

Phase 1 study of Ad-RTS-hIL-12 + veledimex in pediatric brain tumors

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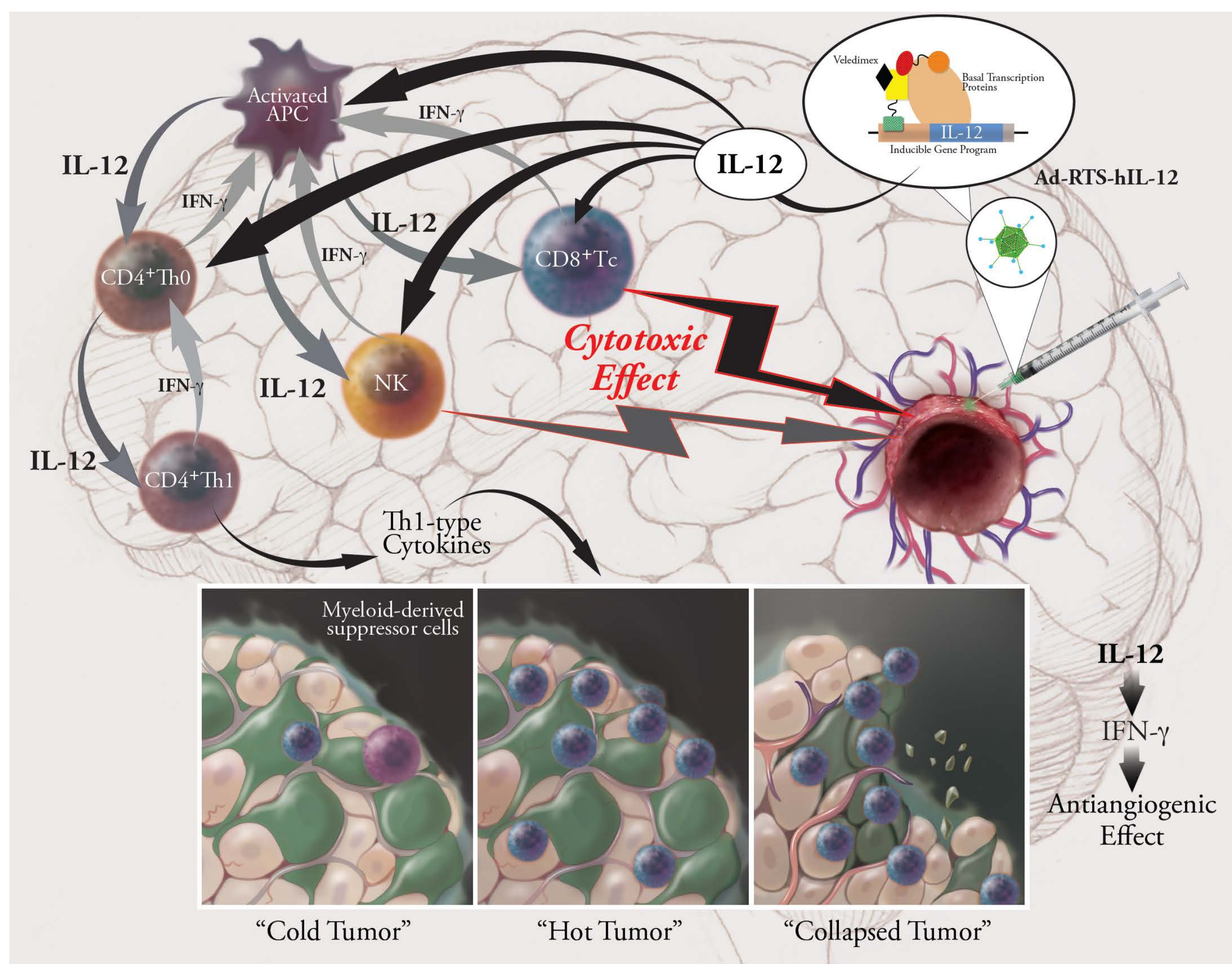
Background

Pediatric glioma has an aggressive clinical course accounting for significant morbidity and mortality among children with brain tumors.

