Intratumoral Regulated Expression of IL-12 as a Gene Therapy Approach to Treatment of Glioma

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Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a cytotoxic immune response.

An adenoviral vector engineered to express IL-12 (Ad-RTS-hIL-12) utilizing the RheoSwitch Therapeutic System® (RTS®) gene switch is injected intratumorally. Expression of IL-12 is controlled through the administration of an oral activator ligand veledimex.

- Localized production of IL-12
- T cell activation toward tumor-associated antigens
- Influx of cytotoxic CD8+ T cells coupled with a reduction in CD4+ regulatory T cells
Intra-tumor injection of Ad-RTS-IL12 treats mouse glioma

GL-261 Orthotopic Glioma Model

Normal Mouse

Control Day 20

Treatment Day 74

AL 450mg/m²/day BID x14 + Ad-RTS-mIL-12 1x10¹⁰vp
Ad-RTS-mIL-12 + Veledimex is on Mechanism in GL-261 Orthotopic Glioma Model

- Dose-related increase in tumor veledimex
- Tumor IL-12 correlates with vector copy, veledimex & mRNA IL-12
- Tumor IL-12 produced is biologically active
- Results indicate activation of innate immune system
Ad-RTS-mIL-12 + Veledimex Results in Increased Survival in the GL261 Orthotopic Glioma Mouse Model
Phase 1 Dose Escalation Study of Ad-RTS-hIL-12 + Veledimex in Recurrent or Progressive Glioblastoma or Grade III Malignant Glioma

Patient Demographics
N=5

<table>
<thead>
<tr>
<th>Age in years Median (Min, Max)</th>
<th>40 (32, 58)</th>
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</thead>
<tbody>
<tr>
<td>Gender Male : Female</td>
<td>3 : 2</td>
</tr>
<tr>
<td>Time Since Initial Diagnosis (months) Median (Min, Max)</td>
<td>42 Months (11, 66)</td>
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<tr>
<td>Grade at Study Entry</td>
<td>Grade III 2, Grade IV 3</td>
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Preliminary Safety Profile
N=5

**Cohort 1**: Ad-RTS-hIL-12 $2 \times 10^{11}$ vp + veledimex 20mg (10mg/m²/day)

Most Common AEs
- Headache, Fever, Hyponatremia, Nausea/Vomiting

Related SAEs
- Aseptic Meningitis
- Neutropenia, Thrombocytopenia, Leukopenia
Veledimex 20 mg (10 mg/m²/day); Pt 004 screen failure
Intra-tumor Administration of Viral Vector Activated by Veledimex Results in Functional IL-12

Veledimex 20 mg (10 mg/m²/day);
Pt 004 not dosed
Conclusions

• Veledimex crosses the blood brain barrier

• Intra-cranial administration of Ad-RTS-hIL-12 is activated by oral veledimex

• Transcribed IL-12 peaked at Day 3 followed by downstream IFN γ

• Ad-RTS-hIL-12 + veledimex administered in patients undergoing tumor resection was well tolerated
  – Toxicity to date appears consistent with “on target” effect
IL-12 and Cancer Immunotherapy

• Interleukin-12 (IL-12)
  • Pro-inflammatory cytokine
  • Can reverse immune escape mechanisms induced by MDSCs and DCs and significantly improve the function of activated CD8\(^+\) T cells resulting in the collapse of the vascularized stroma of solid tumors
  • Expression of functional IL-12 in human subjects by direct intratumoral injection of Ad-RTS-hIL-12 + oral veledimex generates downstream IFN\(\gamma\) production and rapid elevation of IL-10 and IP-10 in melanoma and breast cancer patients
  • We have previously demonstrated that intratumoral administration of Ad-RTS-IL-12 results in targeted tumor cytotoxicity and the induction of systemic T cell memory
  • Ad-RTS-IL-12 + veledimex explores local treatment strategy under the control of the RheoSwitch Therapeutic System\(^{\circledR}\) (RTS\(^{\circledR}\)) gene switch to extend the IL-12 therapeutic window