Adastra: Brief Corporate Overview

ADASTRA PHARMACEUTICALS

Executive Summary: Strong Clinical Findings – Final Clinical Results

Zotiraciclib in the treatment of recurrent high-grade gliomas (rHGG)

rHGG *In each of three well-defined patient groups the final trial results are robust*

All Patients (overall) | **IDH Mutated** (enriched) | **Unmethylated** (predictive)

Adastra zotiraciclib (ZTR) has seen strong efficacy in all patient types and meaningful signals in sub-groups

- **Strong efficacy across all patients** (mPFS of 5.9 mo., ~55% PFS6 for all vs. ~21% seen in historical comparators)
- **Compelling potential for improved efficacy in key sub-populations**
  - IDHmut: mPFS of ~171 days. (vs. ~91 days in the literature*)
  - Unmethylated MGMT: ~2.8 mo. mPFS, ~18% PFS6 (vs. <7% in literature*)

KOLs believe IDHmut data is promising and the target patient group to attain accelerated approval

- **IDHmut signal of zotiraciclib exceeds expected efficacy from TMZ alone** and warrants further investigation
- **Ph 2 trial in IDHmut rHGG** supports accelerated approval
  - Primary Endpoint: PFS6 with PROs considered potentially sufficient registrational endpoint
  - Comparator: US KOLs supportive of TMZ + ZTR experimental arm vs. TMZ

***Historical literature benchmarks:** rHGG literature comparisons are intended to provide a comparable outcomes in rHGG patients, without present definitive outcome information.
Methodology: applied a weighted average of rAA and rGBM outcomes based on segmentation of NCI study (~25% rAA and ~75% rGBM); pooled lomustine data in both rAA and rGBM to generate the base and pooled TMZ for rAA and bev + lomustine for GBM outcomes to determine high end. Note that TMZ outcomes in rAA are at first relapse, whereas rAA lomustine outcomes are in first and second relapse (post-TMZ); additionally, bevacizumab PFS is higher than other commonly used regimens in R/R (e.g., lomustine, TMZ).
Sources: 1) Yung 1999 *J Clin Oncol*, 17: 2762; 2) Chamberlain 2015, *Journal of Neuro-oncology* 122.2:329; 3) Wick (2017) *NEJM*; 377:1954-63

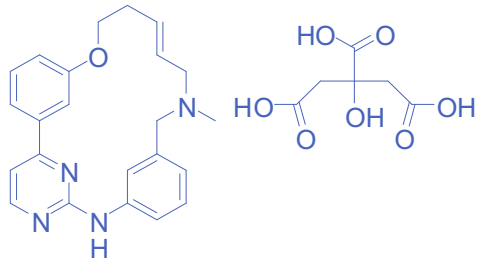
Zotiraciclib (ZTR) is a Potent Oral Kinase Inhibitor that Readily Crosses the Blood Brain Barrier (BBB) – highly efficient Myc depletion

Key Pathway Inhibition

Kinase	IC_{50} *(nM)*	Function	Indication
CDK9	3	Myc depletion	HGG, HCC, TNBC
CDK5	4	DNA damage response	GBM, TNBC
CDK2	5	Cell cycle	GBM, HCC, TNBC
CDK7	37	mRNA transcription	GBM, Ovarian
ERK5	43	Survival and differentiation	DIPG, TNBC

Broad activity addressing tumorigenic kinases

> ***"There are very few drugs out there that hit this constellation of targets****, in GBM at least. This agent addresses potential resistance."*
>
> **– US KOL #2**



ZTR Citrate
$C_{23}H_{24}N_4O \bullet C_6H_8O_7$

Tissue Penetration[1]
Tissue Plasma Ratio

BRAIN	Liver	Lung	Kidney
2.4	15.4	13.8	6.8

~2x **more concentrated in the brain than the plasma** (also absorbed in other tissue types)