The prognosis of children with diffuse intrinsic pontine glioma (DIPG) is even worse and new therapies are urgently needed. The median survival of children with DIPG is about 9 months. Less than 10% of children survived for 2 years from diagnosis.¹

Ad-RTS-hIL-12 is a novel gene therapy expressing IL-12 under the control of an oral activator ligand, veledimex, via the RheoSwitch Therapeutic System[®] (RTS) switch. Intratumoral administration of Ad-RTS-hIL-12 results in targeted tumor cytotoxicity and induction of systemic T-cell memory. Ad-RTS-hIL-12 + veledimex is a treatment strategy to extend the IL-12 therapeutic window.

Figure 1: Controlled transcription of IL-12, the "Master Regulator", by RTS[®]



Study Rationale & Research Hypothesis

Encouraging data from an ongoing phase I dose escalation trial in adults with recurrent/progressive glioma and preclinical data in a GL-261 medullary glioma mouse model warrants a dose escalation study in pediatrics.

In a phase 1 adult study (Figure 2), subjects received intratumoral injections of Ad-RTS-hIL-12 2×10^{11} vp at resection or stereotactically. Daily single dose of oral veledimex was administered for 14 days post surgery.

ATI001-103 will include pediatric subjects with either recurrent or progressive supratentorial tumors or DIPG. Rigorous safety monitoring and ability to induce immune activation will be evaluated.

In adults, Ad-RTS-hIL-12 + veledimex was well tolerated; toxicities were predictable and reversible upon discontinuing veledimex with a correlation between veledimex dose, blood brain barrier penetration and drug related adverse events (AEs).

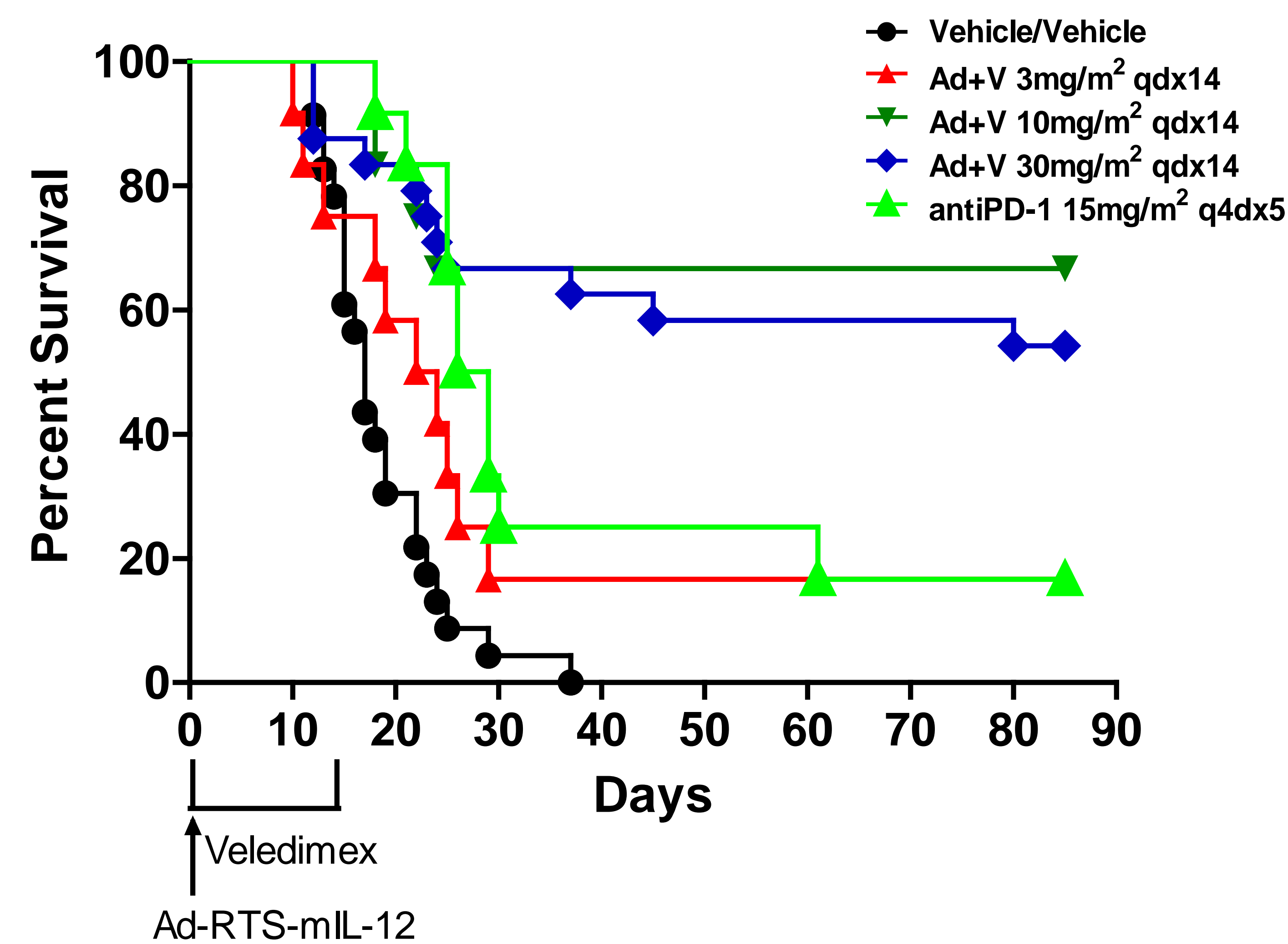
ATI001-103 is designed to explore 10 mg and 20 mg [body surface area (BSA) adjusted] doses of veledimex. Each subject will be monitored for 28 days after injection before continued enrollment. The last subject in each cohort must complete their 28-day dose limiting toxicity (DLT) evaluation period and the cohort must be reviewed by the Safety Review Committee (SRC) prior to opening the next cohort.

