Targeted Therapeutics for the Treatment of Brain Cancer

Company Overview

- *Singularly focused on dramatically improving brain cancer survival in adults and children*
- Privately-held, preclinical-stage drug development company
- Founded in 2013; 5,000-square foot lab/office in Austin, TX
- Scientific co-founder is Santosh Kesari, MD, PhD, an internationally recognized leader in the brain cancer field
- First-in-class, small molecule therapeutic with novel mechanism of action
- Major market opportunities
  - Clinical candidate for glioblastoma in adults
  - Expansion in pediatrics and metastatic disease
- Recipient of $7.6M award from CPRIT in 2014

CPRIT

Lead Program Highlights

Indication: Malignant gliomas, including glioblastoma (GBM) in adults and pediatric high-grade glioma (pHGG) in children

Target: Olig2, a cancer stem cell (CSC)-associated transcription factor found in nearly all gliomas

Clinical Candidate: CT-179, a potent oral Olig2 inhibitor

- **Efficacy:** Most effective when used in combination with chemotherapy and radiation in preclinical animal models
- **Safety:** No significant toxicities identified at therapeutic doses
- **Mechanism:** Direct binding to Olig2 protein leading to apoptosis
- **Regulatory:** Granted orphan-drug designation by the FDA
- **Development:** Initiate two Phase 1b clinical trials in newly diagnosed GBM patients in combination with RT ± TMZ in Q2 2018

Preclinical research collaborations with top brain cancer scientists

UT Southwestern Medical Center

Duke University

The University of Texas MD Anderson Cancer Center

John Wayne Cancer Institute at Providence Saint John's Health Center

Hudson Institute of Medical Research

Baylor College of Medicine

Mayo Clinic

A Diagnosis Of Glioblastoma Is A Death Sentence





People who have died from brain cancer.

- Estimated 12,390 new cases of glioblastoma (GBM) in the U.S. in 2017[1]
- Conventional therapy includes surgery, chemo-therapy with Temodar® and radiation therapy
- Median survival = 14.6 months[2]
- 5-year OS rate = 9.8%[2]

$1 billion worldwide market opportunity[3]

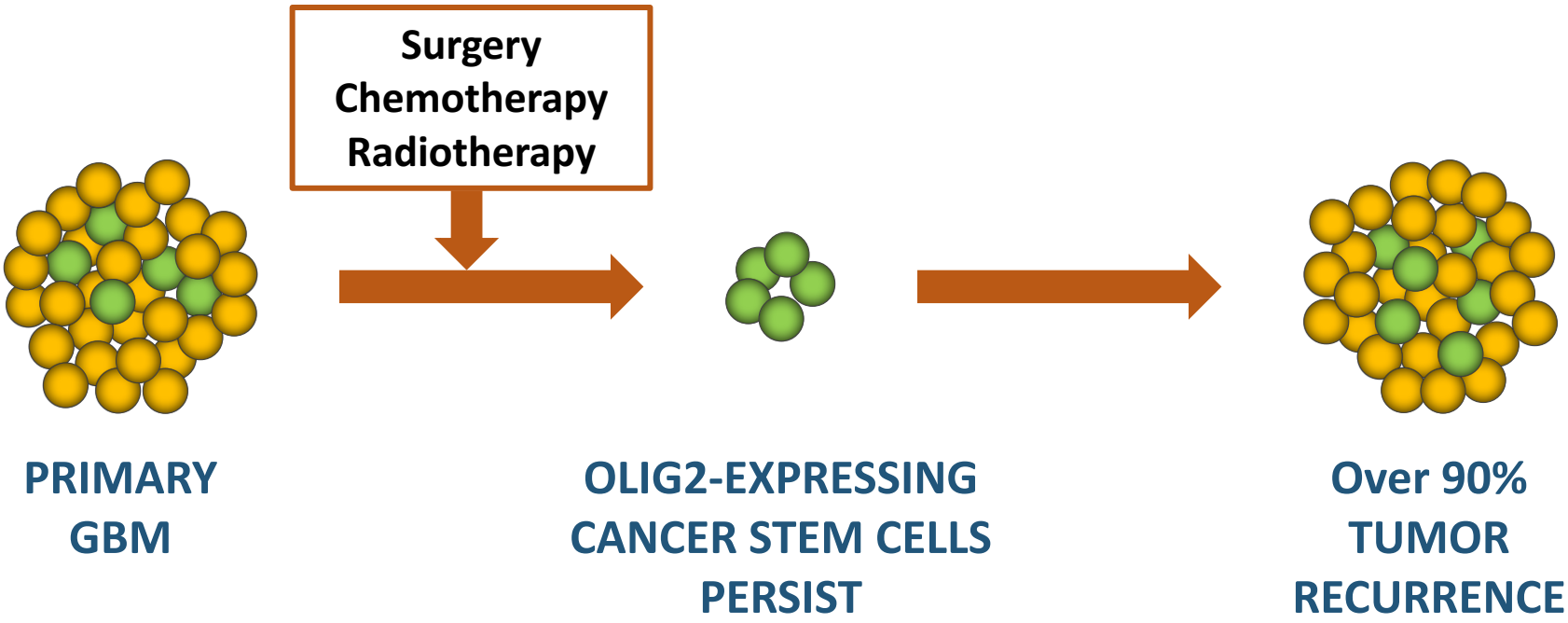
1. http://http://www.abta.org/about-us/news/brain-tumor-statistics/
2. The lancet oncology 10.5 (2009): 459-466.
3. Therapeutic Categories Outlook, Cowen & Co. (2012): 902.

