Controlled Expression of IL-12 Improves Survival in Glioma by Activating the Immune Response in Mice and Humans (IMMU-34)

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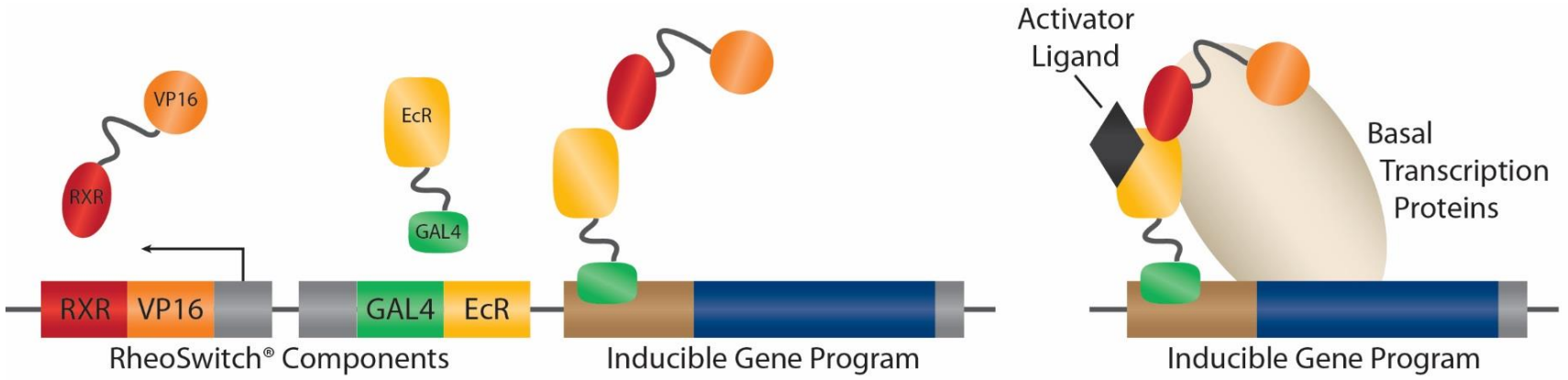
Inducible Gene Regulation: RheoSwitch Therapeutic System®

RheoSwitch Therapeutic System® (RTS®) is a 3-component transcriptional regulator



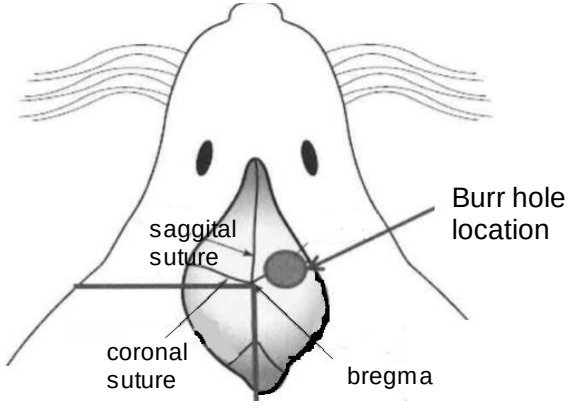
1. **The Switch Components**: The RTS® gene program includes 2 receptor protein fusions: for example, VP16-RXR (co-activation partner, CAP) and Gal4-EcR (ligand-inducible transcription factor, LTF). In the absence of ligand, the LTF binds to the inducible promoter and does not form a stable interaction with the CAP.

2. **The Inducible Promoter**: A customizable promoter to which basal transcription proteins are recruited and the target gene is transcribed.

3. **The Activator Ligand (veledimex):** An ecdysone analog, diacylhydrazine-based small molecule functions as an activator. In the presence of the ligand, a conformational change in the LTF leads to a stable, high affinity interaction with the CAP.

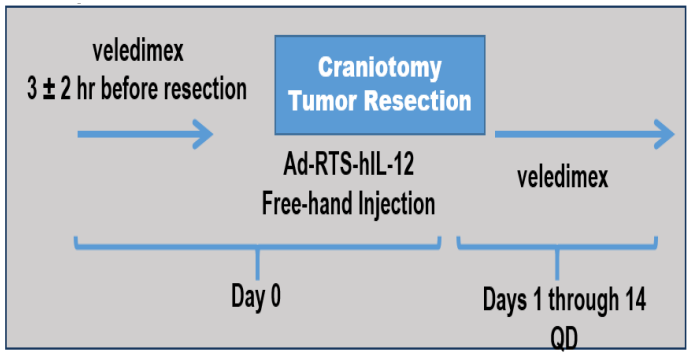
Protocols: Mouse GBM Model & GBM Patients

Mouse GBM Model



- Five Days prior to therapy 1 x 10^5 GL-261 glioma cells volume 3 µl were administered into the brain of C57BL/6 mice.
- On Day 1 a single dose of Ad-RTS-mIL-12 at $5x10^9$vp 5 µl followed by the activator ligand, veledimex p.o. QDx14
- The time to disease progression and death was studied.

