ONC201: The First Imipridone for the Treatment of H3 K27M-mutant High Grade Glioma

Oncoceutics

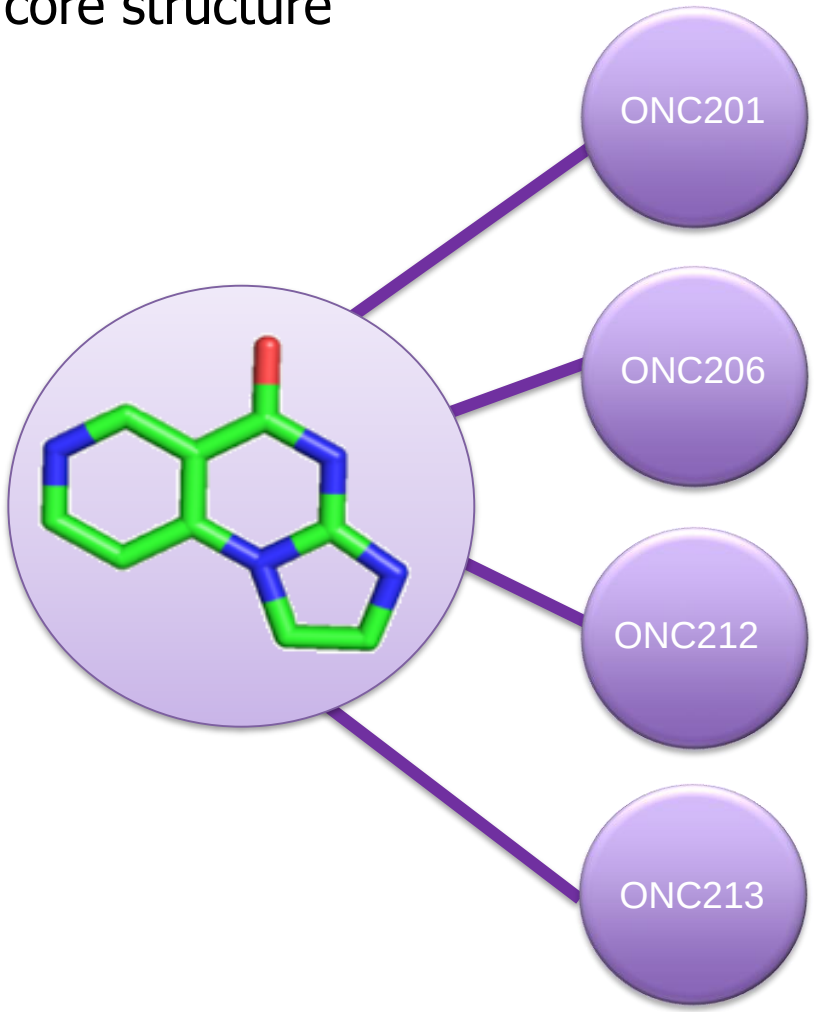
Pediatric Subcommittee of the
Oncologic Drugs Advisory Committee

June 20, 2019

Imipridones: New Class of GPCR-targeting Small Molecules for Oncology

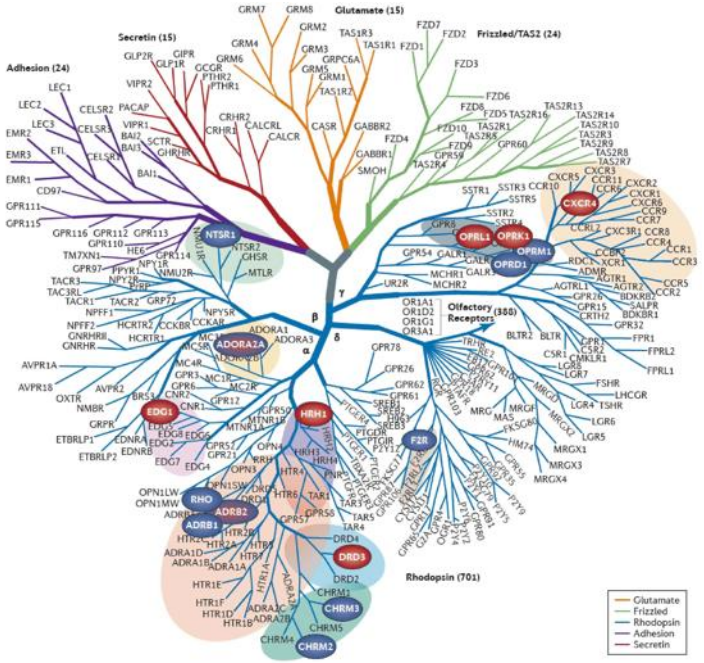
Members of the imipridone family share a unique tri-heterocyclic core structure

- Oral bioavailability
- Wide therapeutic window
- Blood brain barrier penetrance
- Selective GPCR engagement