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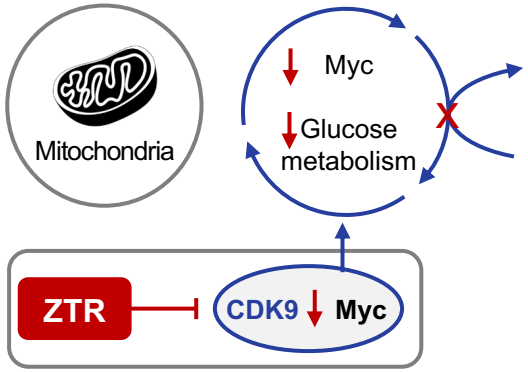
Sources: 1) Report on file

Zotiraciclib depletes Myc ⟶ Decreases Glutarate Activity, Specifically Supportive IDH Mutant as an Enriched Population

1 Myc amplifies glucose[3]

Cellular Metabolism



ZTR depletes MYC levels, lowering glucose metabolism

2 IDH mutant tumors proliferate via 2-HG cellular metabolism to promote tumor formation and growth

IDH1/2

Catalyzes…

NAD^+	**2-HG** 2-hydroxyglutarate
NADPH	
Reaction catalyzed by IDH	*Product of reaction*

Oncogenesis

2-HG promotes cancer through

- Disrupting stem cell formation
- Promoting tumor invasiveness

MYC depletion via CDK9 inhibition decreases glucose / glutarate activity, mitigating the effect of mutant IDH on the oncogenic process[2]

AACR[1] American Association for Cancer Research

Cancer Therapy: Preclinical — Clinical Cancer Research

Novel Targeting of Transcription and Metabolism in Glioblastoma

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Abstract

Purpose: Glioblastoma (GBM) is highly resistant to treatment, largely due to disease heterogeneity and resistance mechanisms. We sought to investigate a promising drug that can inhibit multiple aspects of cancer cell survival mechanisms and become an effective therapeutic for GBM patients.

Experimental Design: To investigate TG02, an agent with known penetration of the blood–brain barrier, we examined the effects as single agent and in combination with temozolomide, a commonly used chemotherapy in GBM. We used human GBM cells and a syngeneic mouse orthotopic GBM model, evaluating survival and the pharmacodynamics of TG02. Mechanistic studies included TG02-induced transcriptional regulation, apoptosis, and RNA sequencing in treated GBM cells as well as the investigation of mitochondrial and glycolytic function assays.

Results: We demonstrated that TG02 inhibited cell proliferation, induced cell death, and synergized with temozolomide in GBM cells with different genetic background but not in astrocytes. TG02-induced cytotoxicity was blocked by the overexpression of phosphorylated CDK9, suggesting a CDK9-dependent cell killing. TG02 suppressed transcriptional progression of antiapoptotic proteins and induced apoptosis in GBM cells. We further demonstrated that TG02 caused mitochondrial dysfunction and glycolytic suppression and ultimately ATP depletion in GBM. A prolonged survival was observed in GBM mice receiving combined treatment of TG02 and temozolomide. The TG02-induced decrease of CDK9 phosphorylation was confirmed in the brain tumor tissue.

Conclusions: TG02 inhibits multiple survival mechanisms and synergistically decreases energy production with temozolomide, representing a promising therapeutic strategy in GBM, currently under investigation in an ongoing clinical trial. *Clin Cancer Res; 1–14. ©2018 AACR.*

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor with an annual incidence rate of 27.86 per 100,000 in the United States (1). Despite the statistical improvement of current standard treatment with radiotherapy and temozolomide (TMZ) compared with radiotherapy alone, less than one third of patients survive beyond 2 years and cure is exceedingly rare (2). Therapies targeting particular altered gene products or signal transduction pathways have not provided durable responses in GBM likely due to multiple dynamic and interactive, compensatory, dysregulated pathways (3, 4). Targeting multiple survival mechanisms in tumor can potentially avoid the development of adaptive resistance. In-depth and well-designed preclinical study is the key to identifying such drug candidates to move forward to the clinical trials.