The SRC can decide to expand the cohort under review, continue enrollment with the next cohort, discontinue the investigation, or de-escalate by 5 mg if 2 or more DLTs were observed.

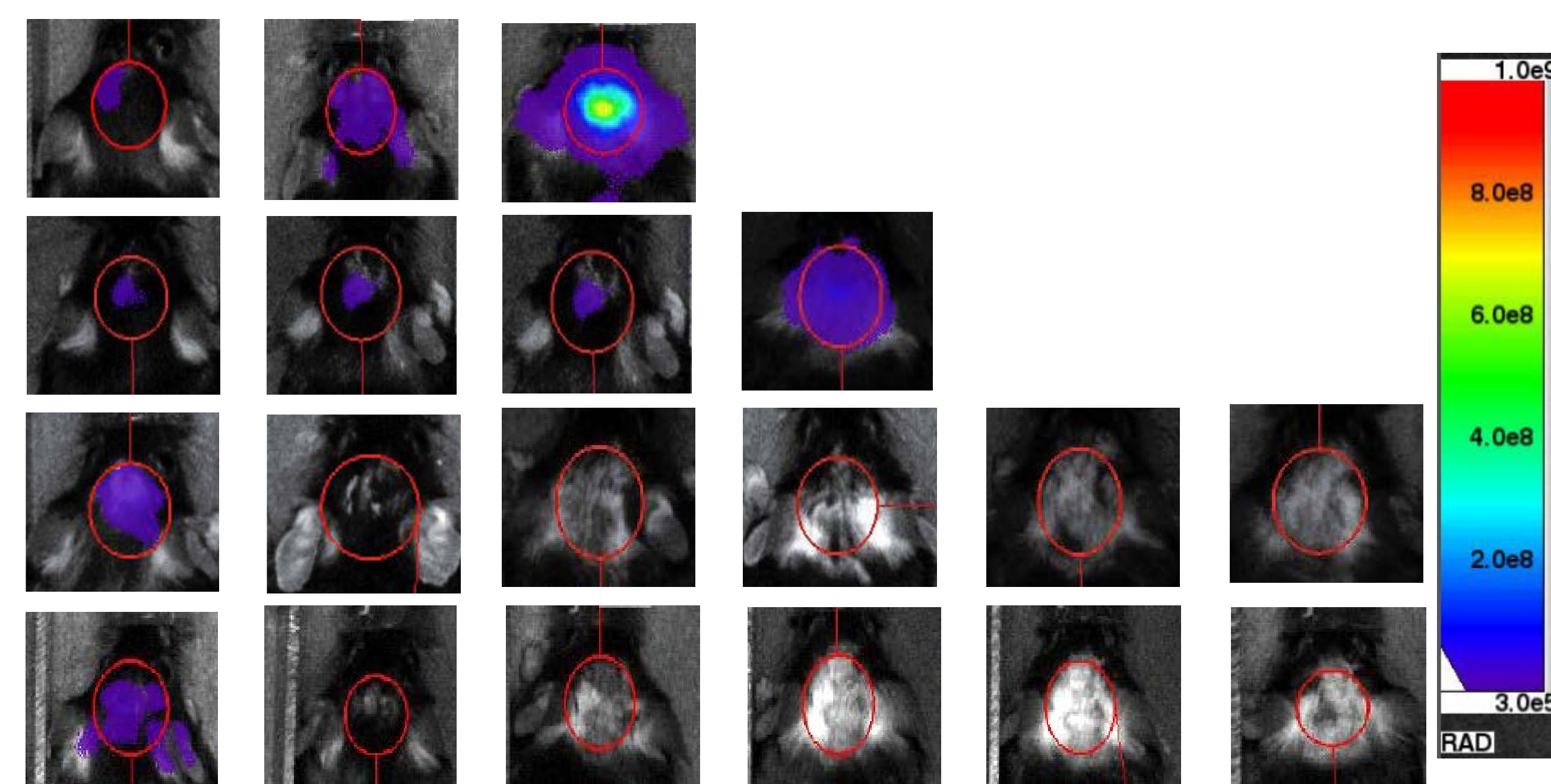
Cohort	Arm	Procedure	Assigned Veledimex Dose*
1	1	Craniotomy	10 mg
2	1	Craniotomy	20 mg
3	2	Stereotactic	10 mg
4	2	Stereotactic	20 mg