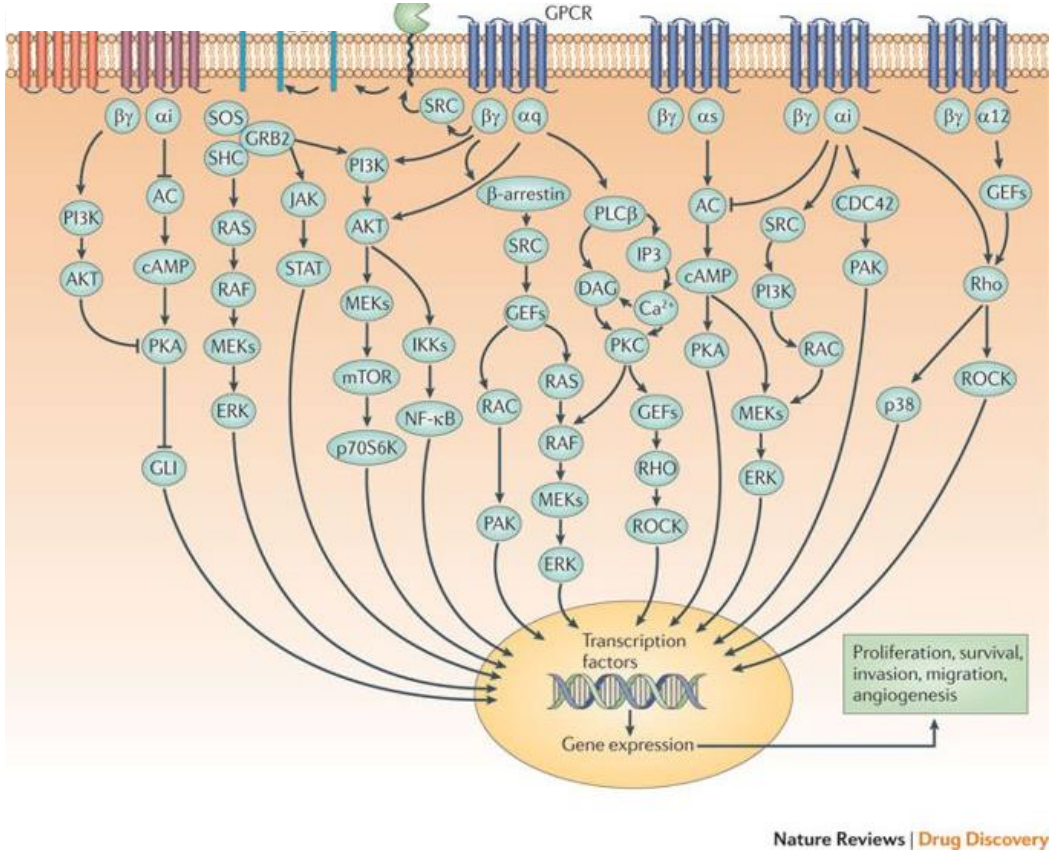


G Protein-Coupled Receptors Are Rationale Targets in Oncology

GPCRs are the largest superfamily of membrane receptors in humans

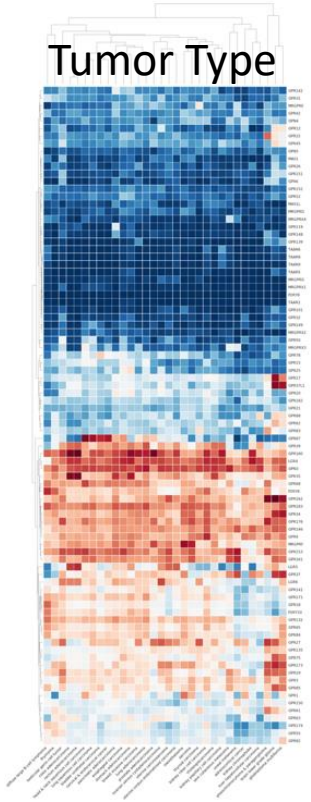


GPCRs control myriad mitogenic pro-survival and stress response pathways



Nature Reviews | Drug Discovery

GPCRs are selectively hijacked by malignant cells



Therapeutic opportunity to reverse dysregulation via specific targeting

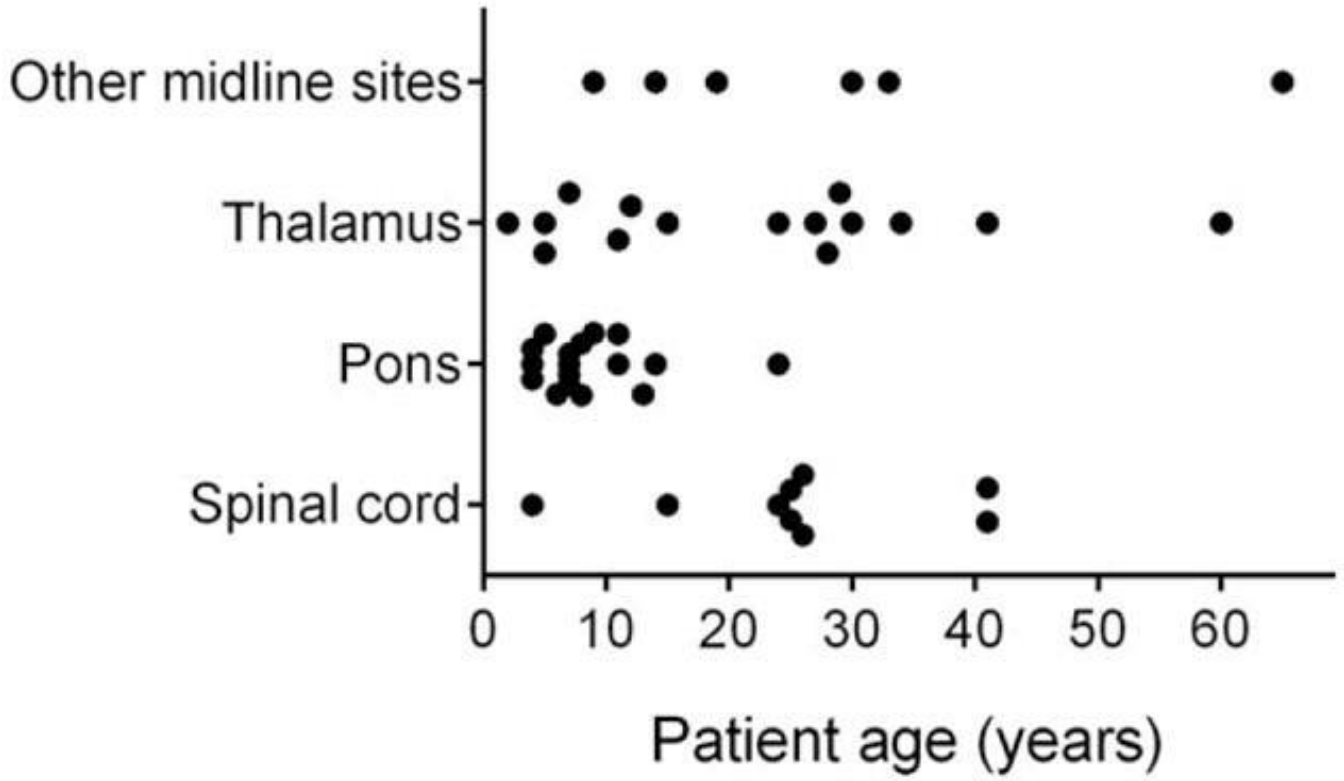
Lappano and Maggiolini, *Nature Reviews Drug Discovery*, 2011

Gutkind, *Experimental Biology*, 2018

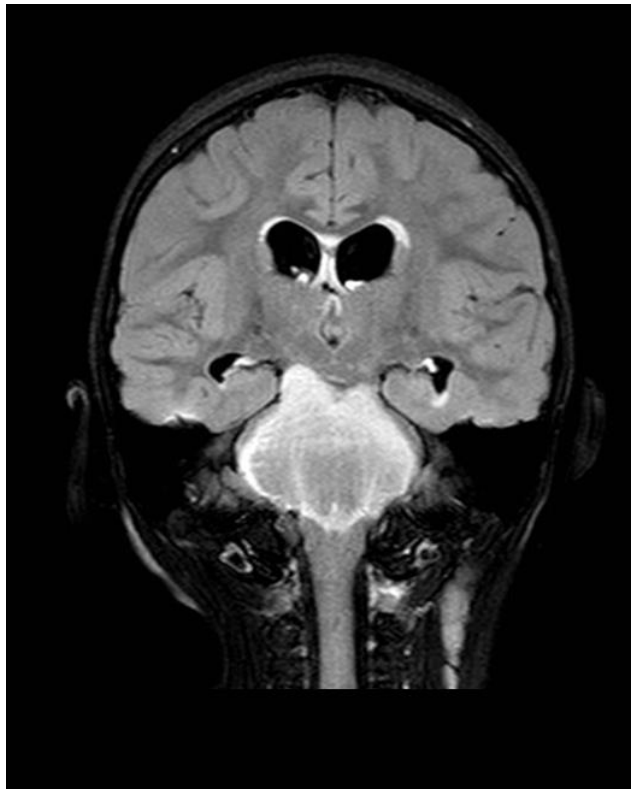
H3 K27M-Mutant Glioma

The H3 K27M mutation predominantly occurs in young patients with gliomas located in midline brain structures

H3 K27M-mutant Glioma



Diffuse Intrinsic Pontine Glioma (DIPG)



Agenda

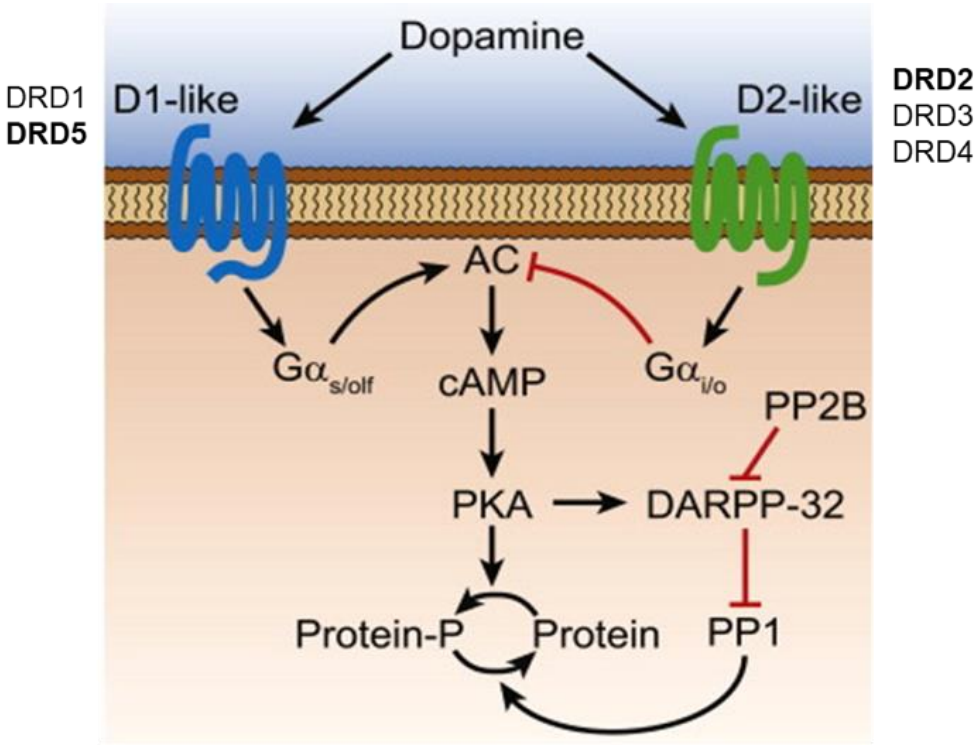
- **Introductory Remarks**
  - Wolfgang Oster, MD, PhD, Oncoceutics
- **ONC201 Mechanism of Action and Rationale for H3 K27M-mutant Glioma**
  - Joshua Allen, PhD, Oncoceutics
- **Clinical Results in Adult H3 K27M-mutant Glioma Clinical Trials**
  - Patrick Wen, MD, Dana Farber Cancer Institute
- **Ongoing and Planned Pediatric Clinical Trials**
  - Sabine Mueller, MD, PhD, University of California, San Francisco (UCSF)
- **Experts Available for Q&A**
  - Yazmin Odia, MD, MS, Miami Cancer Institute; Michael Prados, MD, UCSF; Aparna Anderson, PhD

ONC201 Mechanism of Action and Rationale for H3 K27M-Mutant Glioma

Joshua Allen, PhD, Oncoceutics

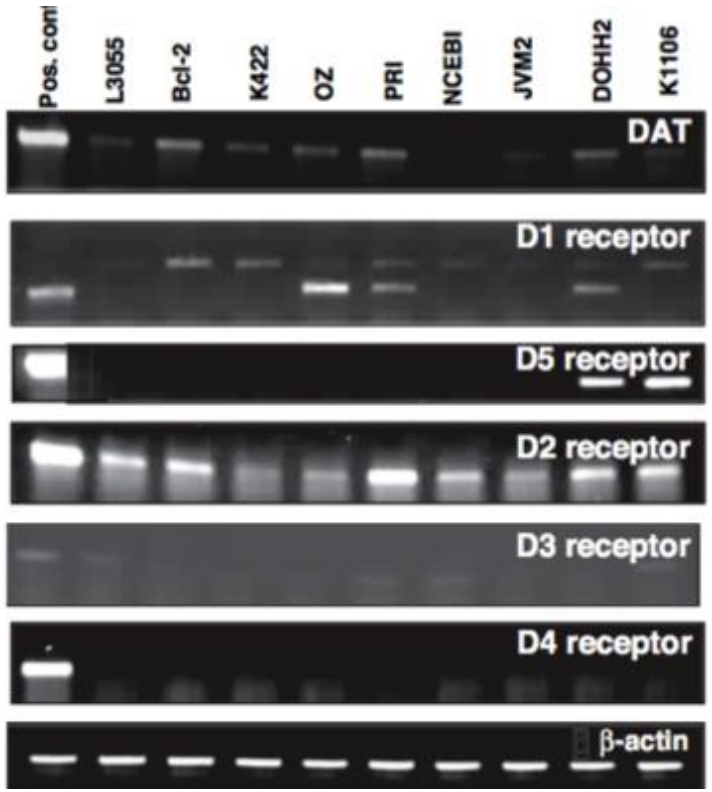
Dopamine Receptor D2 Promotes Tumor Growth in High Grade Glioma