TG02, a pyrimidine-based multikinase inhibitor with good penetration of blood–brain barrier (BBB), has been shown to inhibit multiple cyclin-dependent kinases (CDK) and regulate transcriptional machinery (5, 6). CDK9, the primary target of TG02, is a serine/threonine kinase that is critical for stimulating transcriptional elongation through RNA polymerase II (RNA Pol II; refs. 7–9). CDK7 regulates CDK9 through phosphorylation at Threonine 186 (T186) to facilitate the transcriptional process. CDK9, in turn, controls the RNA Pol II C-terminal domain through phosphorylation of Serine 2 to modulate the transcriptional process (10). When CDK9 activity is inhibited, short-lived proteins are depleted due to their need to be frequently refreshed (11). As a consequence of the transcriptional regulation, TG02 potentially affects multiple essential survival signals of cancers.

TMZ, an orally administered alkylating agent that has proven efficacy in GBM, has a cytotoxic effect associated with induction of cell death (12). However, its treatment effects are limited by multiple resistance mechanisms including, but not limited to, O-6-Methylguanine-DNA Methyltransferase (MGMT) expression (13, 14). We therefore investigated the effects of TG02 in GBM models with both low and high MGMT expression to determine

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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*Tricarboxylic acid cycle

Sources: 1) J. Wu, et al. *Clinical Cancer Research*, (2018) 10.1158; 2) Huang, Juan, et al. *Frontiers in Oncology* 9 (2019): 506
3) www.pnas.orgcgidoi10.1073pnas.0810199105

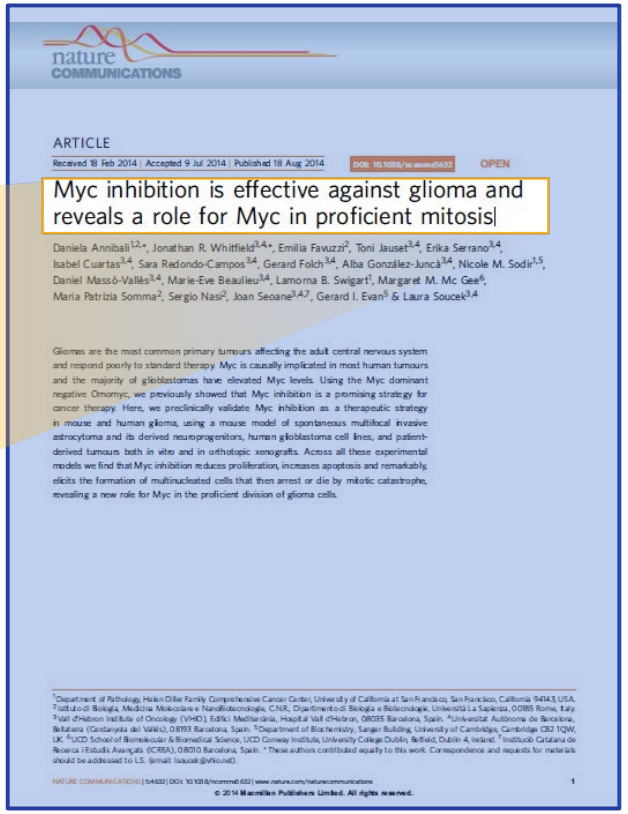
Target Myc Protein: Overexpressed in ~80% of Glioma Patients
(Prevalent in Many Other Cancer Types)

Gliomas

A well-defined opportunity to spearhead zotiraciclib development, characterized by Myc overexpression

Cancer Types with Myc Overexpression

Myc inhibition is effective against glioma and reveals a role for Myc in proficient mitosis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ARTICLE

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Myc inhibition is effective against glioma and reveals a role for Myc in proficient mitosis

