Introduction

• Patients with glioblastoma have few treatment options that offer durable response. Immunotherapy has the potential to create a durable response if a robust intra-tumoral T-cell response can be elicited without causing significant swelling and edema.
• Interleukin-2 (IL-2) is a cytokine that activates and expands tumor killing lymphocytes, but also potently activates suppressive T regulatory cells (Tregs) by binding to the heterodimeric IL-2Rαβγ.
• NKTR-214 is a CD122-biased cytokine agonist conjugated with multiple releasable chains of polyethylene glycol and designed to provide sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rαβγ) to preferentially activate and expand effector CD8+ T and NK cells over Tregs.

NKTR-214

• NKTR-214 is being evaluated in a human Phase I dose escalation trial. NKTR-214 has a favorable safety and tolerability profile.
• As a single agent, NKTR-214 demonstrates a substantial increase in CD8+ T-cells in the tumor microenvironment even in subjects pretreated with multiple prior immunotherapeutic agents.
• Here we evaluated the anti-tumor activity, tumor immunology and bio-distribution of NKTR-214 in an orthotopic, immunocompetent rat survival model of glioblastoma.
• This rat model has 100% penetrance when using 10^6 glioma cells. Typically control animals do not live past day 14.

Results

NKTR-214 significantly prolongs survival in the C6 rat glioma model with >25% of animals living up to 50 days

Wistar rats received 0.1 or 0.3 mg/kg NKTR214 IV Day 2 or Day 7 days post-implant of 10^6 C6 glioma cells into the right striatum (D0, D7). Rats received subsequent NKTR214 injections q2 weeks starting 15 days post-implant. A. Animals receiving NKTR214 had longer survival than controls B. 28% of rats starting treatment D7 had long-term survival. No D2 rats died. There was no survival difference based on dose.

Treatment of NKTR-214 beginning on Day 7, when tumors are larger, produced 28% long-term survivors; interestingly, there were no long-term survivors in the group treated beginning Day 2, when tumors are smaller.

NKTR-214 mobilizes CD8+ T-cells into the brain tumor micro-environment of rats treated D7, but does not mobilize CD4+ T-cells, consistent with the proposed mechanism of NKTR-214.

NKTR-214's increases the CD8+ T-cell population in glioma tissue of rats treated on D7. Animals were sacrificed 5 days after treatment with NKTR214 or vehicle. The difference in CD8+ staining was not noted on animals treated at D2.

Conclusions

• NKTR-214 is well tolerated and prolongs survival when given to rats harboring large C6 glioma tumors.
• A marked improvement in survival was noted when treatment was started on larger D7 tumors versus smaller D2 tumors.
• NKTR-214 administration was associated with an increased number of CD8+ cells within tumor when drug was delivered at D7 but not D2. CD4+ cells were unchanged, consistent with the design of NKTR-214.
• We hypothesize that the increased efficacy observed with larger more established tumors correlates with neo-angiogenesis and rapid tumor growth which begins at Day 5 post-implant. Further studies are underway.
• NKTR-214’s PEG backbone is retained up to 72h in tumor tissues.
• The marked increase in survival in this aggressive rodent brain tumor model after treatment with single agent NKTR-214 suggests its potential benefit for the treatment of human malignant glioma.