

Phase I Clinical Study of Intratumoral Injection of *Clostridium Novyi-NT* Spores in Patients with Advanced Cancer

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BACKGROUND

Intratumoral (IT) injection of *Clostridium novyi-NT* (*C. novyi-NT*), an attenuated strain of Clostridium, induced a microscopically precise, tumor-localized response in a rat orthotopic brain tumor model and in companion dogs bearing spontaneous solid tumors.¹

In rats, *C. novyi-NT* spores injected into implanted glioma tumors resulted in a significant survival advantage. Brain edema was a common toxicity and was able to be managed medically.¹

In companion dogs, *C. novyi-NT* spores injected into single solid tumors resulted in a response rate (CR or PR) of 37.5% (6/16 dogs). The most common toxicities were expected and associated with bacterial infection. These included tumor inflammation, abscess, and pain.¹

Additionally, preclinical studies have shown that *C. novyi-NT* injection can induce a systemic anti-tumor immune response.²

METHODS

Study Design

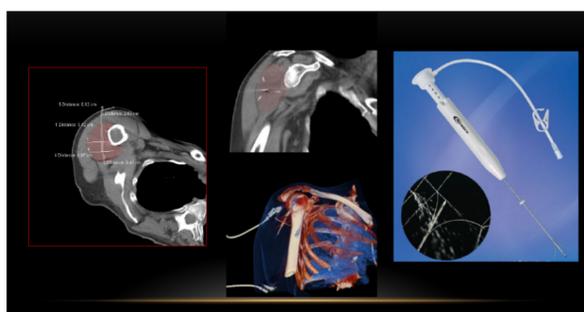
Endpoints

- To determine the maximum tolerated dose (MTD), and dose-limiting toxicities (DLT) of a single intratumoral injection of *C. novyi-NT* using the standard 3+3 dose escalation schedule
- To document preliminary anti-tumor activity of both the injected tumor and an overall response
- To study the disposition of circulating *C. novyi-NT* spores
- To measure the host immune and inflammatory response to *C. novyi-NT* administered as a single IT injection in humans with treatment-refractory solid tumor malignancies

Major eligibility criteria

- Adult patients with advanced refractory cancers
- Target tumor that is amenable to percutaneous injection of *C. novyi-NT* spores
- ECOG 0-2
- ANC \geq 1,000/uL
- Hemoglobin \geq 9 g/dL
- Platelets \geq 100,000/uL
- Total bilirubin \leq 1.5 x upper limit of normal (ULN)
- ALT/AST \leq 2.5 x ULN
- INR \geq 1.3
- No primary brain malignancies or brain metastases
- No active infection or treatment with antibiotics

Intratumoral Injection



RESULTS

Dose Escalation

| Dose Level | Dose of Intratumoral <i>C. Novyi-NT</i> Spores | Number of patients | Dose-limiting toxicities (DLT) |
|------------|--|--------------------|--------------------------------|
| 1 | 1 x 10 ⁴ | 3 | None |
| 2 | 3 x 10 ⁴ | 3 | None |
| 3 | 10 x 10 ⁴ | Enrolling | |
| 4 | 30 x 10 ⁴ | | |
| 5 | 100 x 10 ⁴ | | |

Patients Characteristics (n=6)

| | |
|--------------------------------|--------------|
| Median age – years (range) | 53.5 (39-68) |
| Male/Female | 2/4 |
| Median prior therapies (range) | 6.5 (4-9) |
| Cancer types: | |
| Leimyosarcoma | 2 (34%) |
| Chondrosarcoma | 1 (17%) |
| Carcinosarcoma | 1 (17%) |
| Angiosarcoma | 1 (17%) |
| Papillary thyroid cancer | 1 (17%) |