In Children, Pediatric High-Grade Glioma[1] Has An Equally Dismal Prognosis

- ~700 cases per year in the US[2]
- Treatment includes surgery and radiation[2]
- 5-year survival less than 35%[2]
- Shorter time and lower cost to NDA vs. traditional clinical development
- Opportunity to receive a priority review voucher from the FDA worth >$300M

1. Includes anaplastic astrocytoma, anaplastic oligodendroglioma, glioblastoma, mixed glioma, and malignant glioma
2. Fangusaro, J. (2012). Pediatric High Grade Glioma: a Review and Update on Tumor Clinical Characteristics and Biology. Frontiers in Oncology, 2(August), 1–10.

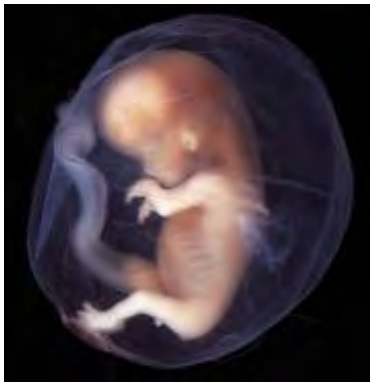
Problem: Conventional Therapies Are Ineffective Against Olig2-Expressing Cancer Stem Cells, Leading To Recurrence



What Is Olig2 And Why Target It In Gliomas?

Required For Normal Brain Development

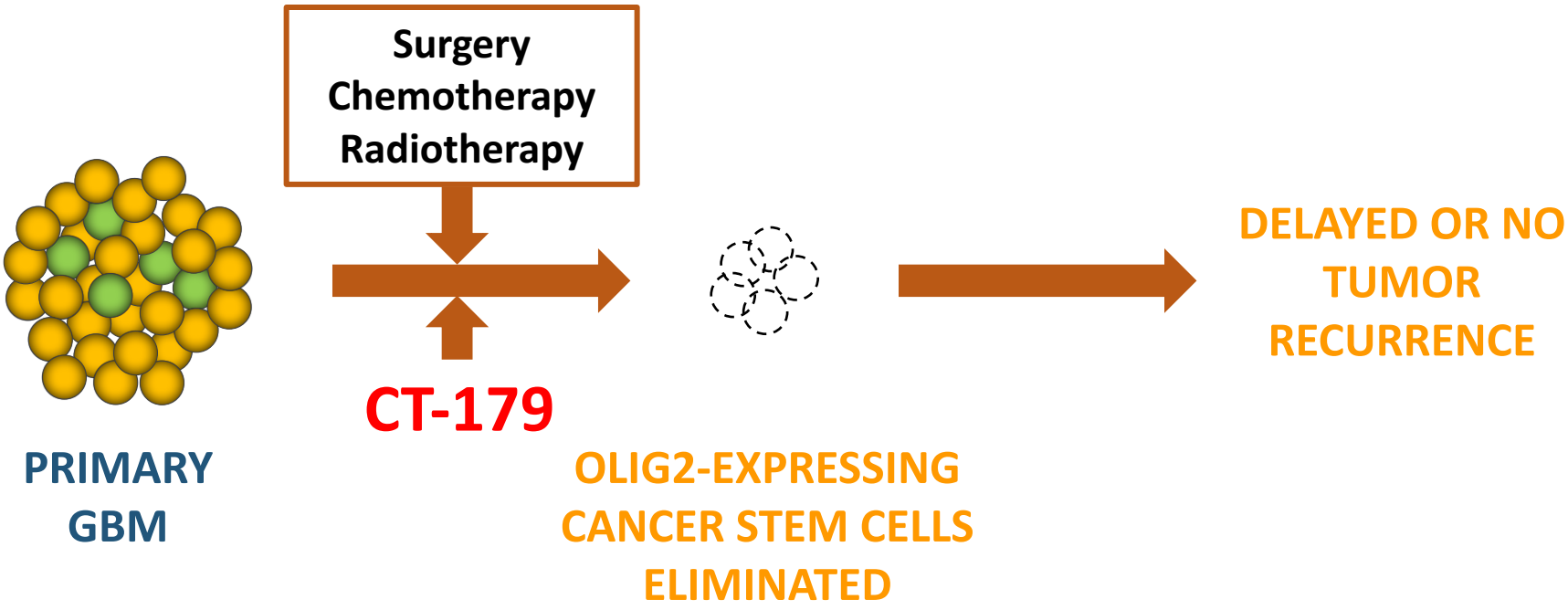
- Transcription factor
- Critical to embryologic brain development
- Typically not active in normal adult brain tissue
- Not found in normal tissues outside the CNS