Dopamine receptors are GPCRs divided into two functionally opposing subfamilies

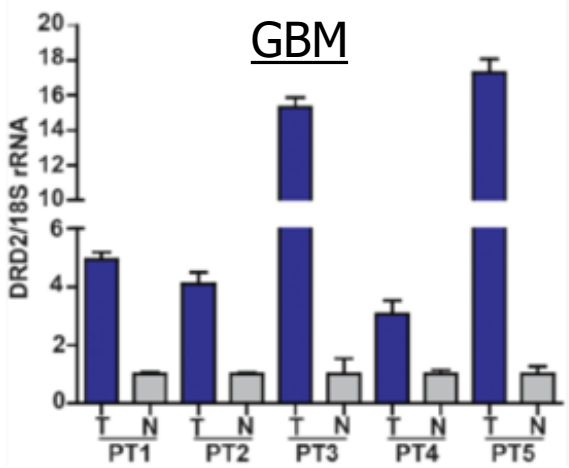


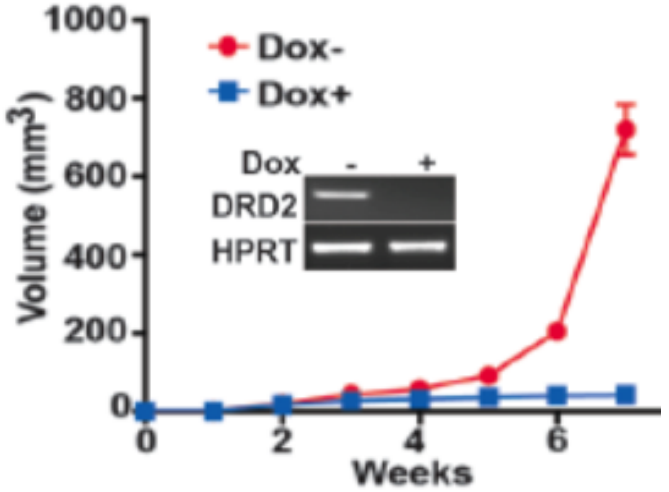
DRD2 is a selectively overexpressed GPCR target for oncology