*Doses will be adjusted for BSA using a prespecified nomogram

Increased Survival in Orthotopic Pontine Glioma Mouse Model

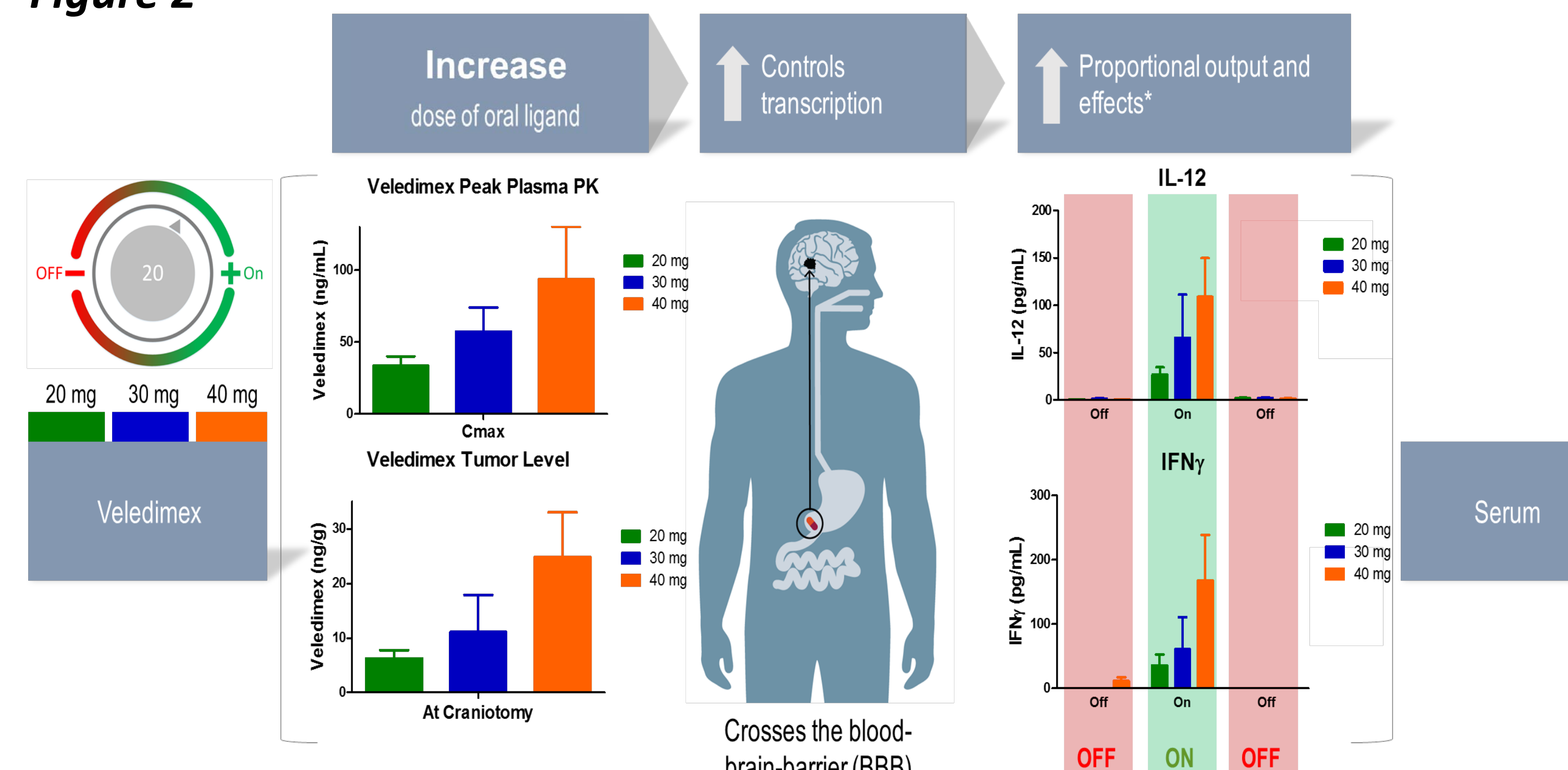


Ad-RTS-mIL-12 + Veledimex Efficacy Using Red-Luc GL-261 Pontine Mouse Model



ATI001-102 Adult GBM Study RTS[®] Dose Response to Veledimex

Figure 2



- Tumor veledimex levels are ~40% of plasma levels
- Based on the mouse model, the 20 mg dose is projected to generate 30-fold higher level of IL-12 and IFN-g in the tumor