Critical For Tumor Growth And Invasion

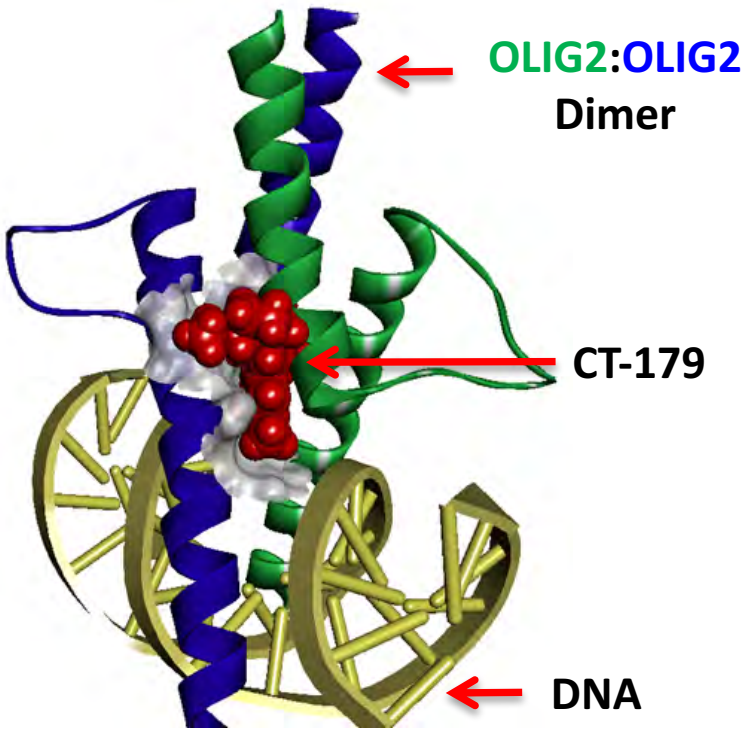
- Drives tumorigenesis
- Promotes resistance to radiation therapy
- Drives tumor invasion into healthy tissue
- CSCs are immunosuppressive
- Highly expressed in all gliomas