Human Cancer Cell Lines



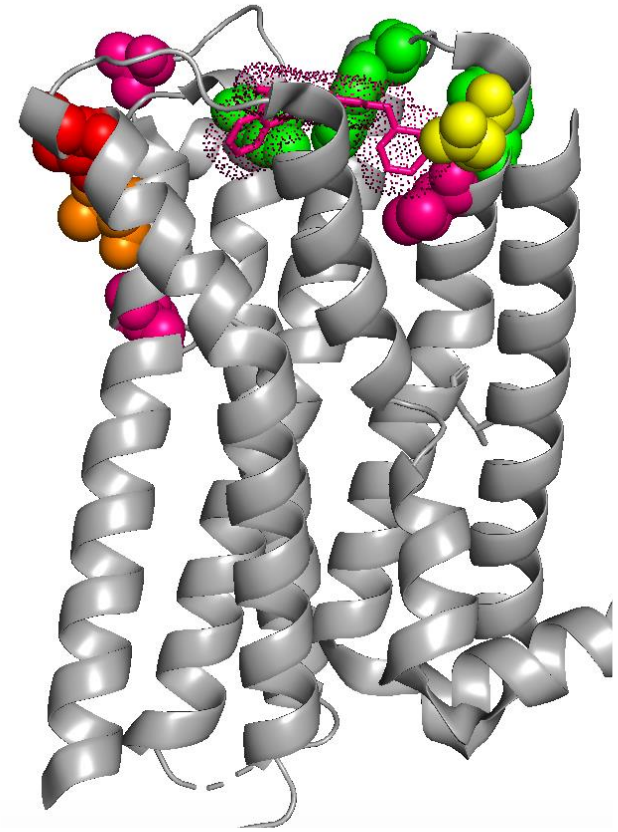
GBM



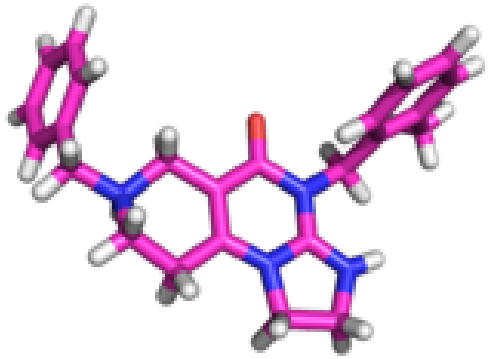


ONC201: First Clinical Bitopic DRD2 Antagonist

ONC201 selectivity antagonizes DRD2 via orthosteric and allosteric residues



DRD2



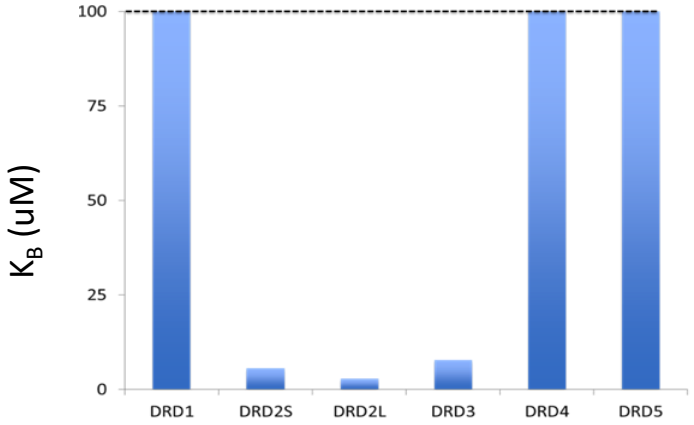
ONC201

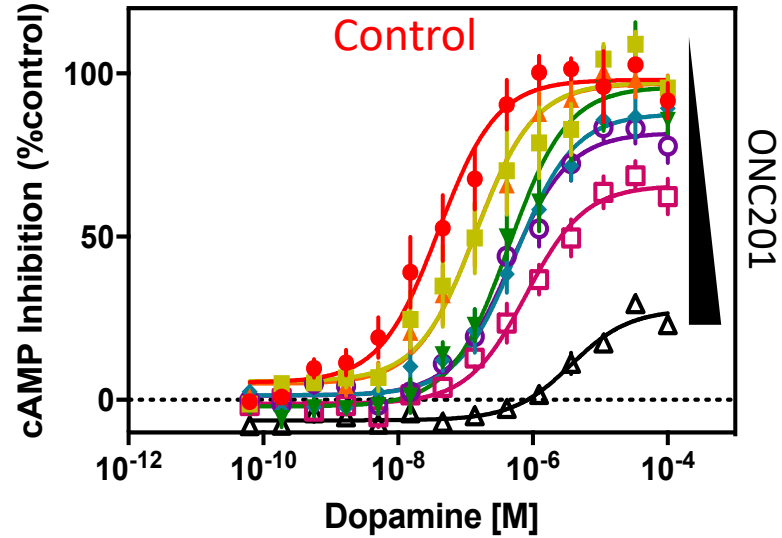
Orthosteric Residues

DR Conservation of ONC201-critical residues

20% 40% 60% 80%100%

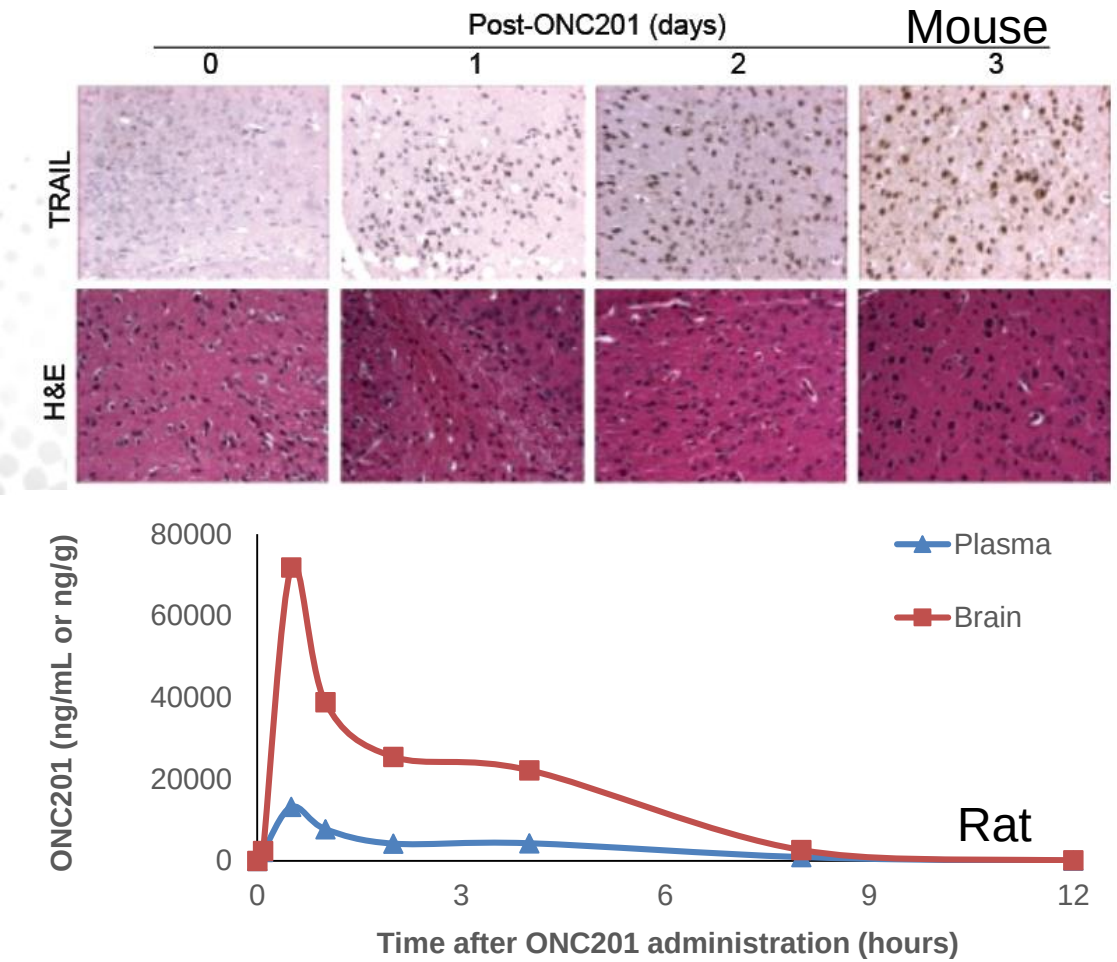
Enables selective and unique DRD2 antagonism



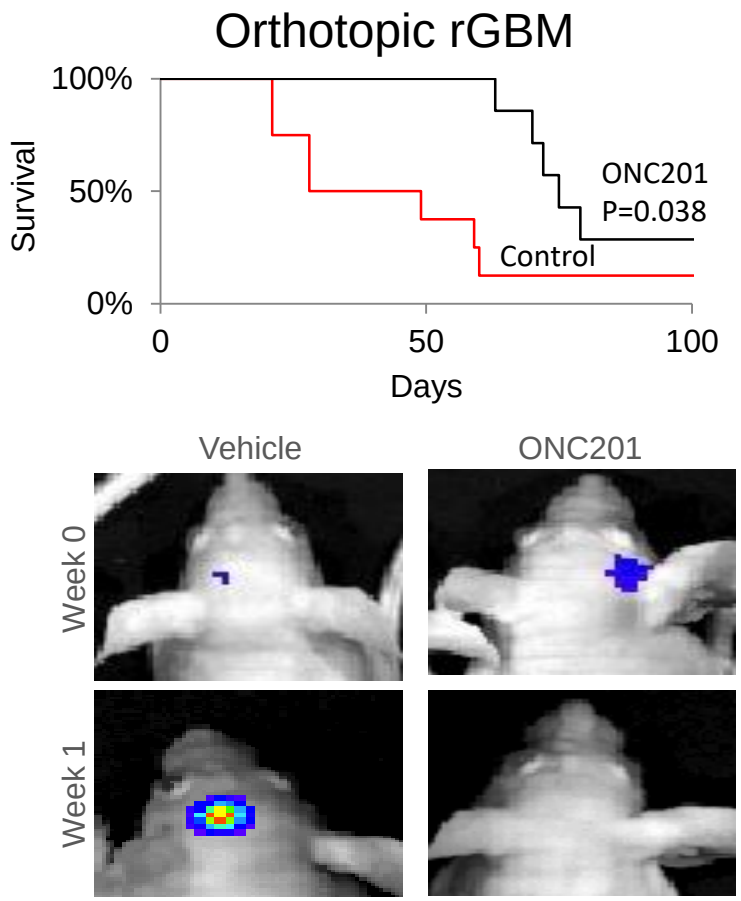


Effective in Preclinical Models of High Grade Glioma

Achieves biologically active brain concentrations

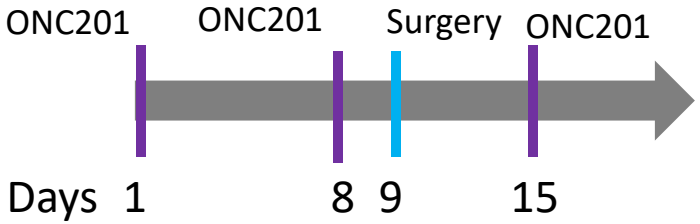


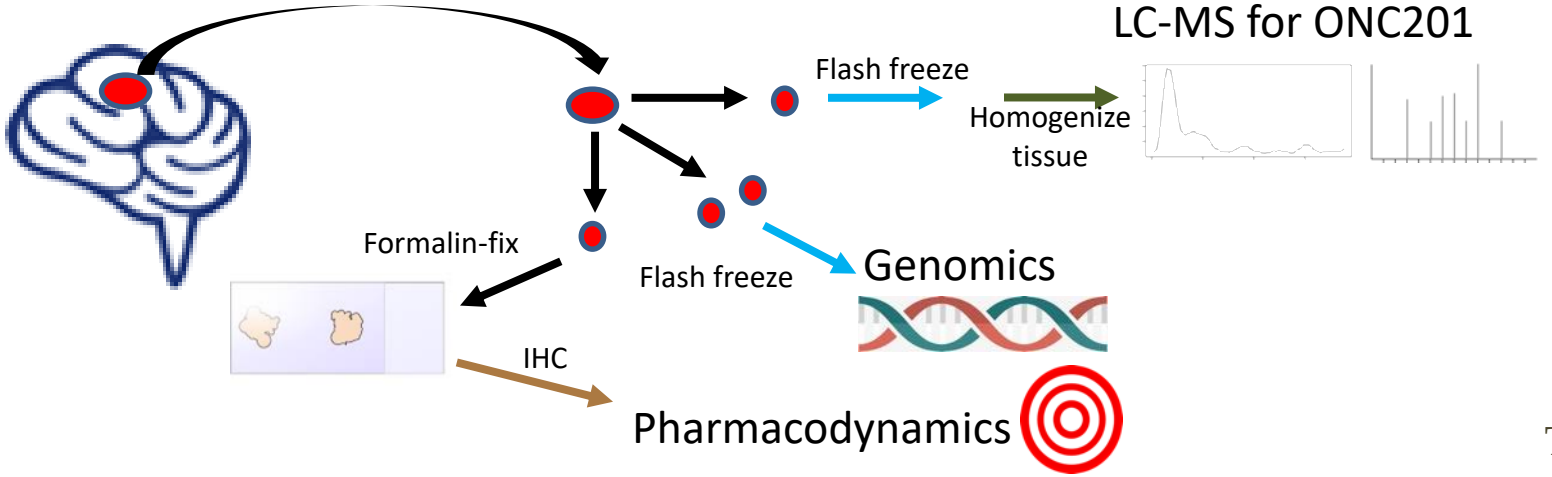
Active in preclinical models of high grade glioma

