) tumors. NTX-010 (1×10^{13} vp/kg) was administered via a single injection into the tail vein of tumor-bearing nude mice to start the experiment (filled arrow). Tumor volume were assessed for each animal in the NTX-010 treated cohort for up to 50 days post-injection (N=10 animals). Vehicle treated animals (N=3) could only be assessed up to Day 12 due to overwhelming tumor burden.

Compelling Pre-Clinical Safety Profile

In addition to its potent anti-tumor activity in xenograft models, NTX-010 shows an improved safety profile compared to standard cytotoxic agents. In pre-clinical safety and toxicology models, no dose limiting toxicities were observed in mice up to 1×10^{14} vp/kg; in swine up to 3×10^{11} vp/kg; and in non-human primates up to 5×10^{11} vp/kg. Intravenously administered NTX-010 virus is cleared from the circulation within days of injection with minor observed effects on white blood cell and platelet counts that are quickly resolved back to pre-treatment baselines. NTX-010 virus is detected in tumor tissue at concentrations 4 – 11 log orders higher than normal tissues following blood clearance and only tumor cells are observed to be infected providing further evidence of the tumor selectivity and *in situ* replication of the NTX-010 agent. Furthermore, co-mingling of mice receiving injections of NTX-010 with untreated mice produced no evidence of transmission of the NTX-010 virus from the treated to the untreated mice.

On the basis of the NTX-010 pre-clinical safety package, the FDA agreed to open the IND for Phase I/II patient treatment on an out-patient basis.

FEASIBLE MANUFACTURING AND FORMULATION

Neotropix has developed a prototype manufacturing process and master virus bank to support its pre-clinical and clinical programs. Current production of the NTX-010 clinical material is performed in a FDA-approved host cell line. Multiple lots of the active agent have been successfully produced and passed all tests according to accepted CMC standards. Given the excellent yields of viral particles achieved thus far by Neotropix (at least 50,000 viral particles/host cell) and the dose ranges currently active in the clinical program, it is estimated that annual production of NTX-010 in quantities sufficient to satisfy worldwide treatment demand could be accommodated by less than 4000 liters of total culture.

NTX-010 is currently administered to patients as an one hour IV infusion employing an isotonic saline vehicle. The drug is expected to be stored as a frozen suspension prior to preparation of the IV infusate. Preliminary work is underway to assess alternative formulations that would support extended storage at more modest temperatures.

Neotropix has initiated strategic manufacturing partnership discussions with companies that have the proven ability to produce cGMP virus products. The purpose of these discussions is the establishment of a commercial cGMP manufacturing capability for NTX-010 in support of (i) Neotropix's development and commercialization needs; and (ii) the elimination of a specialized manufacturing requirement from broader strategic partnering discussions with interested companies currently lacking captive cGMP virus product manufacturing.

INTELLECTUAL PROPERTY

Worldwide Patent Applications Cover Both Composition of Matter and Methods of Use

Neotropix has patent applications pending worldwide covering the composition of matter of NTX-010, methods of use of the agent to treat disease, and other aspects of NTX-010 important for the protection of the drug franchise. Additional patent applications will be filed covering methods of manufacturing, the broad mechanism of action of the drug as well as the composition and method of use of the permissivity biomarkers.

CONCLUSION

NTX-010 is a unique anti-cancer drug with a novel targeted mode of action. NTX-010 has been shown to be highly active against *in vivo* models of SCLC and other cancers expressing certain biomarkers. Pre-clinical animal studies in three relevant species (e.g. mouse, swine, and non-human primate) predict that the agent will be well-tolerated and display a very attractive therapeutic index in the treatment of disease dominated today by highly toxic, untargeted treatments. Human Phase I/II studies of NTX-010 to date suggest that the product will be well-tolerated in man, and that the active pharmaceutical agent is undergoing replicative expansion of the therapeutic virus in permissive tumors.

It is anticipated that NTX-010 would be ideally suited for Pharma, Vaccine, or Biotech companies with:

- A strategic interest in breakthrough oncology therapies, and established virus product manufacturing capabilities; or
- A strategic interest in breakthrough oncology therapies, and a willingness to have product manufacturing occur via a third party relationship.

ADVISORY BOARD

The development of NTX-010 is being directed by several renowned cancer researchers who are members of the Neotropix Oncology Advisory Board.

- **Charles Rudin, M.D., Ph.D. (Principal Clinical Investigator)**, John Hopkins University - Sidney Kimmel Cancer Center
- **William Kaelin, Jr., M.D.** , Dana-Farber Cancer Institute & Harvard Medical School
- **John Minna, M.D.**, University of Texas Southwestern Medical Center, Dallas
- **Vincent Racaniello, Ph.D.**, Columbia University College of Physicians & Surgeons
- **Jack Roth, M.D.**, MD Anderson Cancer Center
- **Daniel Von Hoff, M.D., F.A.C.P.**, Arizona Cancer Center

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