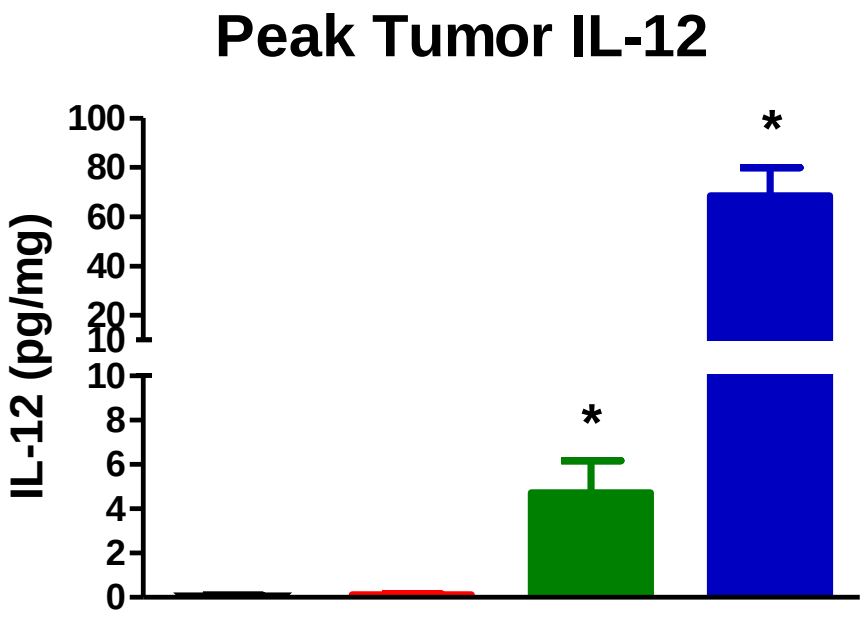
GBM Clinical Trial

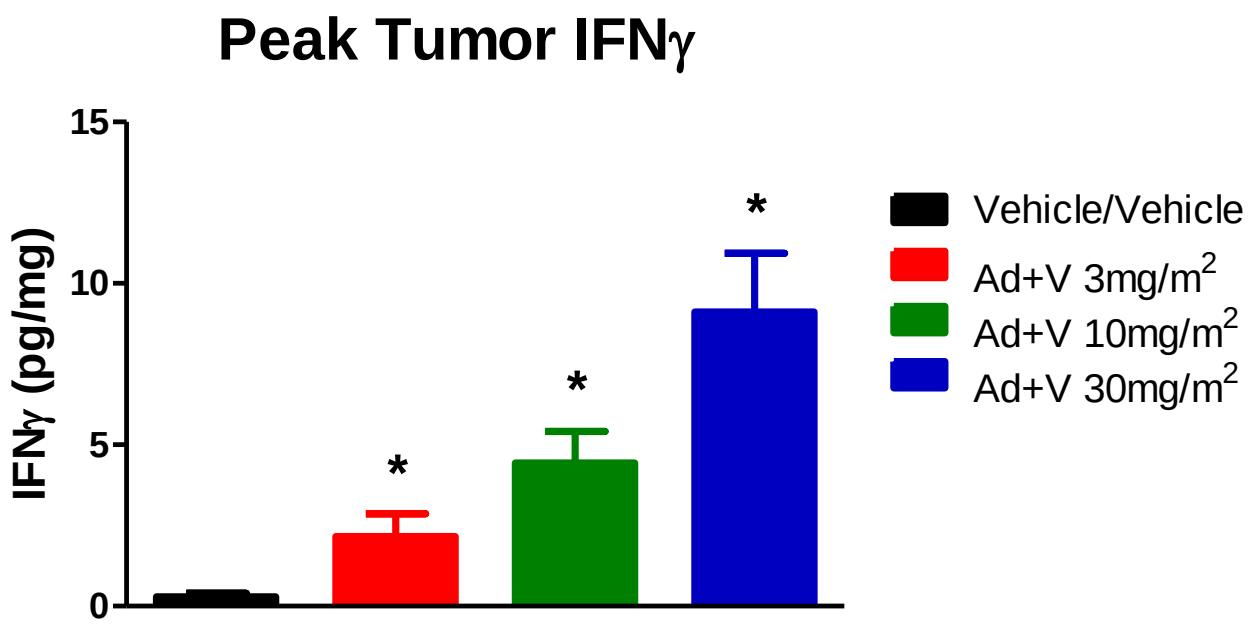


Ad-RTS-IL-12 $2x10^{11}$vp
20mg
30mg
40mg

Mouse Dose (mg/m^2)	HED (mg)
3	6
10	20
15	30
20	40
30	60

Tumor Peak Cytokines in GL-261 Orthotopic Mouse Model

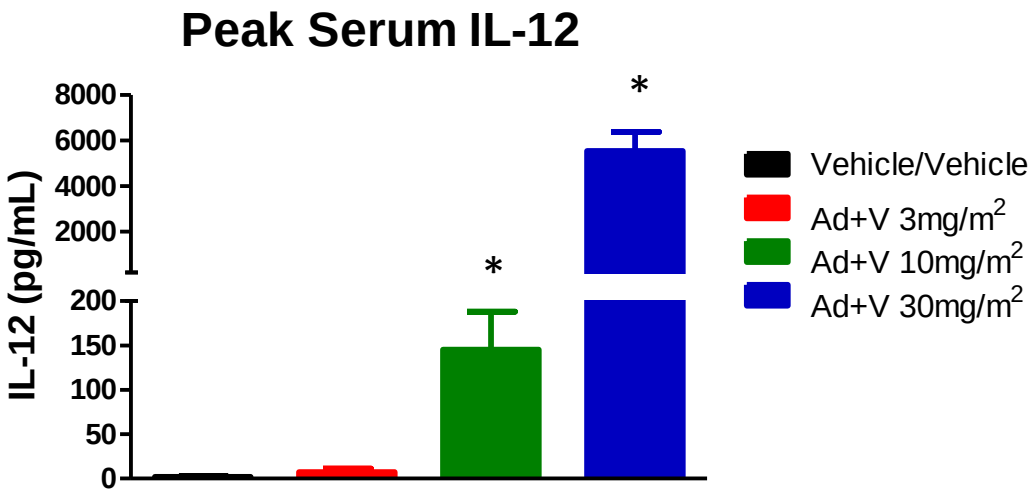