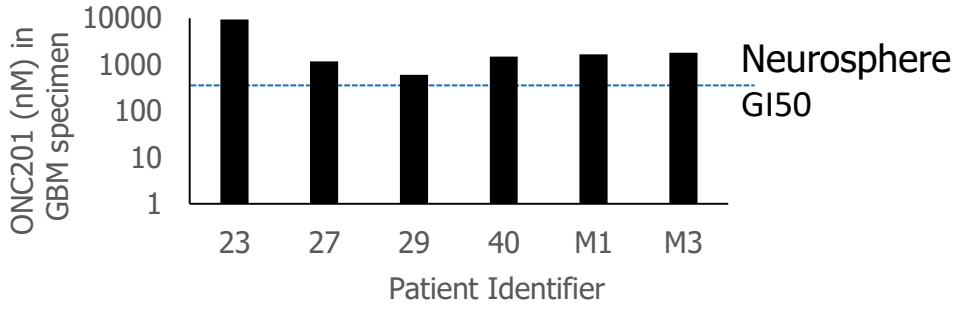


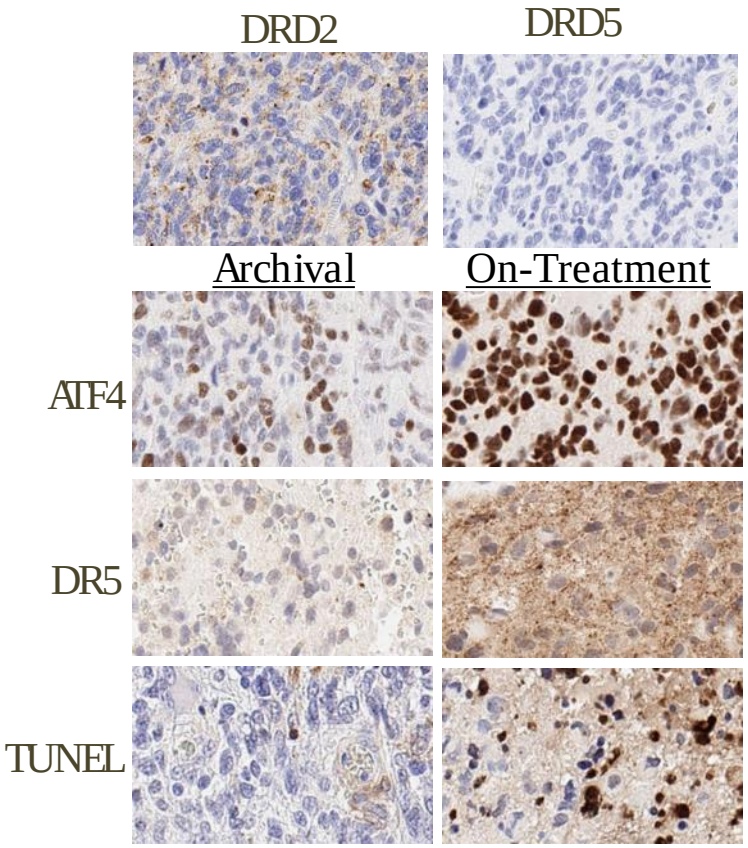
Therapeutic Intratumoral Concentrations and Pharmacodynamics in HGG Patients

Neoadjuvant ONC201 achieved therapeutic intratumoral concentrations and pharmacodynamics in recurrent GBM patients



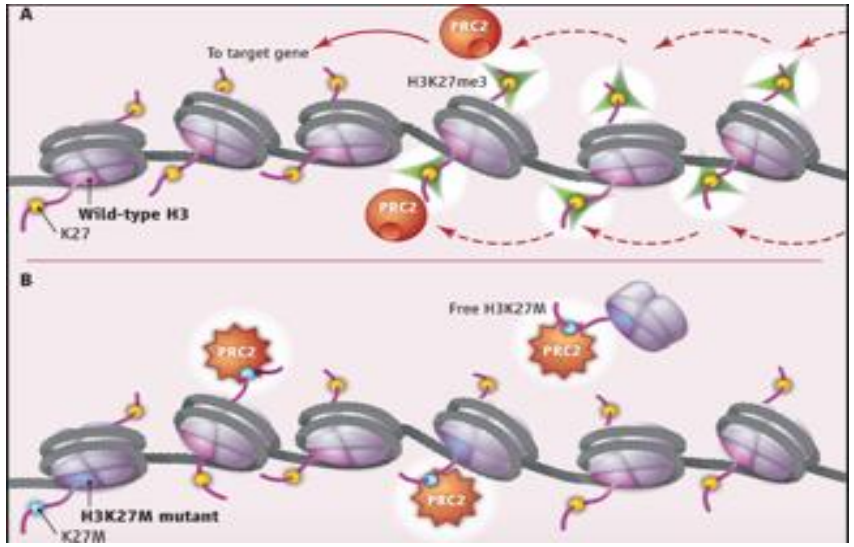




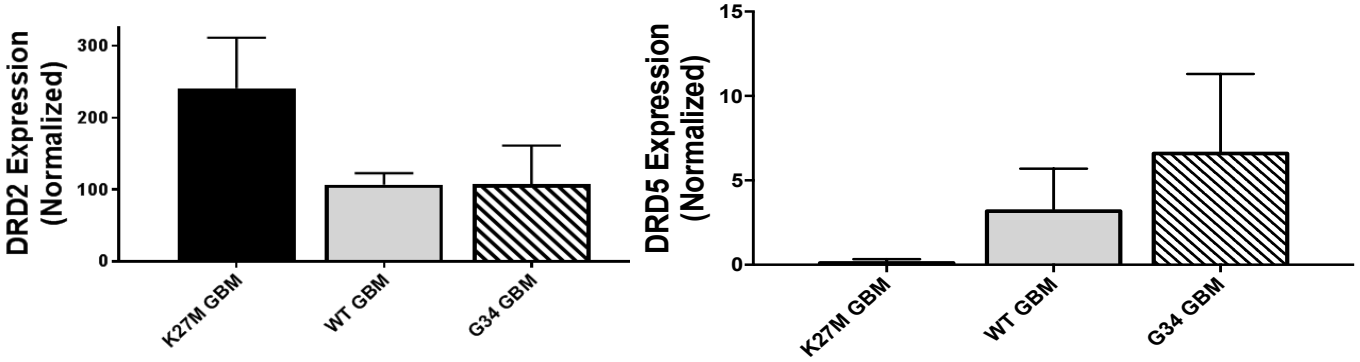


H3 K27M-mutant Gliomas: Dopamine Receptor Dysregulation and Response to ONC201

H3 K27M-mutant gliomas exhibit epigenetic dysregulation and altered dopamine receptor expression

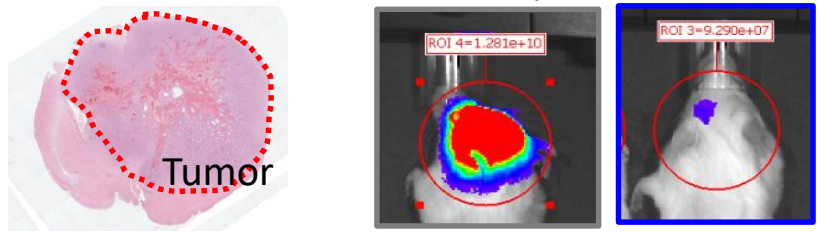


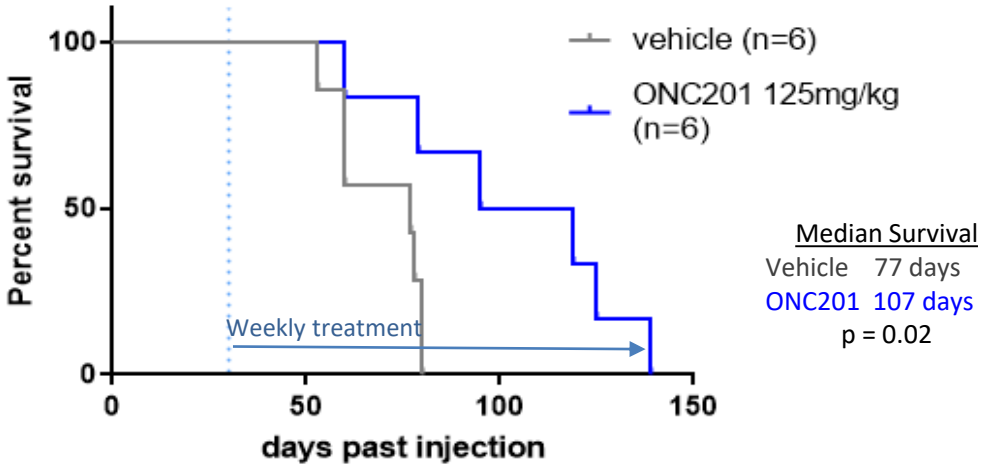
Morgan and Shilatifard, *Science,* 2013



H3 K27M-mutant gliomas respond to ONC201

Tp53, PDGFRA H3K27M (PPK) Tumors - IUE





Median Survival
Vehicle 77 days
ONC201 107 days
p = 0.02

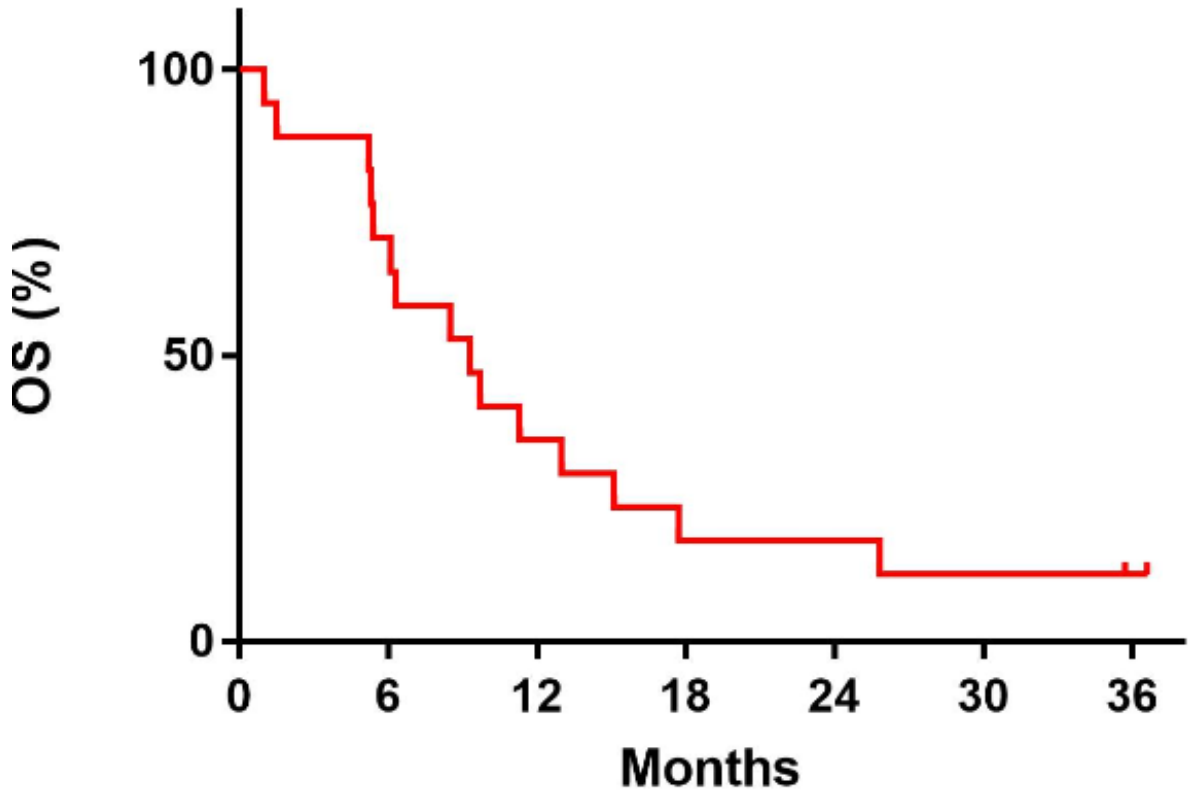
Clinical Results in Adult H3 K27M-Mutant Glioma Clinical Trials