Daniela Annibali[1,2,*], Jonathan R. Whitfield[3,4,*], Emilia Favuzzi[2], Toni Jauset[3,4], Erika Serrano[3,4], Isabel Cuartas[3,4], Sara Redondo-Campos[3,4], Gerard Folch[3,4], Alba González-Juncà[3,4], Nicole M. Sodir[1,5], Daniel Massó-Vallés[3,4], Marie-Ève Beaulieu[3,4], Lamorna B. Swigart[1], Margaret M. Mc Gee[6], Maria Patrizia Somma[2], Sergio Nasi[2], Joan Seoane[3,4,7], Gerard I. Evan[5] & Laura Soucek[3,4]

Gliomas are the most common primary tumours affecting the adult central nervous system and respond poorly to standard therapy. Myc is causally implicated in most human tumours and the majority of glioblastomas have elevated Myc levels. Using the Myc dominant negative Omomyc, we previously showed that Myc inhibition is a promising strategy for cancer therapy. Here, we preclinically validate Myc inhibition as a therapeutic strategy in mouse and human glioma, using a mouse model of spontaneous multifocal invasive astrocytoma and its derived neuroprogenitors, human glioblastoma cell lines, and patient-derived tumours both *in vitro* and in orthotopic xenografts. Across all these experimental models we find that Myc inhibition reduces proliferation, increases apoptosis and remarkably, elicits the formation of multinucleated cells that then arrest or die by mitotic catastrophe, revealing a new role for Myc in the proficient division of glioma cells.

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Sources: 1) Annibali et al. (2014) Nature Communications;

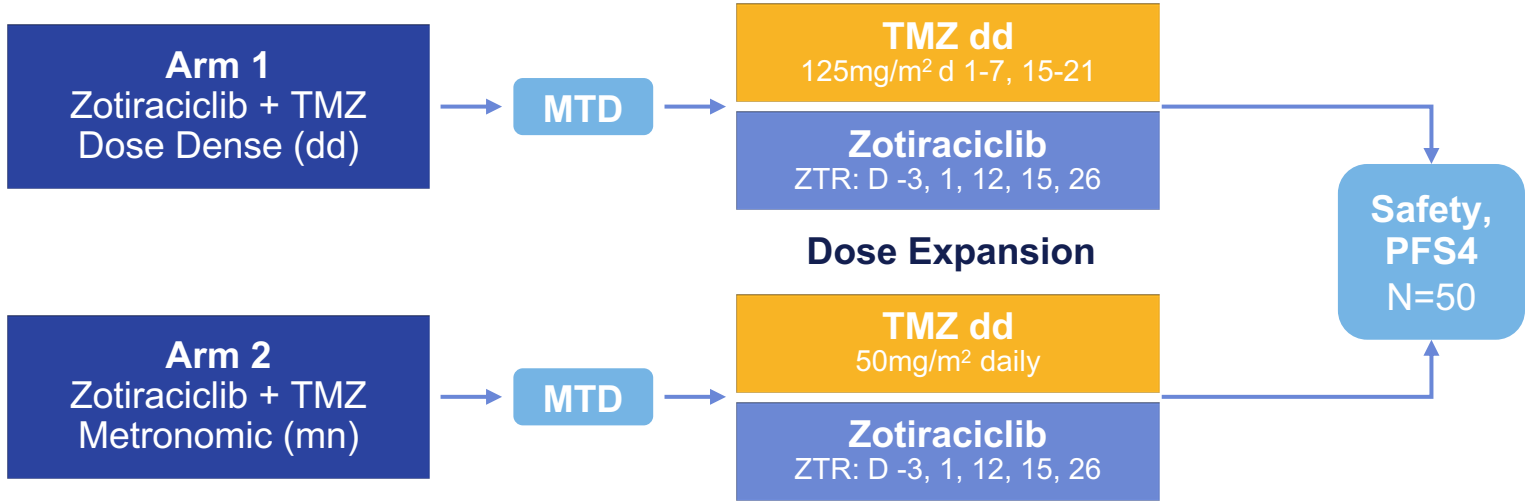
Adastra Successful Completion of the NCI Ph 1b Trial in rHGG

"Strong efficacy in all patient groups"