Solution:
Eliminate The Treatment-Resistant CSCs By Targeting Olig2



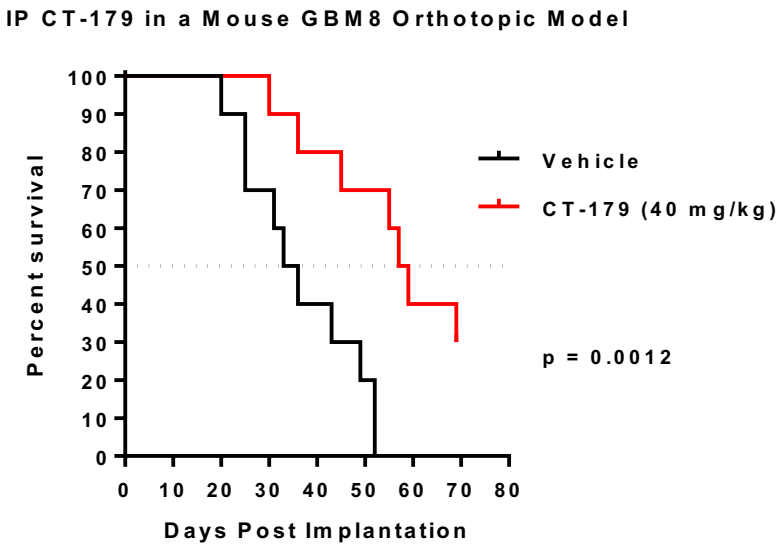
- CT-179 will be given as adjunctive therapy with SOC
- Treatment goal is to debulk the tumor AND eliminate the chemo- and radiation-resistant cancer stem cells (CSC)
- As with temozolomide, maintenance therapy is planned

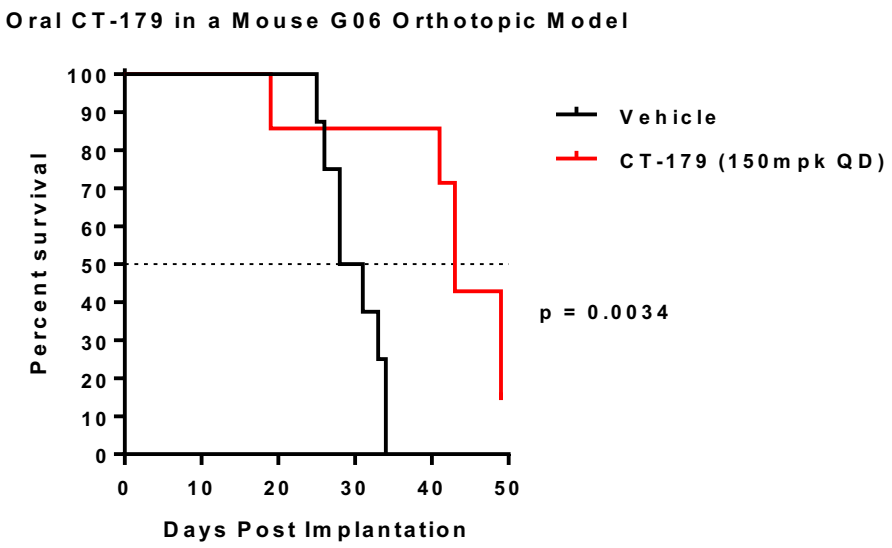
CT-179 Has Excellent Pharmacologic Properties



- ✓ ~60% orally bioavailable in monkeys
- ✓ Once daily dosing
- ✓ Crosses the blood-brain-barrier
- ✓ Therapeutic drug levels in brain tissue at steady-state
- ✓ Well-tolerated at therapeutic doses in preclinical studies
- ✓ Low COGS
- ✓ Straightforward manufacturing
- ✓ No major formulation issues
- ✓ Multiple patent applications