Patrick Wen, MD, Dana Farber Cancer Institute

First ONC201 Phase II Clinical Trial: Adult Recurrent Glioblastoma

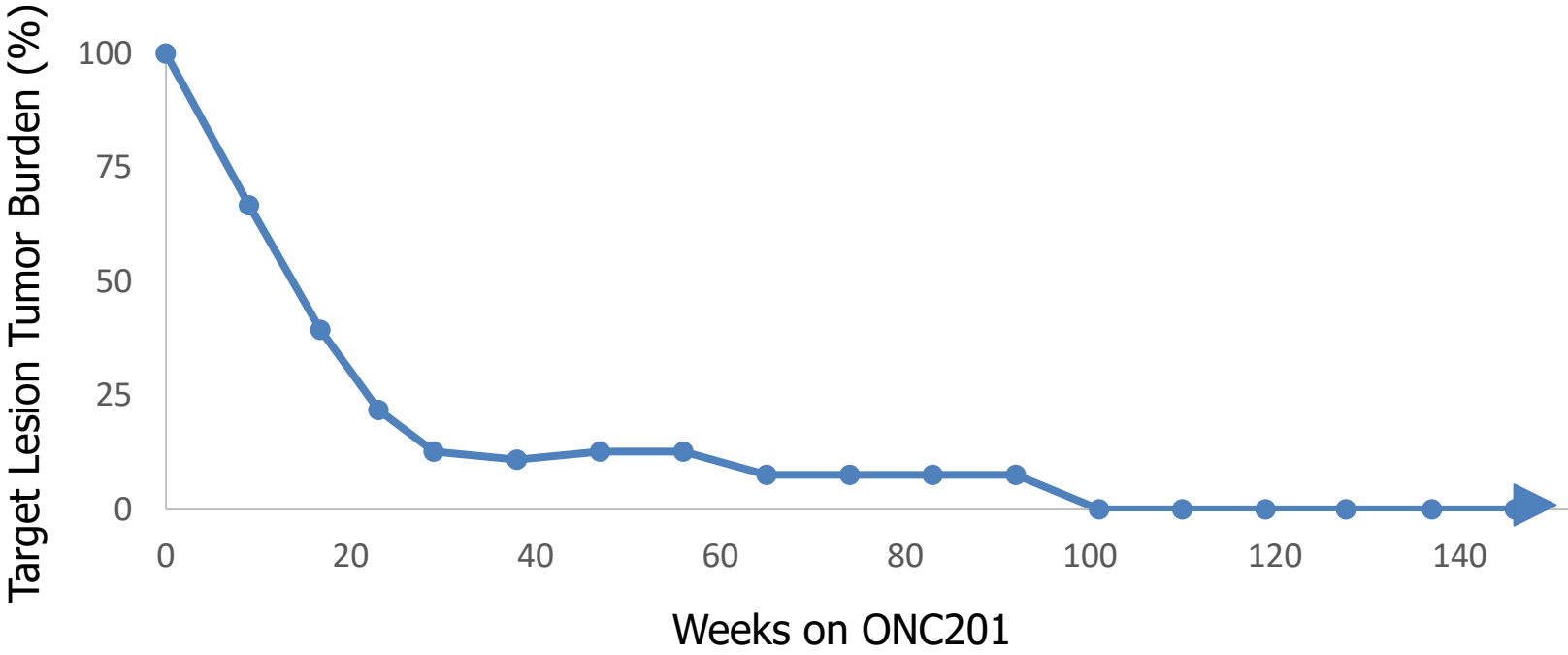
- ONC201 was evaluated initially at 625mg once every 3 weeks in 17 adult recurrent glioblastoma patients
- Median OS was 9.7 months; compared to historical outcomes of 5-7 months

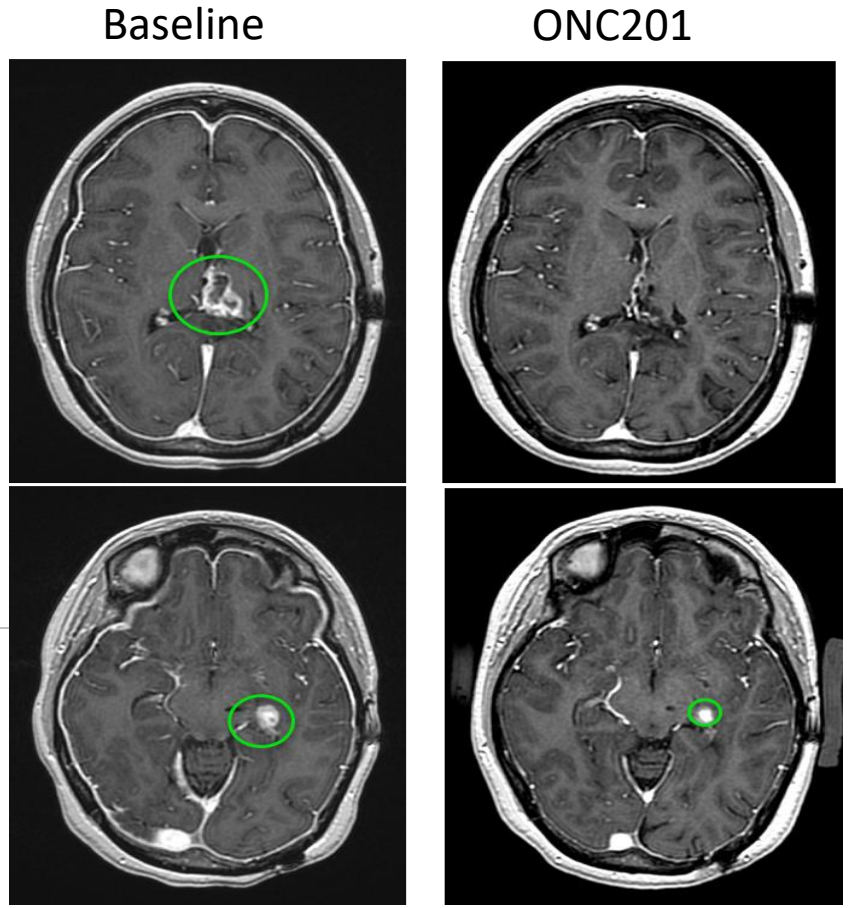
Age, median (range)	57 (22-74) y/o
Male : Female	9 : 8
KPS, median (range)	90 (70-100)
Number of baseline lesions, median (range)	1 (1-3)
Prior low grade	4
Prior TMZ/RT	17
Extent of resection at the latest surgery	
Subtotal	9
Gross total	7
Unknown	1
Salvage surgery at time of recurrence	6
MGMT	
methylated	2
unmethylated	13
unknown	2
Corticosteroid use	13