US and EU Clinical Advisors

Recurrent High-grade Glioma (rHGG) Trial Design and Study Objectives

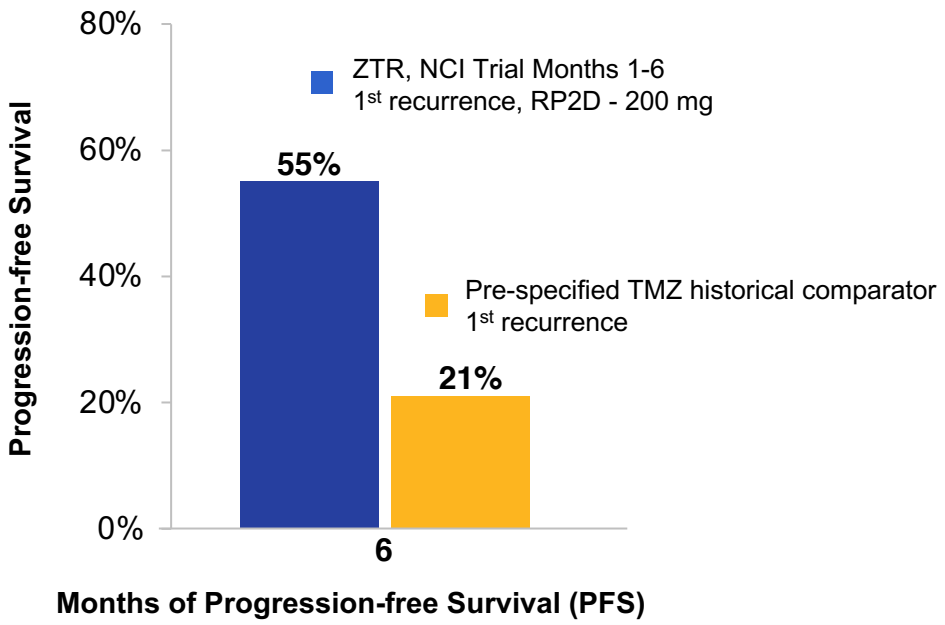
- Determine zotiraciclib optimal tolerated dose (RP2D) – 200 mg
- Determine optimal ZTR dosing schedule with TMZ
- **Efficacy primary:** Progression-free survival (PFS4) months and safety



Zotiraciclib Demonstrated *Strong Clinical Result: PFS6 55%*
(First Recurrence, RP2D)

All Patients (1st Recurrence) | **IDH Mutated** (enriched) | **Unmethylated** (predictive)

ZTR ~3x Improvement in PFS6 – matched recurrence



Category: Final Dose Analysis – RP2D

No. of pts	**19**
No. of pts censored*	7 (36%)
No. pts with PD	12 (63%)
PFS6	**55%**
mPFS	**5.9 mo**, CI 2.5-9.0

"Unmet need is extremely high in recurrent gliomas patients. *This additive benefit over SoC is very meaningful."*