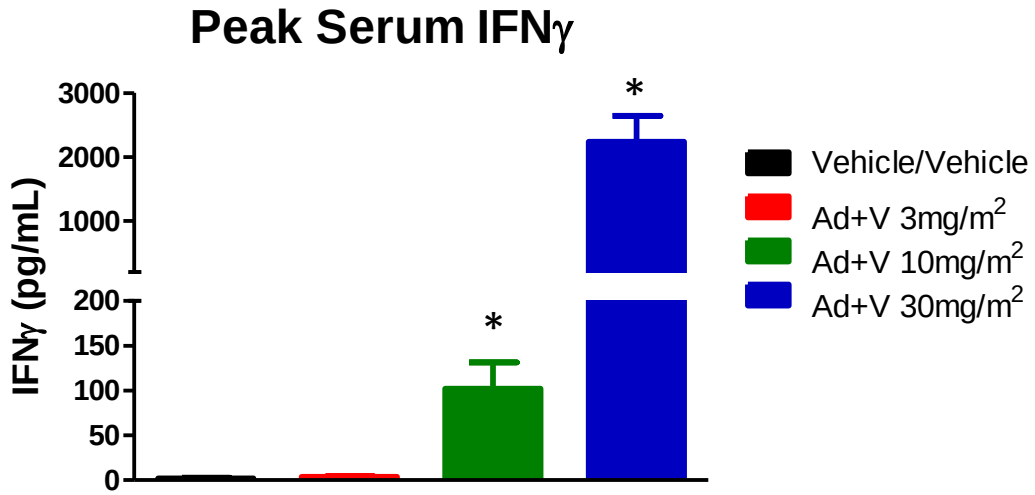


Each histogram is the mean ± SEM N=6; * P<0.05

Peak Serum Cytokine in GL-261 Mice & in GBM Patients

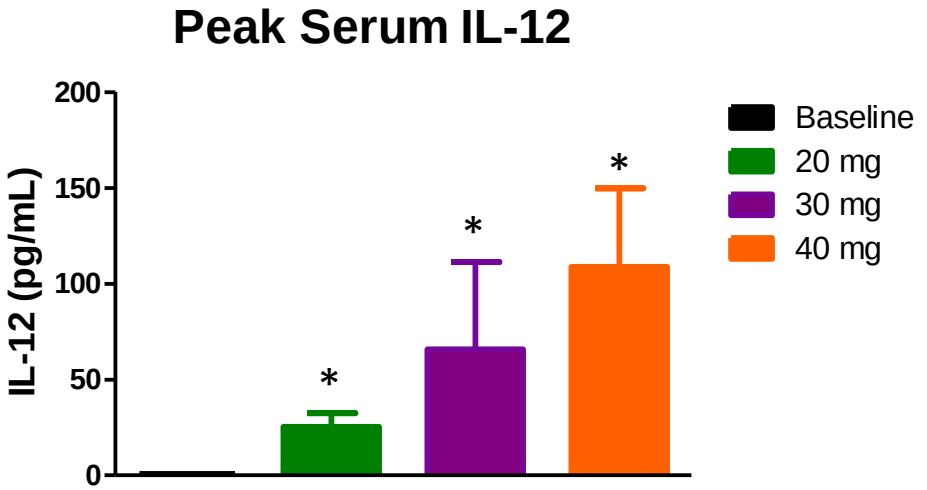
GL261 Mice

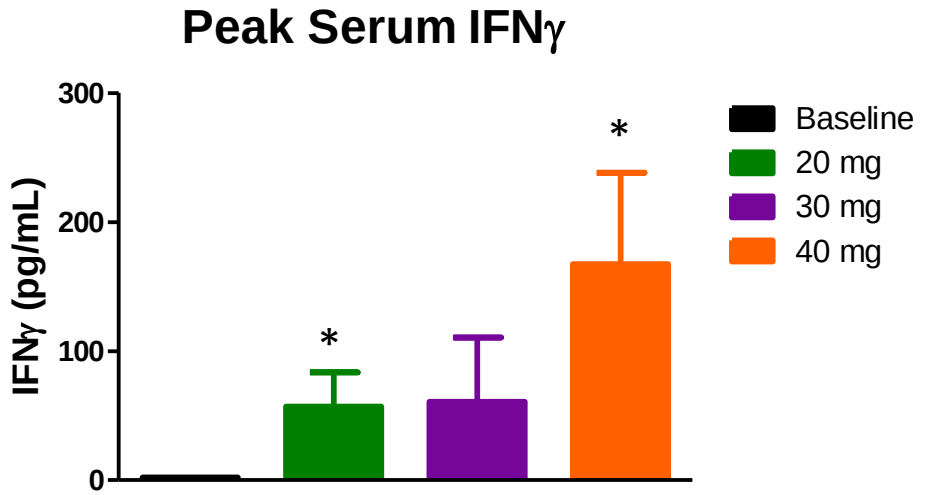




Cytokines in mouse tumor were ~32x higher than serum for IL-12 & 43x for IFNγ at veledimex 10mg/m^2