Durable Objective Response in First H3 K27M-Mutant Glioma Treated with ONC201

Outlier durable response observed in recurrent glioblastoma patient



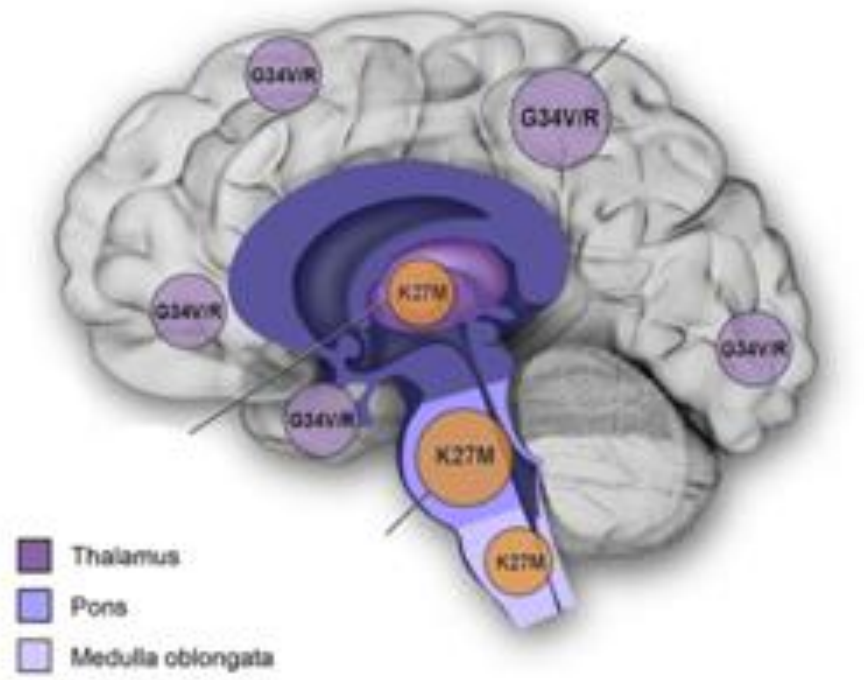


Molecular profiling revealed exclusive H3 K27M mutation

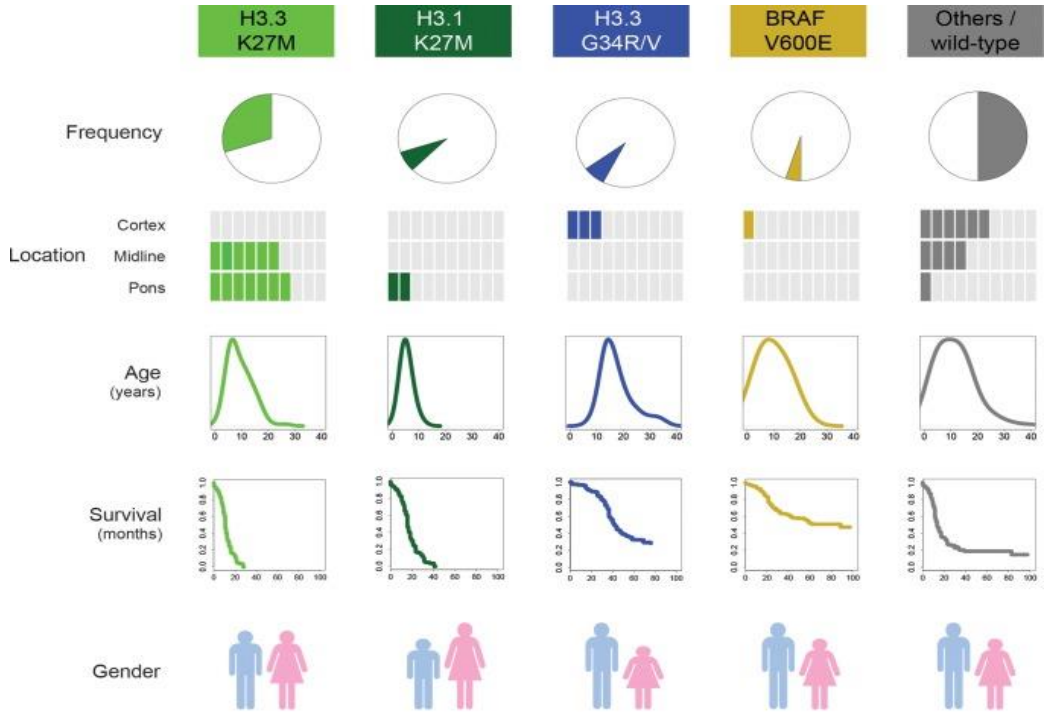
H3 K27M-Mutant Glioma Is A Grade IV Glioma

Diffuse midline glioma, H3 K27M-mutant: Grade IV glioma by 2016 WHO criteria

H3 K27M is detected in 50-90% of midline gliomas



H3 K27M is the most frequent histone mutation in pediatric glioma and carries a poor prognosis



No spontaneous or drug-induced responses reported in recurrent H3 K27M-mutant glioma

Lulla et al., *Science Advances,* 2016

Jones et al., *Neuro-oncology*, 2017

Adult Recurrent H3 K27M-Mutant Glioma: ORR By RANO

15 patients who meet the following prespecified sub-group analysis criteria were enrolled by 12/15/18

- Histone H3 K27M mutation by IHC or sequencing test in CLIA lab
- Measurable and progressive disease by RANO
- At least prior radiotherapy
- ≥3 months from prior radiation
- Corticosteroid dose must be stable or decreasing for at least 3 days prior to baseline scan
- KPS ≥ 60
- Evidence of spinal cord, pontine, or leptomeningeal disease, or evidence of CSF dissemination excluded
- Single agent ONC201 until disease progression (no current anti-cancer therapies, including bevacizumab)

Adult Recurrent H3 K27M-Mutant Glioma: Demographics

Ongoing enrollment of adult recurrent H3 K27M-mutant glioma patients to receive 625mg ONC201 Q1W PO

NCT02525692

- Single arm, open label
- Target accrual: n=30
- Primary endpoint: PFS6
- Sites: MGH, DFCI, Miami Cancer Institute, UCLA

NCT03295396

- Single arm, open-label
- Target accrual: n=39
- Primary endpoint: ORR
- Sites: NYU, Levine Cancer Institute, MDACC, UCSF, Columbia, Stanford, UMinnesota, UMichigan

	All Patients	ONC006	ONC013	Expanded Access
	N=15	N=5	N=9	N=1
Gender (N%)				
Female	7 (47%)	2 (40%)	5 (56%)	-
Male	8 (53%)	3 (60%)	4 (44%)	1 (100%)
Age, years, median (range)	28 (17-58)	28 (17-58)	28 (19-55)	37
Weight, kilograms, median (range)	71.5 (56.2-106.1)	71.5 (67.3-89.9)	71 (56.2-106.1)	95.5
KPS, median (range)	90 (70-90)	90 (70-90)	90 (80-90)	80
Primary tumor location (N%)				
Thalamus	8 (53%)	2 (40%)	5 (55%)	1 (100%)
Brain Stem (Non-DIPG)	4 (27%)	2 (40%)	2 (22%)	-
Cerebellum	1 (7%)	-	1 (11%)	-
Frontal Lobe	1 (7%)	1(20%)	-	-
Basal Ganglia	1 (7%)	-	1 (11%)	-
Histology (N%)				
Diffuse Glioma	7 (46%)	1(20%)	6 (66%)	-
Glioblastoma	3 (20%)	2 (40%)	1(12%)	-
Astrocytoma	3 (20%)	-	2(22%)	1(100%)
Pilocytic astrocytoma	1 (7%)	1(20%)	-	-
Gliosarcoma	1 (7%)	1(20%)	-	-
Multifocal disease (N%)				
Yes	7 (47%)	2 (40%)	4 (44%)	1 (100%)
No	8 (53%)	3(60%)	5 (56%)	-
Number of lesions, median, (range)	1 (1-3)	1 (1-3)	2 (1-3)	2 (2)
Number of recurrences, median (range)	1 (1-3)	2 (1-3)	1 (1-2)	3
Time from prior radiation, weeks, median, (range)	51.7 (12-101.4)	44 (19.0-52)	58 (12-101.4)	38.4
Levetiracetam (N%)				
Yes	3 (20%)	2 (40%)	1 (11%)	-
No	12 (80%)	3 (60%)	8 (89%)	1 (100%)
Dexamethasone, mg, median (range)	4 (0-16)	3(2.5-4)	4 (0-16)	0 (0)

Enrollment cutoff: 12/15/2018

Adult Recurrent H3 K27M-Mutant Glioma: Criteria for Radiographic Evaluation

- Tumor extent or response to therapy relies on MRI changes in T2-weighted/FLAIR images, which have poor sensitivity in detecting response/progression that can be enhanced with contrast agents
- Midline gliomas often exhibit contrast-enhancing regions and non-contrast-enhancing regions that partly do not overlap
- Response criteria have not been developed for midline gliomas
  - Contrast-enhancing gliomas are assessed by RANO-HGG, developed initially for supratentorial glioblastoma that often contrast enhance
  - Non-contrast-enhancing gliomas are assessed by RANO-LGG, developed initially for low grade gliomas that often do not contrast enhance similar to midline high grade gliomas

Adult Recurrent H3 K27M-Mutant Glioma: ORR

- Blinded, independent central review performed for contrast-enhancing disease by RANO-HGG and non-contrast-enhancing disease by RANO-LGG
- Six patients remain on-treatment; ORR not final