– US KOL #1

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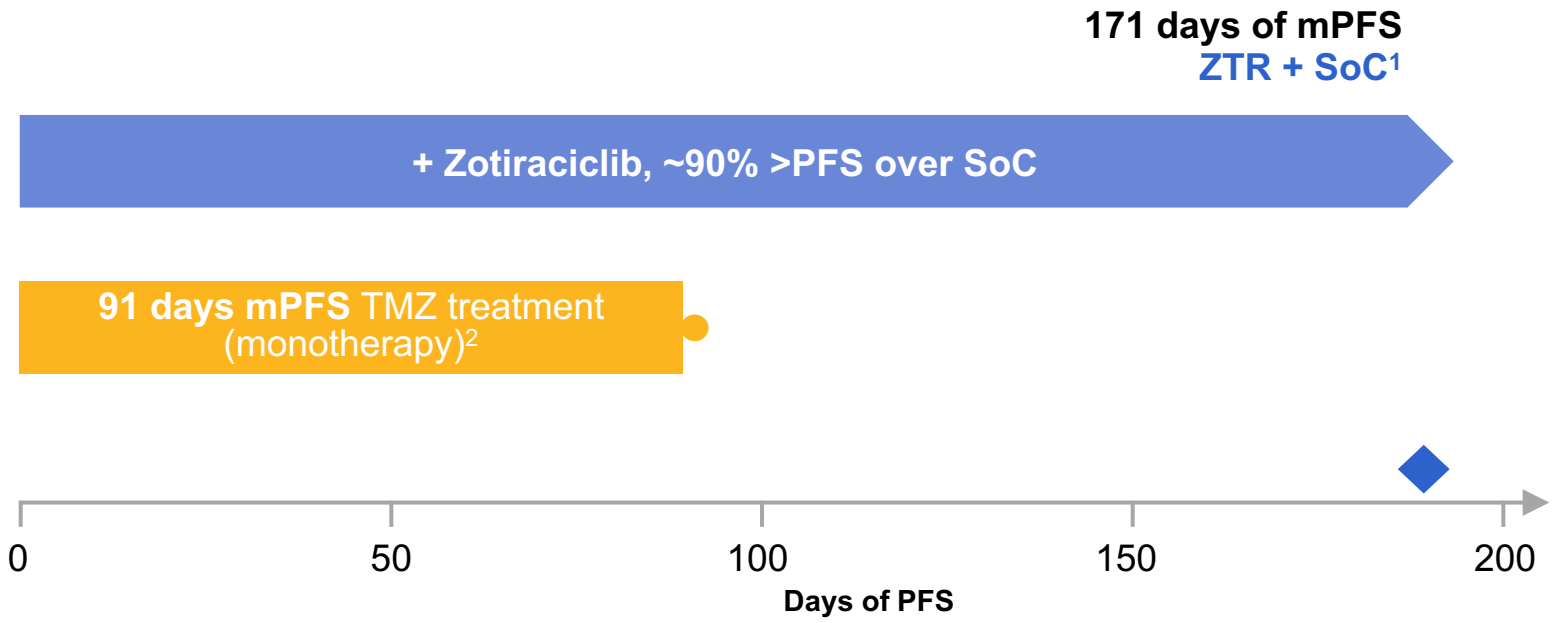
Enriched Tumor Response, ~2x Improvement in mPFS ZTR in rHGG IDHmut Tumors Versus TMZ Control

All Patients (overall) | **IDH Mutated** (enriched) | Unmethylated (predictive)

+ZTR ~2x Doubling of Benefit in IDHmut Sub-group



- ZTR, NCI Trial mPFS additional improvement[1] n = 20, including 5 patients at 12 months, 1st and 2nd recurrence – (73% / 27%)
- Pre-specified TMZ historical comparator[2] 1st recurrence (100%)

"No question IDHmut recurrent glioma patients are the most logical place for next development… *options today are very limited."*