CT-179: Significantly Improves Survival In Orthotopic GBM PDX Models

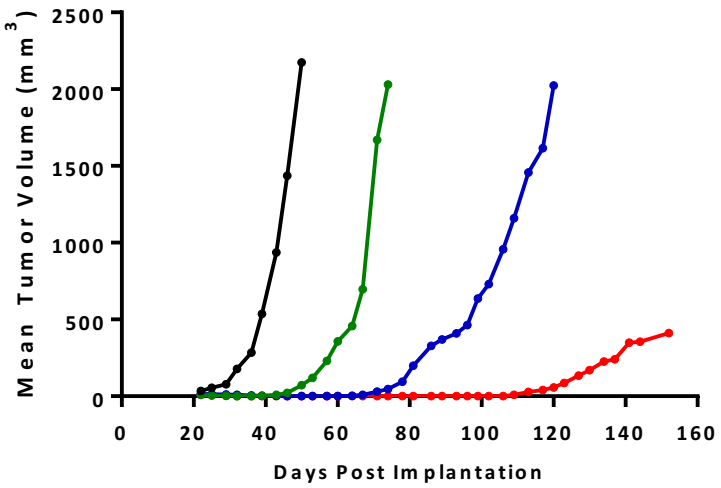




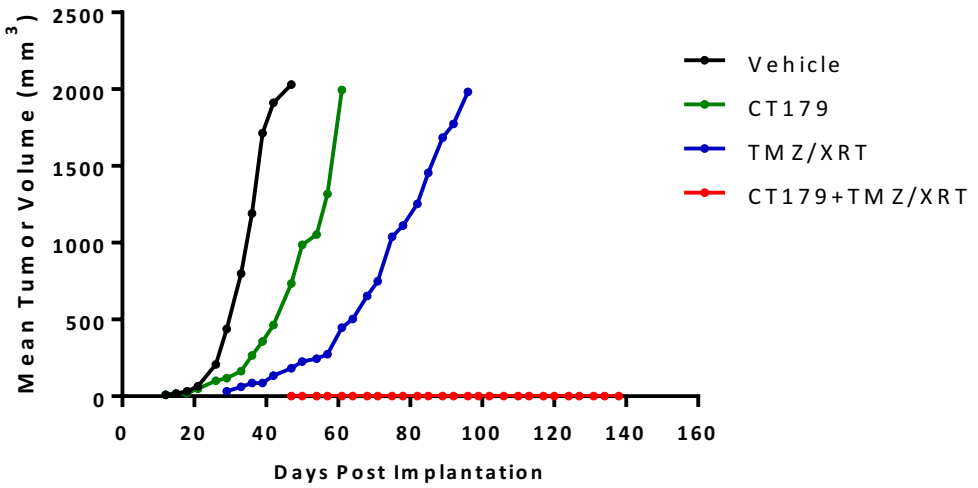
- Orthotopic implantation of human Olig2-expressing GBM8 and G06 cells ; cell lines selected for rapid growth rate of tumors and *in vitro* sensitivity
- IP administration in GBM8 model and PO administration in G06 model
- All treatment groups with significant survival benefit

CT-179: Tumor Growth Inhibition And Treatment Combination Synergy In GBM4 & GBM8 Flank Models

CT-179 at 105 mg/kg ± TMZ/RT In a Mouse GBM4 Flank Model



CT-179 at 105 mg/kg ± TMZ/RT In a Mouse GBM8 Flank Model

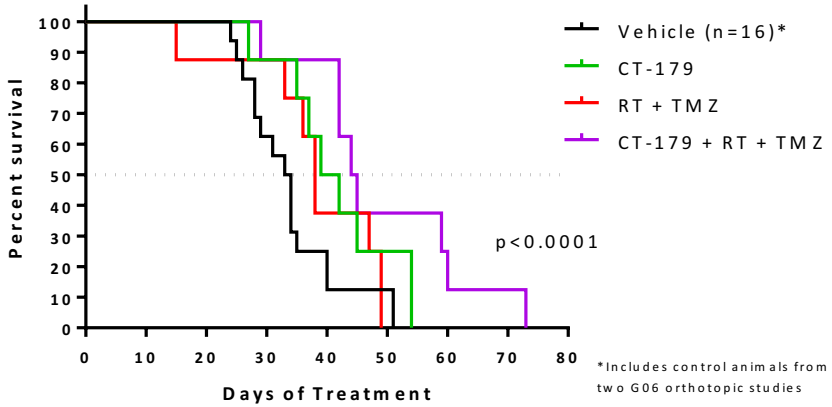


- SQ implantation of human Olig2-expressing GBM4 and GBM8 cells
- PO administration of CT-179 at 105 mg/kg ± temozolomide/radiation (TMZ/RT)
- All treatment groups with significant tumor growth inhibition (TGI)
- **Combination significantly better TGI compared to either CT-179 or TMZ/RT alone**

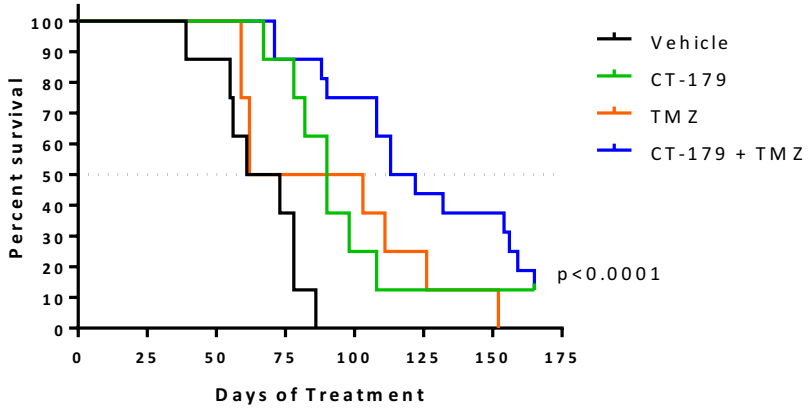
Note: Study numbers are GBM4e201 and GBM8e203