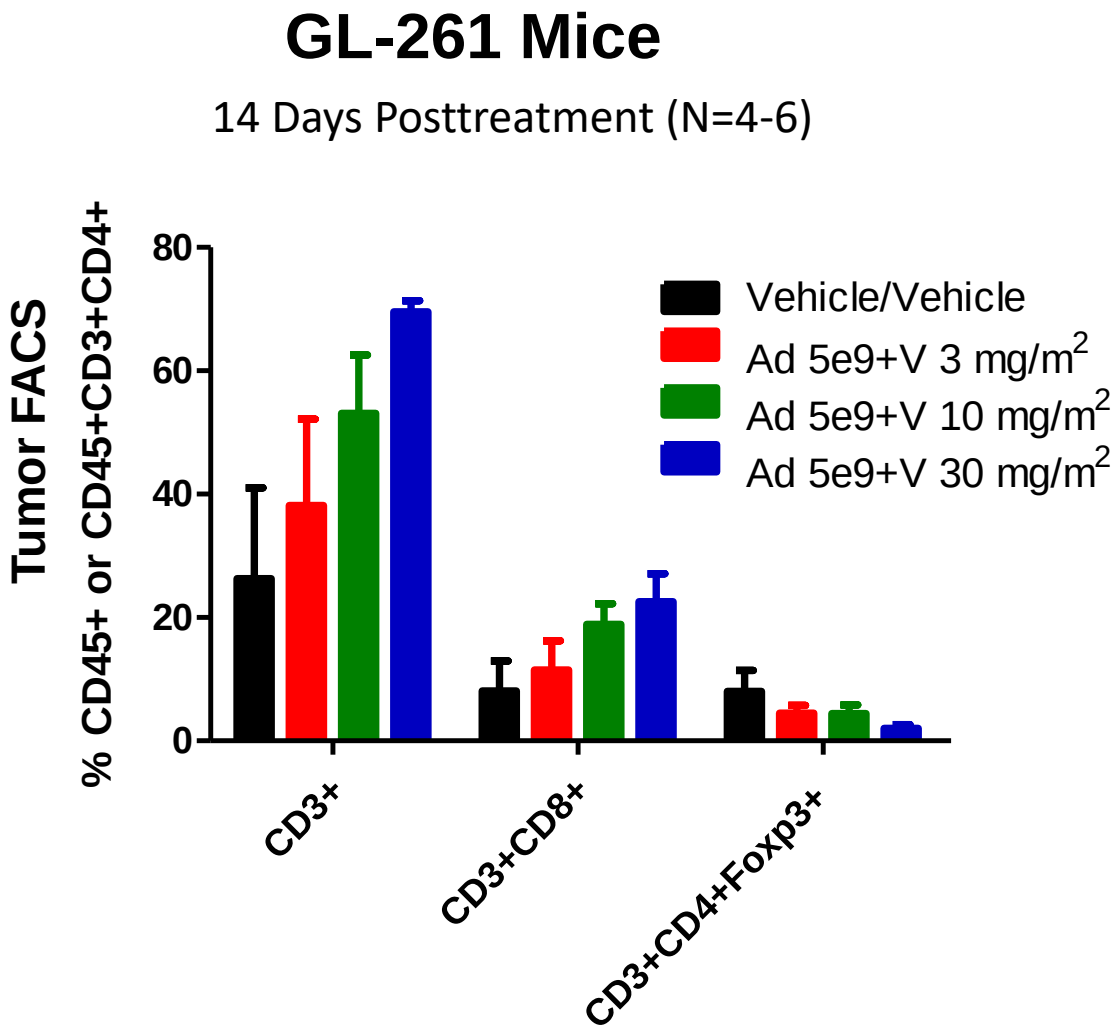
GBM Patients

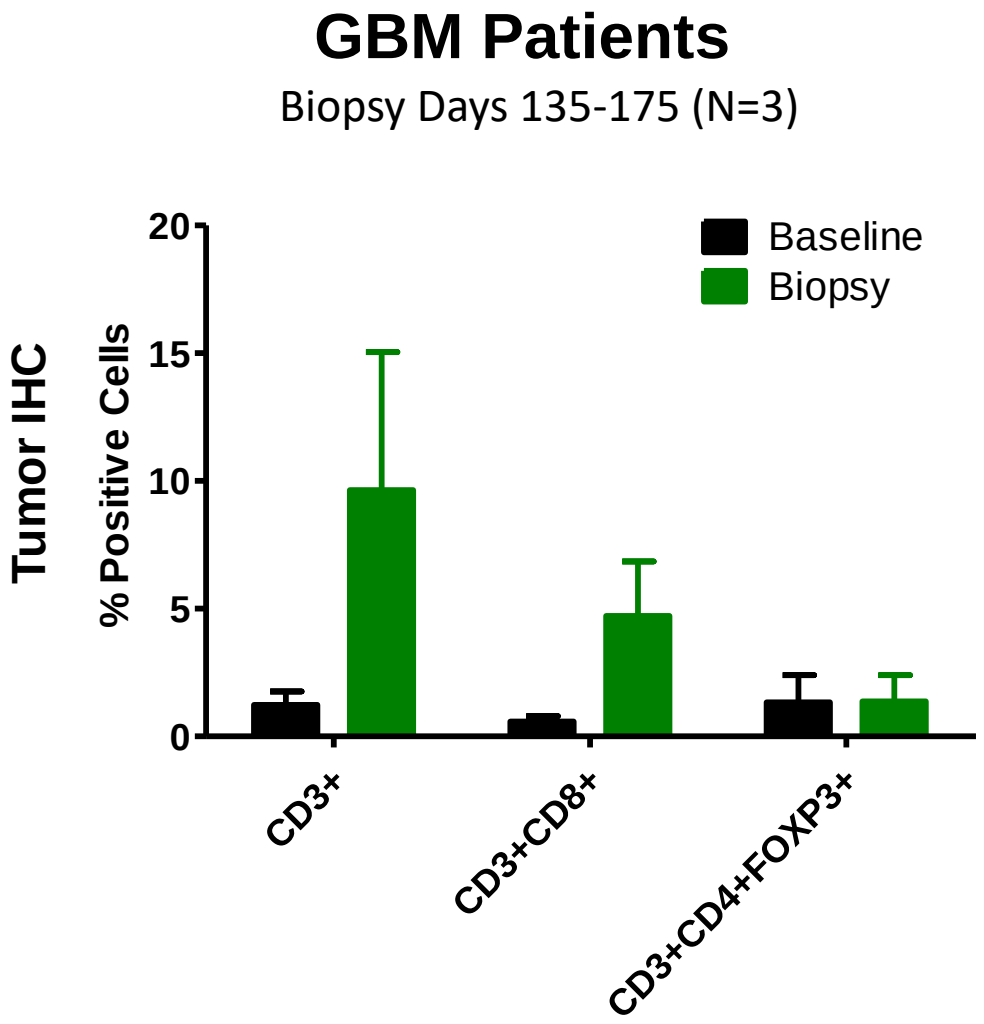




* P< 0.05