– DE KOL #1

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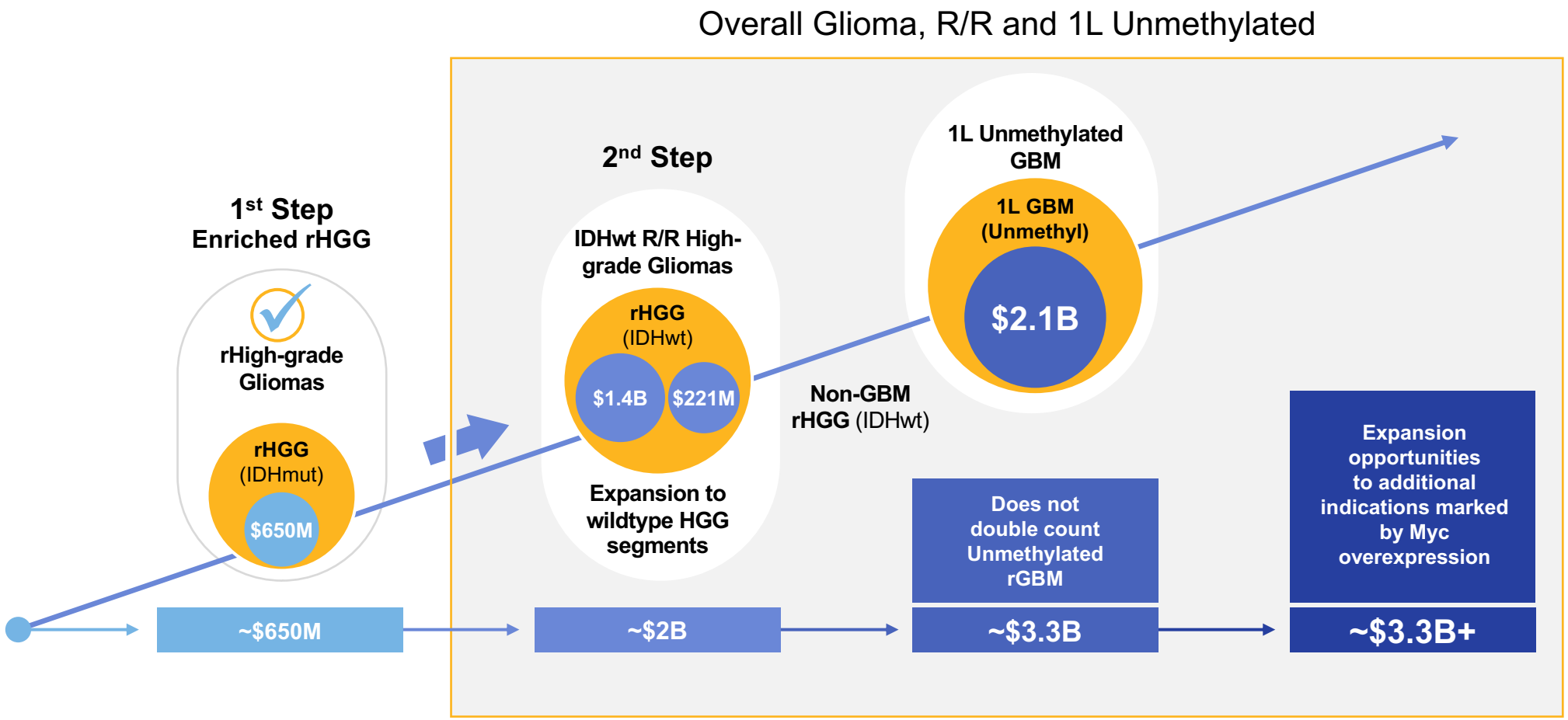
Recurrent High-grade Gliomas Represent a Significant 1st Step into a Large Glioma Market Opportunity: ~$3.3B



Methodology: 90% of patients initiate 1L therapy and 75% initiate 2L therapy5,6;; assume 5 months on therapy for rGBM patients because PFS is ~3 mos (+2 mos for ZTR efficacy)[7], 7 months for AA because PFS is ~5 mos (+2 mos for ZTR efficacy)[8], and ~6 month PFS for unmethylated (+2 for ZTR efficacy)[1]; trial duration based on analog analysis from ct.gov | Sources: 1) Hegi et al. (2005); 2) Rivera et al. (2010) *Neuro Oncol*; 3) GLOBOCAN 2018; 4) NCCN; 5) Fabbro-Peray, Pascale, et al. *J of Neuro-oncol* 142.1 (2019); 6) 91-101.Girvan, Allicia C., et al., Drugs in context 4 (2015).; 7) Wick, Wolfgang, et al, *NEJM* 377.20 (2017): 1954-1963.; 8) Chamberlain, Marc C. *J Neuro oncol* 122.2 (2015):329-338.

Summary: Zotiraciclib, recurrent high-grade gliomas (rHGG)

NCI Trial Data has been Exceptionally Well-received by Leading US and EU KOLs

All Patients (overall) → **IDH Mutated** (enriched) → **Unmethylated** (predictive)

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- **Strong efficacy across all patients** (mPFS of 5.9 mo., ~55% PFS6 for all vs. ~21% seen in historical comparators)
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Thank You

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