

### Scientific Abstract

This is a Phase I gene transfer clinical trial of AdV-tk + anti-herpetic prodrug (valacyclovir) in combination with surgery and radiation for pediatric supratentorial malignant gliomas. The rationale is based on preclinical studies demonstrating improved efficacy without added toxicity when the AdV-tk approach is combined with surgery and radiation therapy. The approach is further justified by the poor prognosis from current therapeutic approaches for malignant gliomas. This AdV-tk vector has been evaluated in multiple human tumor types, including malignant gliomas in adults and one pediatric study for retinoblastoma, with over 300 patient doses delivered to more than 150 patients. The approach has demonstrated a good safety profile and encouraging efficacy results. The proposed study is a follow on to a completed adult phase Ib study with the same design. Dose limiting toxicity was not observed in the adult trial in 12 participants at three dose levels with 3 each at dose 1 ( $3 \times 10^{10}$  vp) and 2 ( $1 \times 10^{11}$  vp) and six at dose 3 ( $3 \times 10^{11}$  vp). This pediatric study will evaluate dose levels 2 and 3 using a standard 3 + 3 design with up to 12 total participants. The methodology for administration of the AdV-tk vector will be the same as in the adult study; at the time of surgical resection, the vector will be injected into the resection margins of the tumor cavity (injected by the neurosurgeon). Valacyclovir will be given for 14 days beginning 1-3 days after AdV-tk injection and radiation therapy will begin by day 7 at standard doses. The mechanistic rationale for this approach is that HSV-tk phosphorylates the prodrug, converting it into nucleotide analogs, which are toxic to dividing or DNA-repairing cells. Normal, quiescent brain cells are less susceptible to this effect. DNA damaging agents, such as radiation and some chemotherapies, increase DNA repair activity and consequently increase susceptibility to AdV-tk + prodrug activity. In addition, radiation has been shown to potentiate the anti-tumor immunity induced by AdV-tk + prodrug. While there is little pediatric data that proves that temozolomide, a very well tolerated oral chemotherapy agent, delays the time to tumor progression, there is positive data in adults and thus many pediatric oncologists add this drug to children with malignant gliomas. Participants in this study will therefore be allowed to receive temozolomide after completion of the valacyclovir as in the adult phase Ib study. The primary objective of this trial will be to evaluate the safety of AdV-tk with a fixed dose of valacyclovir in pediatric malignant gliomas and determine the appropriate AdV-tk dose for a subsequent Phase II study to evaluate potential efficacy of this approach.