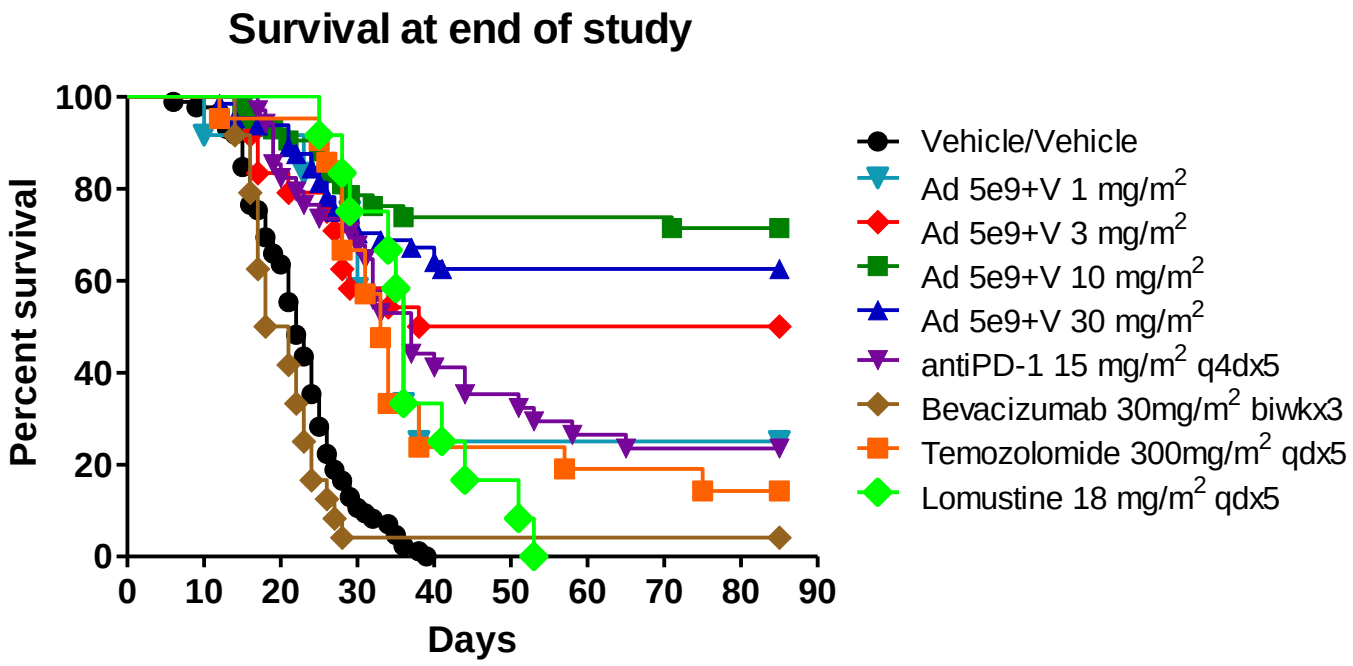
Ad-RTS-IL-12 + V Demonstrates Prolonged Tumor T Cell Infiltration in GL-261 Mouse & GBM Patients