Best Response

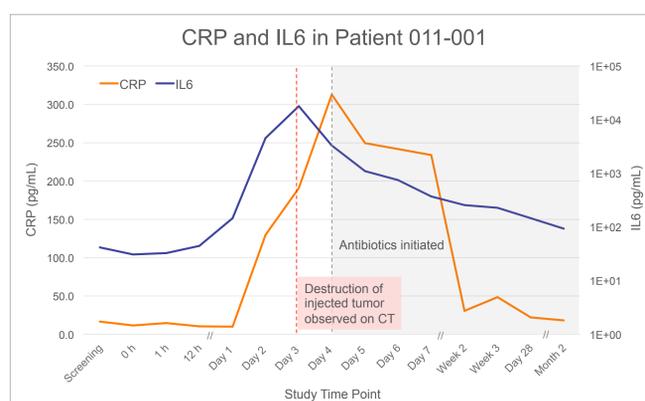
| Tumor type | Dose Level | Injected Lesion Response at Month1 (% reduction, if observed) | Overall response |
|-----------------------------|------------|---|---------------------|
| Leimyosarcoma | 1 | Stable disease (-24%) | Stable disease |
| Chondrosarcoma | 1 | Stable disease | Stable disease |
| Leimyosarcoma | 1 | Stable disease | Progressive disease |
| Carcinosarcoma | 2 | Stable disease (-22%) | Progressive disease |
| Angiosarcoma | 2 | Complete necrosis | Progressive disease |
| Papillary thyroid carcinoma | 2 | Stable disease | Stable disease |

Toxicity Data Summary

Fever has been observed in half of treated patients; this event is expected due to the nature of the therapy. All other related adverse events to-date have been observed in single patients. Grade 3 events have been observed in one patient, and include post-traumatic pain, pathologic fracture of the humerus, shoulder pain, and respiratory insufficiency.

Inflammation and Immune Markers

CRP and IL6 showed significant increases in this patient that were coincident with the changes observed on CT and MRI.



RESULTS

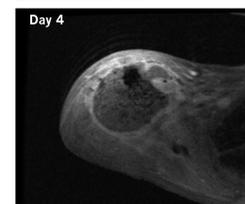
53-year-old female with leiomyosarcoma treated at dose level 1: right shoulder lesion with the adjacent humerus involvement¹

- Dramatic local tumor destruction within 72 hours demonstrated by MRI and CT scans
- No viable tumor cells in biopsies from soft tissue tumor and adjacent bone on Day 4
- Antibiotics initiated on Day 4 after MRI confirmation of tumor destruction
- No evidence of any systemic infection

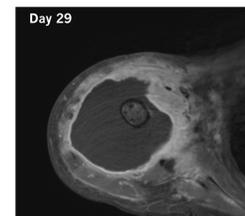
MRI with contrast



Baseline: contrast enhancing mass involving soft tissue and possibly adjacent bone. Lesion measures about 7.2cm AP x 7.4cm transverse in the axial dimensions

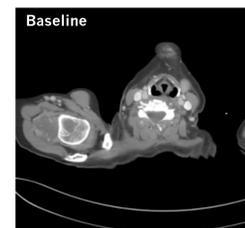


Day 4: markedly diminished contrast enhancement within the tumor mass of soft tissue and possibly adjacent bone component



Day 29: non-enhancing tumor mass becomes more homogeneous consistent with ongoing necrosis

CT with contrast



Baseline: soft tissue mass prior to *C. novyi-NT* treatment



Day 3: internal development of intra- and extra-medullary air collection



Day 28: impatiably imaged soft tissue necrosis with reduced intra- and extra-medullary air collection

CONCLUSIONS

- Intratumoral injection of *C. novyi-NT* is feasible and has led to significant destruction of injected tumor masses in the first two doses studied
- Dose escalation is ongoing

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¹ Roberts, N, Zhang, L, et al. (2014). Intratumoral injection of *Clostridium novyi-NT* spores induces antitumor responses. *Sci Transl Med.* 6(249):249ra111

² Agrawal N, Bettgeowda C, et al. (2004) Bacteriolytic therapy can generate a potent immune response against experimental tumors. *Proc Natl Acad Sci U S A* 101:15172-7