CT-179: Survival Benefit In G06 & GBM8 Orthotopic Models

CT-179 at 150 mg/kg ± TMZ/RT
In a Mouse G06 Orthotopic Model



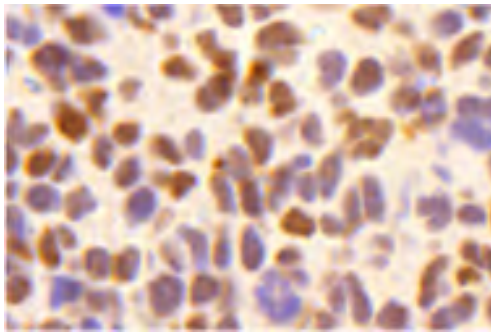
CT-179 at 150 mg/kg ± TMZ
In a Mouse GBM8 Orthotopic Model



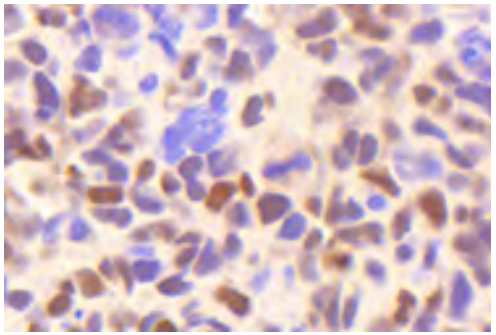
- SQ implantation of human G06 and GBM8 cells
- PO administration of CT-179 at 150 mg/kg ± temozolomide/radiation (TMZ/RT) or ± TMZ
- Survival benefit from monotherapy and combination with SOC therapies
- **Combination significantly better survival compared to monotherapy**
- GBM8 study still in-progress; final results expected in November