Summary of Survival in GL-261 Mice & GBM Patients

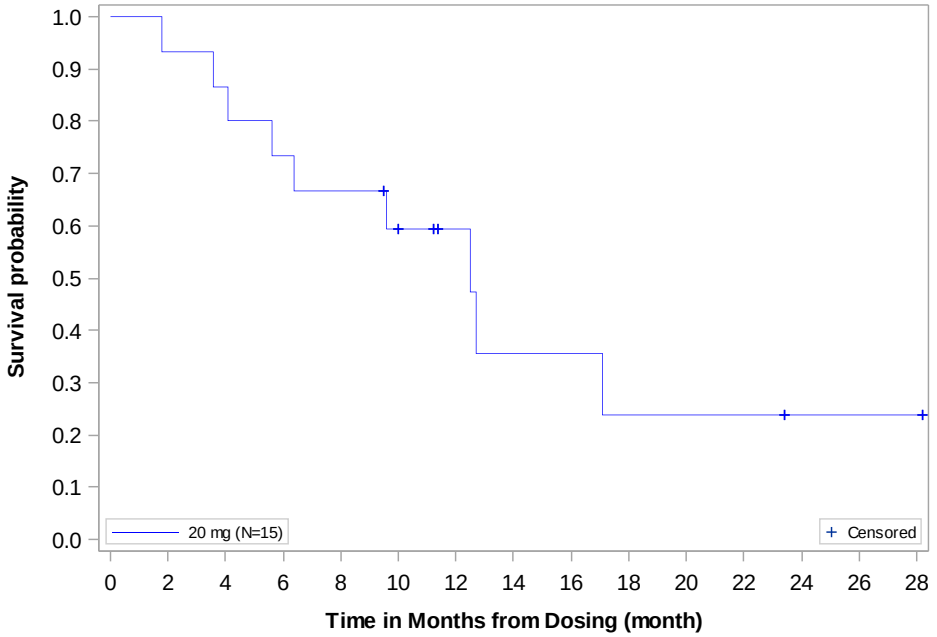
GL-261 Mice



10mg/m^2 (HED 20mg) 67% at Day 85 with majority of the mice tumor free.