Key Study Objectives

Primary Objective

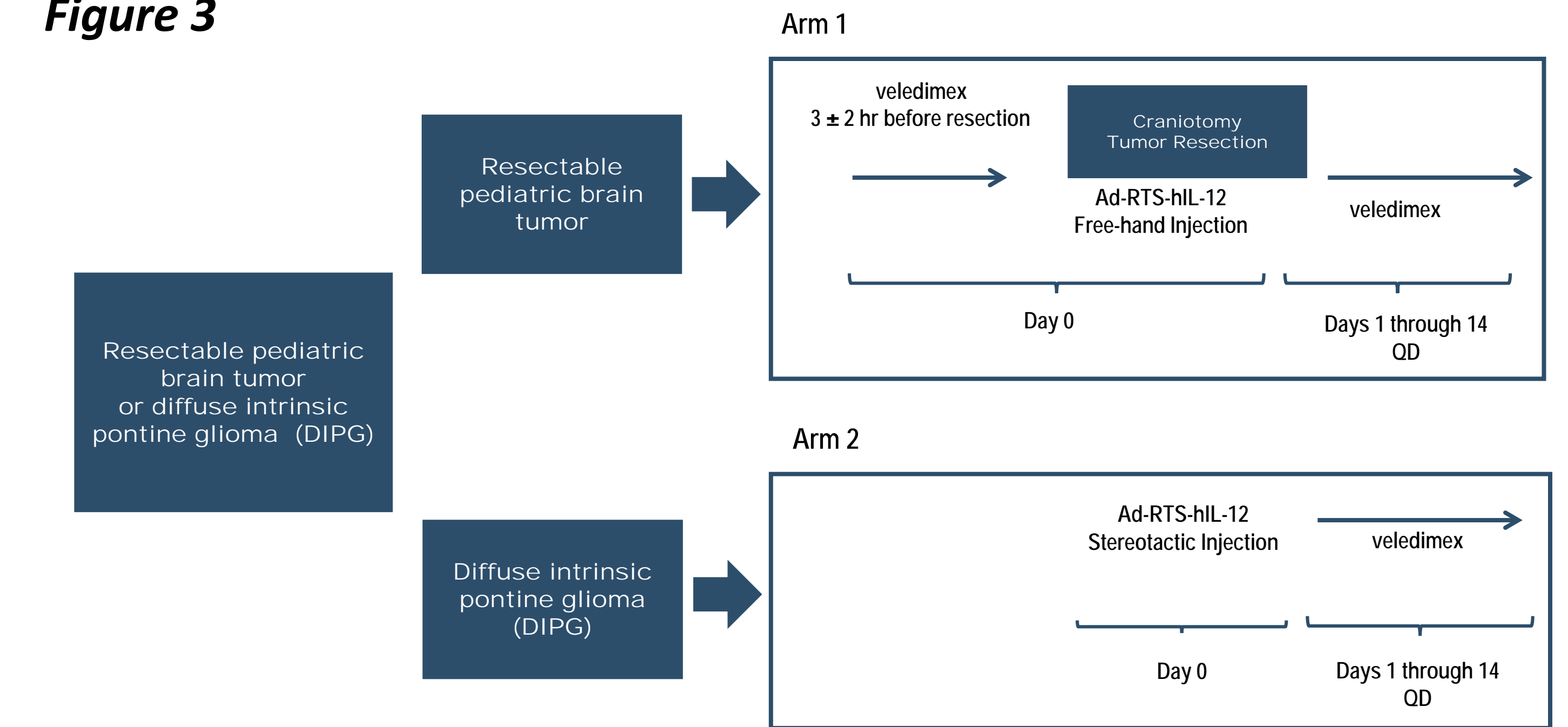
- Safety and tolerability

Key Secondary Objectives

- Determine recommended Phase II dose
- Pharmacokinetic (PK) profile
- Establish veledimex ratio of tumor/plasma
- Overall survival

Study Design

Figure 3



Two groups of subjects receiving Ad-RTS-hIL-12 2×10^{11} viral particles (vp) are planned:

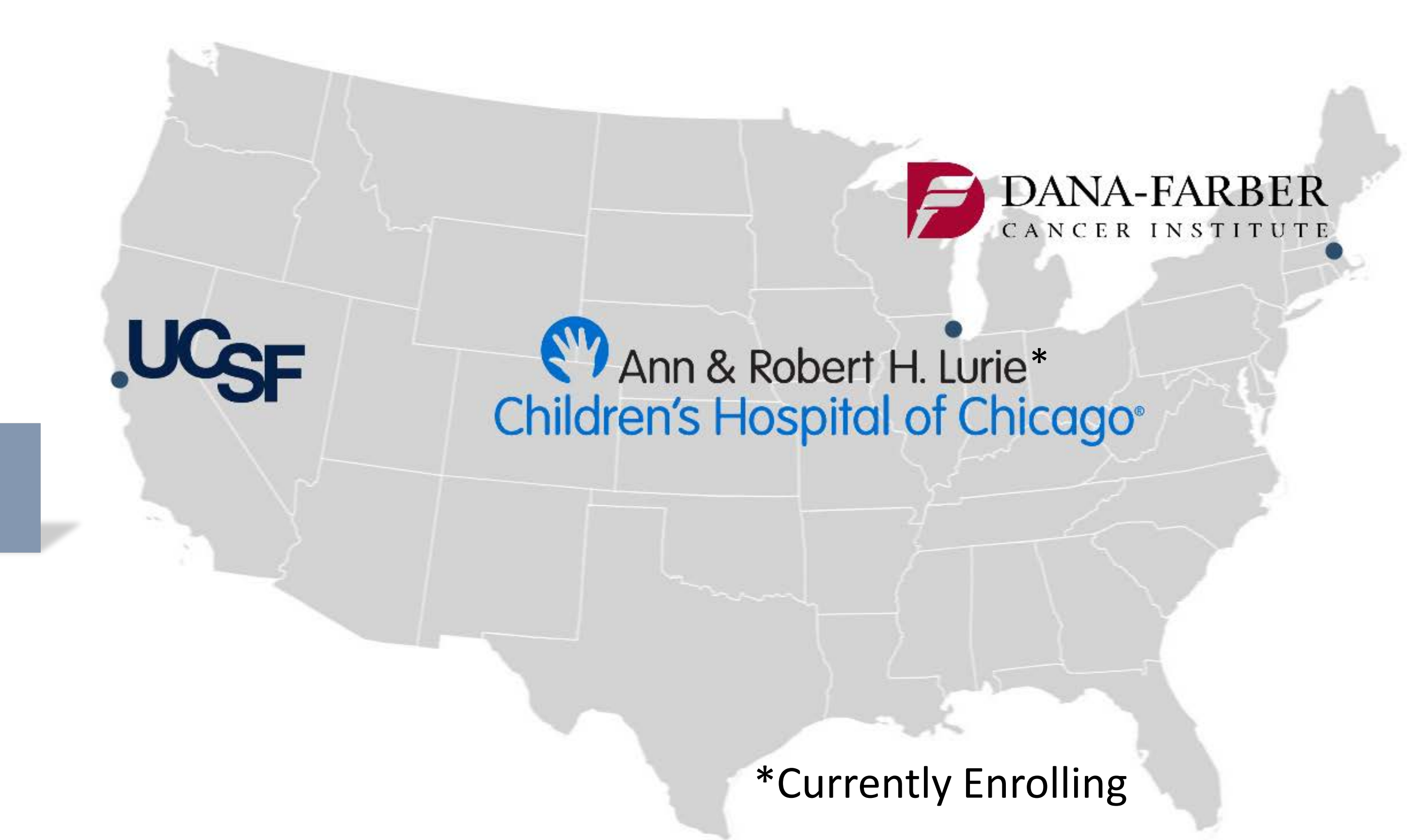
Arm 1: Receives Ad-RTS-hIL-12 intratumorally after resection of supratentorial tumors that are unresponsive to conventional treatment or for which there is no alternative curative therapy;

Arm 2: Stereotactic injection in subjects with DIPG post prior standard focal radiotherapy and for which a diagnostic biopsy has previously been documented.

Key Eligibility Criteria

- Male or female subjects ≤ 21 years-of-age with the demonstrated ability to swallow capsules
- **Arm 1:** Evidence of recurrent or progressive supratentorial tumor, which has shown a $> 25\%$ increase in bi dimensional measurements by MRI or is refractory with significant neuro deterioration that is not otherwise explained with no known curative therapy
- **Arm 2:** Clinical presentation of DIPG and compatible MRI with approximately 2/3 of the pons included. Subject should be ≥ 2 weeks and ≤ 10 weeks post standard focal radiotherapy (i.e. dose of 5400 to 5960 cGy and maximum dexamethasone of 1 mg/m²/day)
- On a stable or decreasing dose of dexamethasone for the previous 7 days
- Lansky score ≥ 50 or Karnofsky performance status > 50 or Eastern Cooperative Oncology Group (ECOG) score ≤ 2
- Adequate bone marrow, liver, and kidney function

Current Study Status



The ATI001-103 study is actively recruiting in Cohort 1.

Reference

(1)Warren, K. E. (2012). "Diffuse intrinsic pontine glioma: poised for progress." *Frontiers in Oncology* 2; 205