CT-179: Olig2 Expression In GBM12 Tumors *In Vivo* Is Markedly Reduced

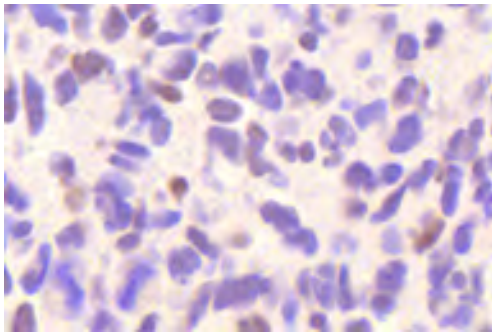
Vehicle



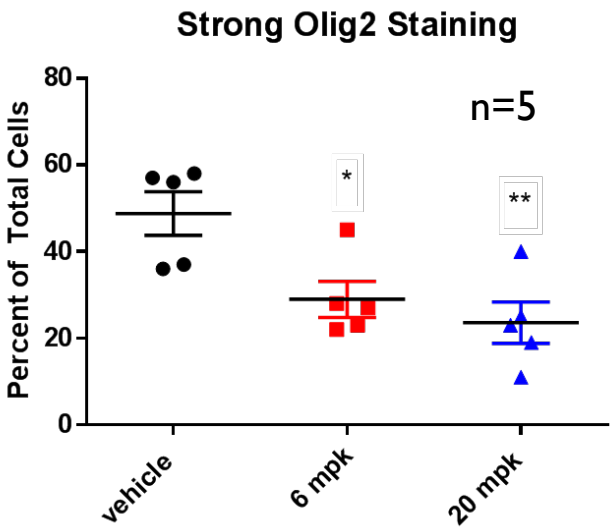
6 mpk CT-179



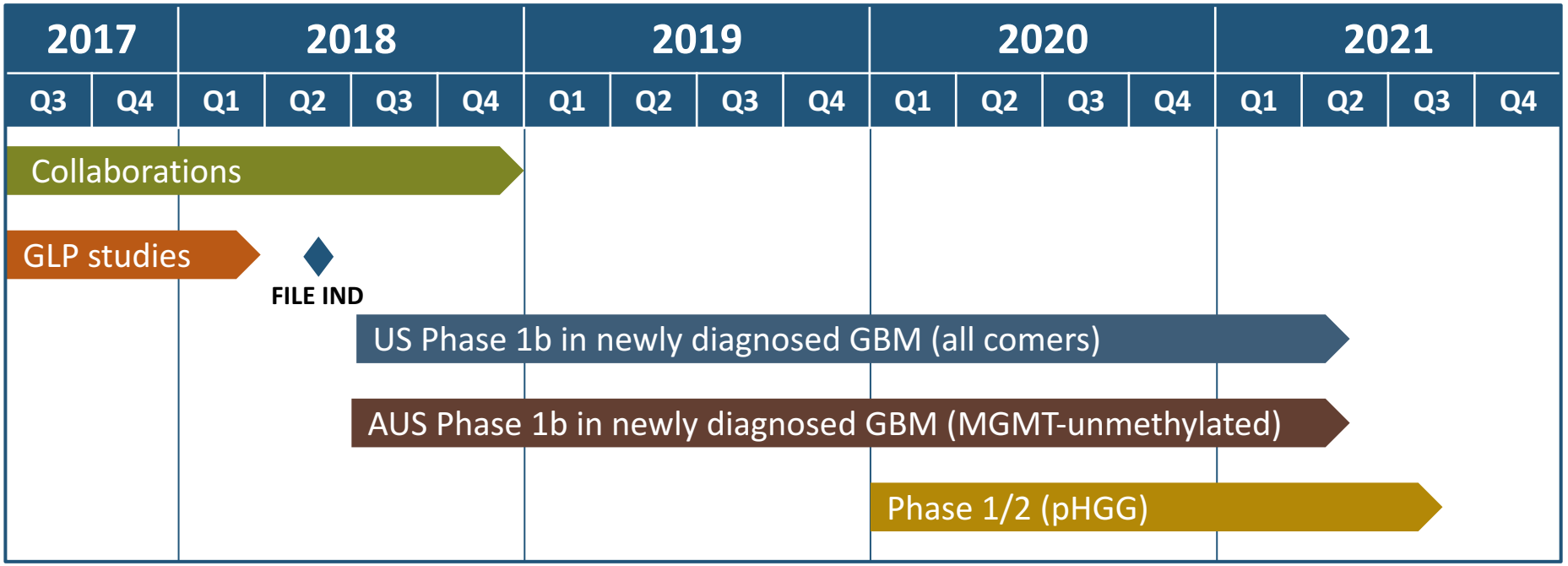
20 mpk CT-179



- Mice implanted orthotopically with GBM12 tumor cells
- Treated with CT-179 at 6 mg/kg and 20 mg/kg PO for 15 days
- Olig2 antibody stain is reddish brown
- CT-179 at 6 mg/kg and 20 mg/kg significantly reduces Olig2 staining



4-Year Drug Development Timeline To Human Safety and Early Efficacy Data



- IND submission in Q2 2018
- US Phase 1b clinical trial – CT-179 in combination with TMZ and RT in newly diagnosed glioblastoma (GBM) in adults (all comers)
- Australian Phase 1b clinical trial – CT-179 in combination with RT in newly diagnosed glioblastoma (GBM) in adults (MGMT-unmethylated only)
- 40-patient P1/2 study planned in pediatric high grade glioma (pHGG)

Management Team Members With Decades Of Experience Developing New And Innovative Drugs

Gregory Stein, M.D., M.B.A.
Chief Executive Officer

20+ years in clinical medicine and life science company formation and operations.

Graham Beaton, Ph.D.
VP, Medicinal Chemistry & Drug Discovery

20+ years in industrial science and pharmaceutical drug development.

Gordon Alton, Ph.D.
VP, Research and Development

20+ years of leading numerous drug discovery project teams.

Daniel Pertschuk, M.D.
VP, Clinical Development

20+ years of leading numerous clinical development programs.

Targeted Therapeutics For The Treatment Of Brain Cancer

Unmet Medical Need

- Glioblastoma and pediatric high grade glioma are devastating tumors with high morbidity and mortality rates
- Current standard-of-care only extends median survival by a few months

Significant Market Opportunity

- $1B worldwide market for glioblastoma
- Pediatric market offers increased speed and lower cost to approval along with priority review voucher
- Expansion into other primary and metastatic brain cancers

CT-179 Differentiation

- Novel, truly targeted mechanism of action
- Kills cancer stem cells, limits invasion, radiation sensitizer while sparing non-Olig2-expressing cells
- Excellent safety and tolerability profile