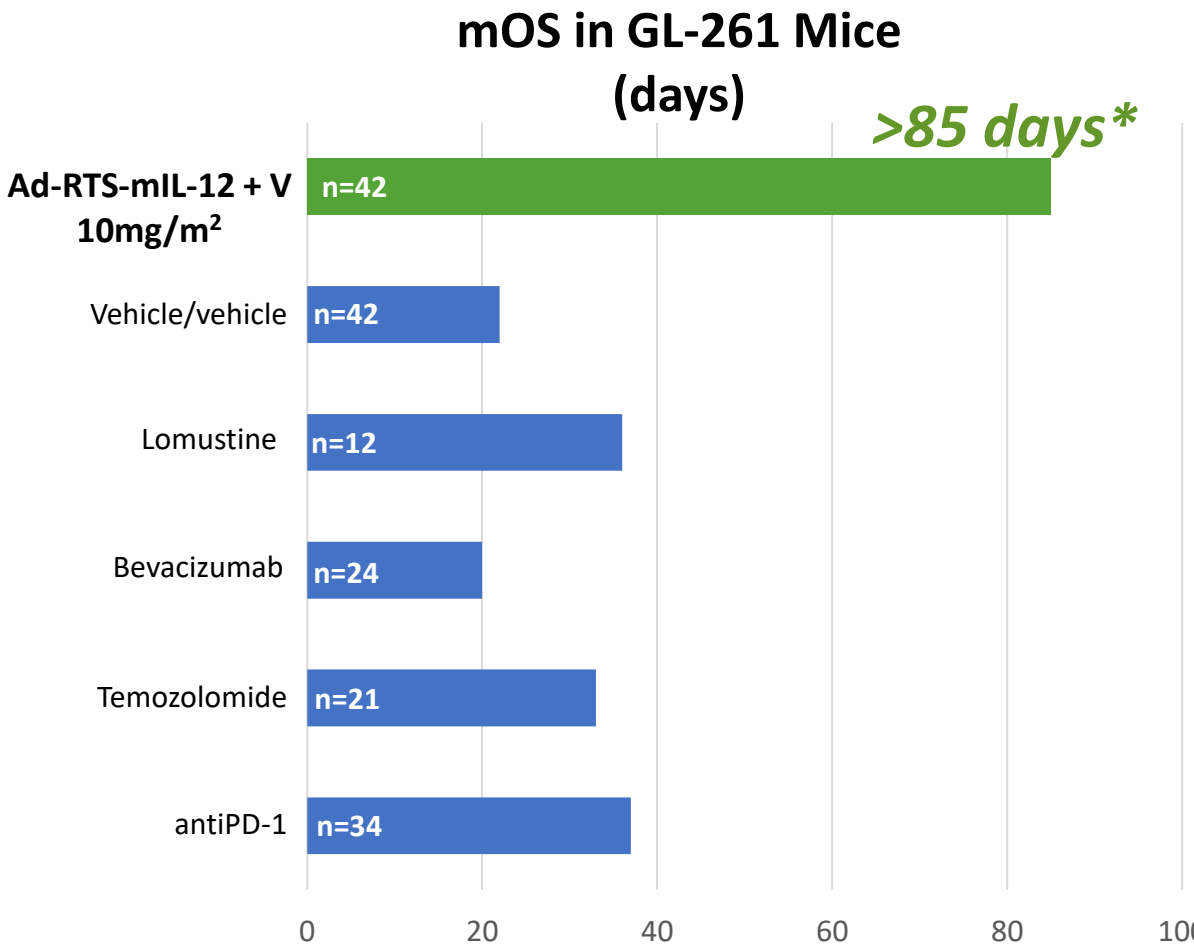
GBM Patients

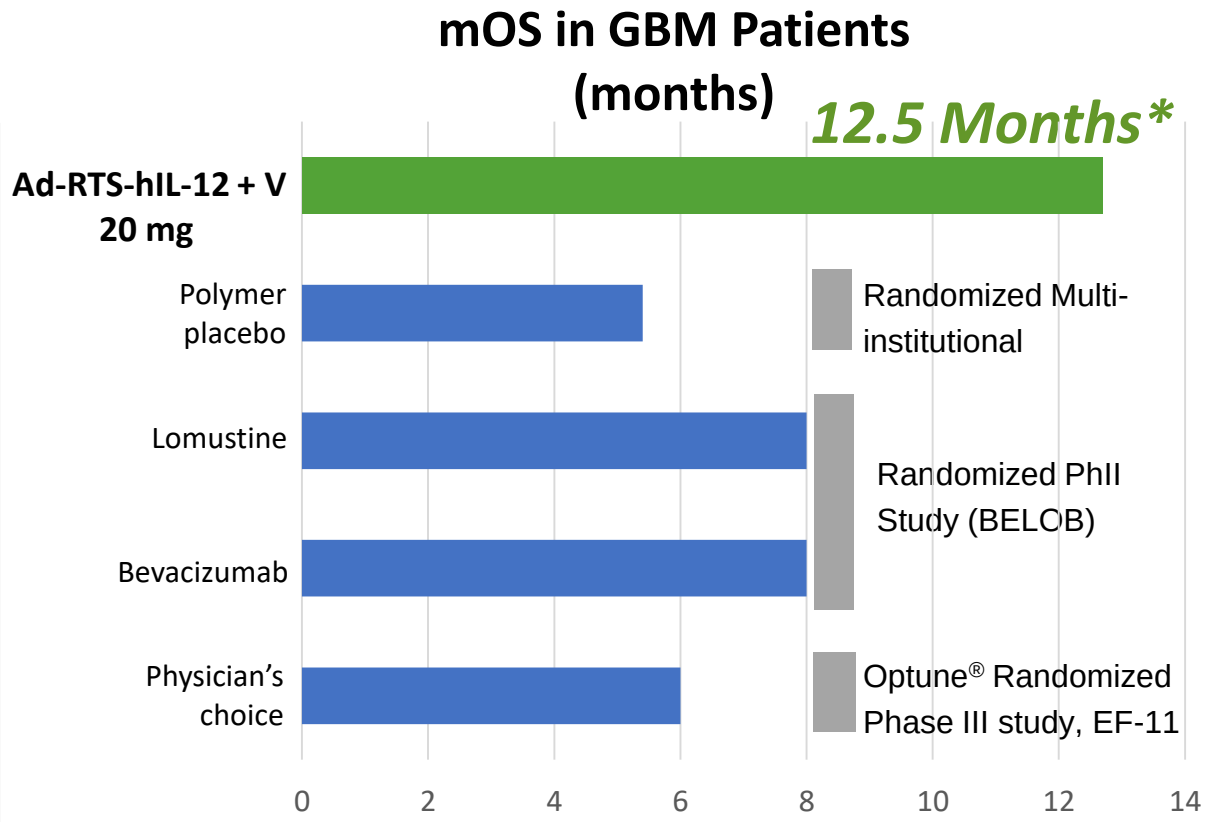
Veledimex 20 mg Cohort



20 mg cohort, based on Kaplan-Meyer plot, estimated Median OS (mOS) is 12.5 months and mean follow-up of 11.1 months with 6 of 15 subjects alive 18 Oct 2017

Median Overall Survival (mOS) in GL-261 Mice & GBM Patients





- * Ad-RTS-mIL-12 5e9 vp + veledimex 10 mg/m² qdx14; Lomustine 18 mg/m² qdx5; bevacizumab 30 mg/m² biwkx3; temozolamide 300 mg/m² qdx5; antiPD-1 15 mg/m² q4dx5 (End of Study D 85)

- * Ad-RTS-hIL-12 2e11 vp + veledimex 20 mg qdx14
- Median OS (mOS) is at 12.5 months with a mean follow up of 11.1 months (range: 1.8, 28.2)
- 6 of 15 subjects alive in 20 mg veledimex cohort (18 Oct 2017)

Conclusions

- Ad-RTS-IL-12+veledimex treatment demonstrated that veledimex crosses BBB in mice and patients
- RTS® gene switch controls the expression of IL-12 in both mice and humans
- In mice and patients we have observed an increase in overall survival when compared to current therapies