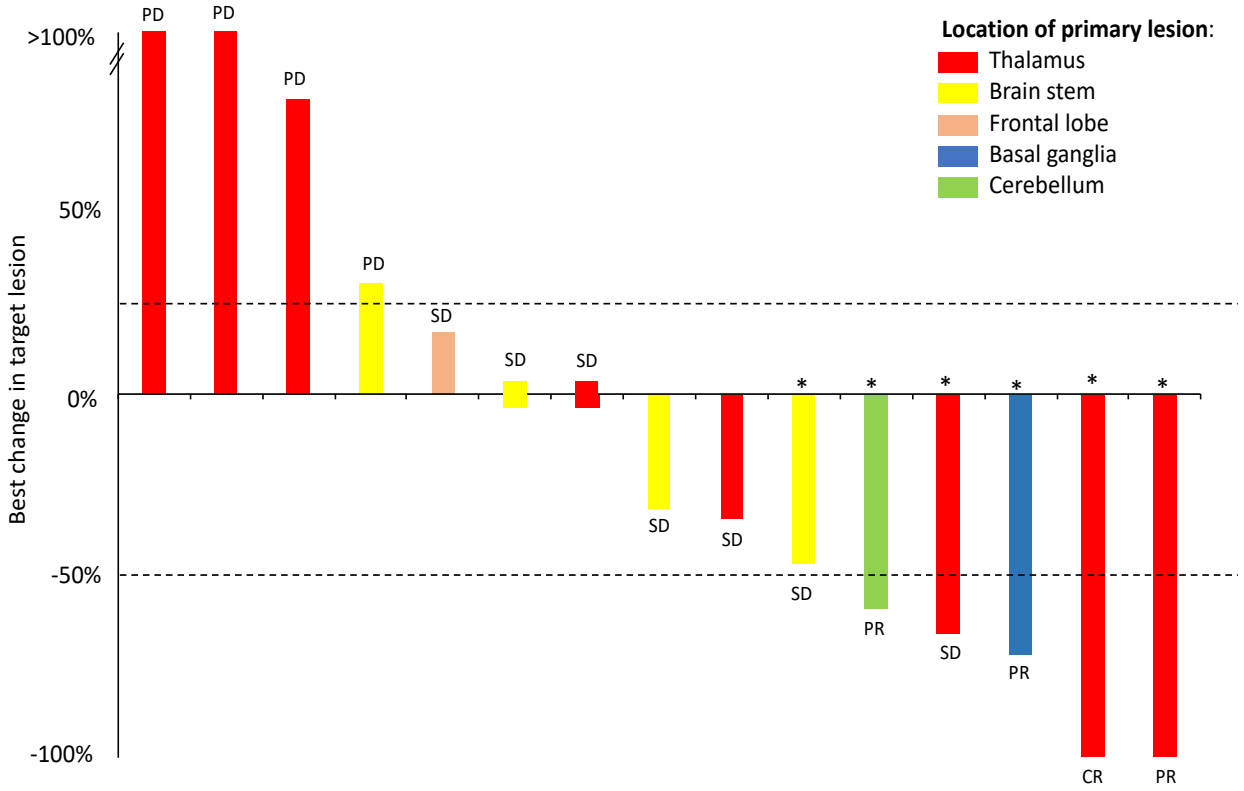
	Best RANO Response (N=15)		
	CE*	NCE**	CE* or NCE**
Complete Response	1	1	2
Partial Response	3	1	2
Minor Response	-	3	3
Stable Disease	7	4	5
Progress Disease	4	5	3
Unevaluable	0	1	0
Objective Response Rate (MR + PR + CR) (95% CI)	**27% (8-55%)**	**36% (13-65%)**	**47% (21-73%)**
Disease Control Rate (SD + MR + PR + CR) (95% CI)	**73% (45-92%)**	**64% (35-87%)**	**80% (52-96%)**

*CE: Contrast-enhancing disease evaluated by RANO-HGG (Wen et al *Journal of Clinical Oncology*, 2010)
**NCE: Non-contrast-enhancing disease evaluated by RANO-LGG (van den Bent, *Lancet Oncology*, 2011)

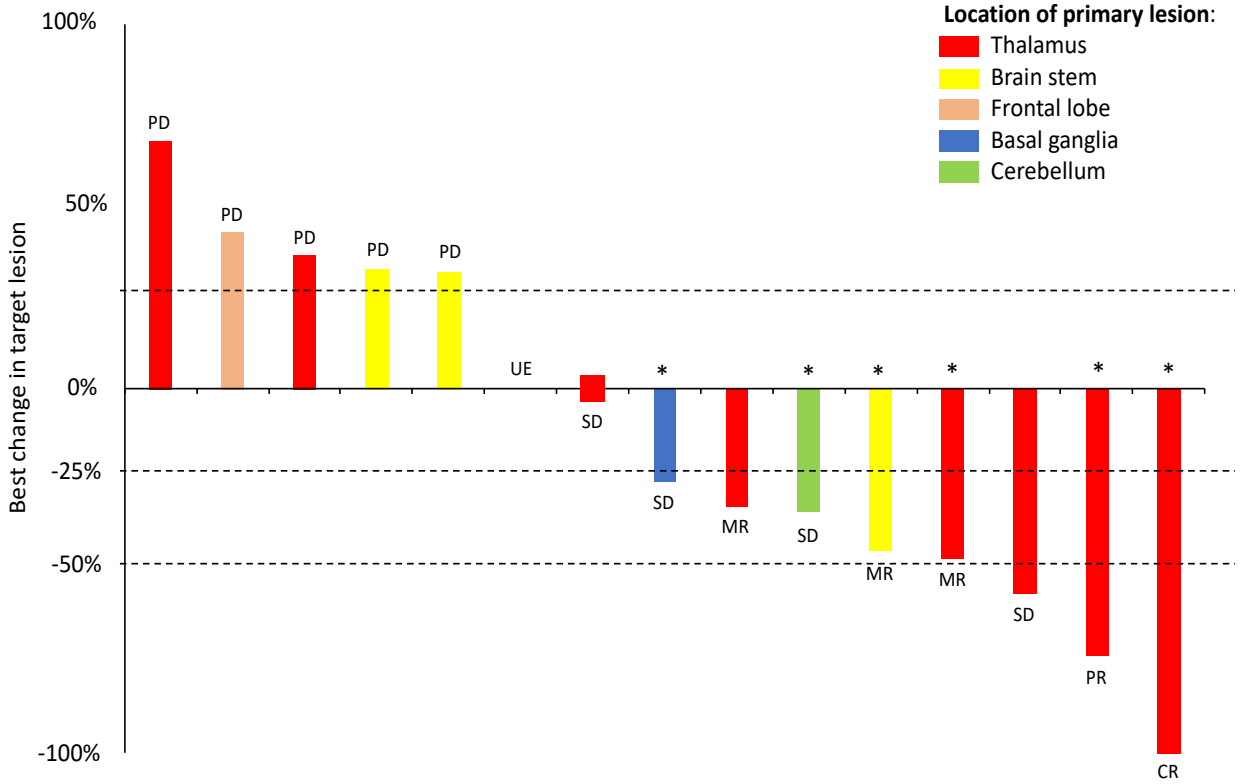
Enrollment cutoff: 12/15/2018

Adult Recurrent H3 K27M-Mutant Glioma: Best Change in Overall Tumor Size

Contrast-enhancing assessment



Non-contrast-enhancing assessment

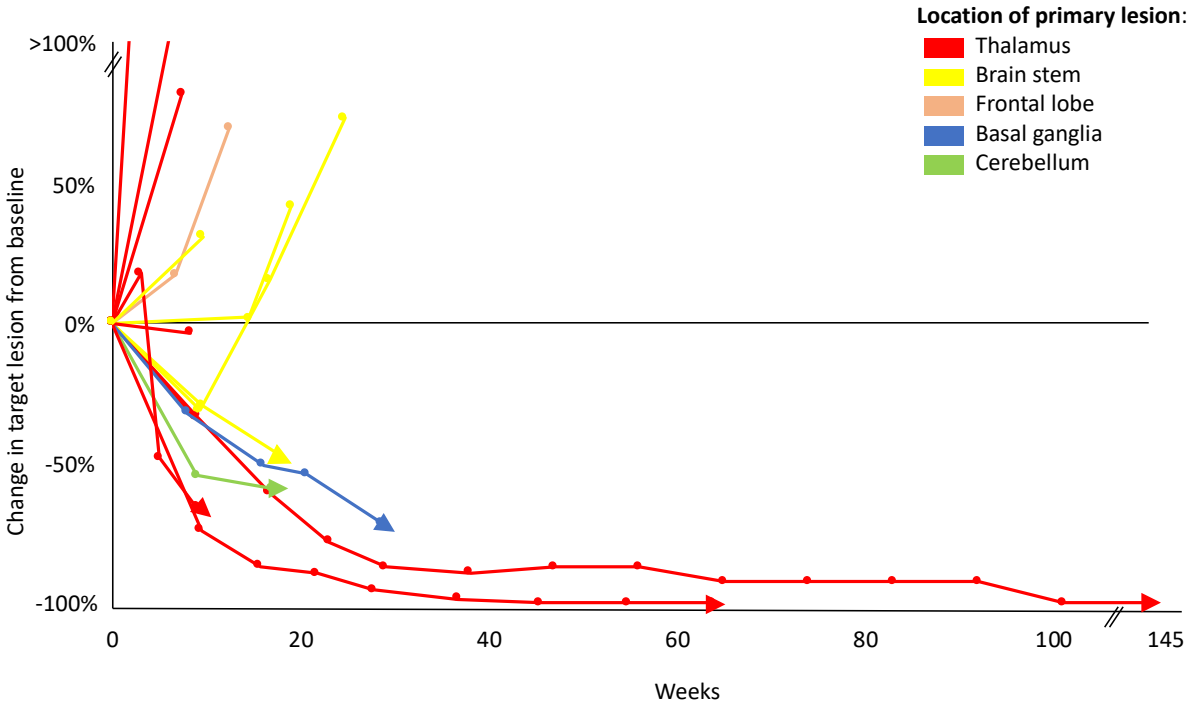


RANO: CR – complete response; PR – partial response; MR – minor response; SD – stable disease; PD – progressive disease
*patient remains on study

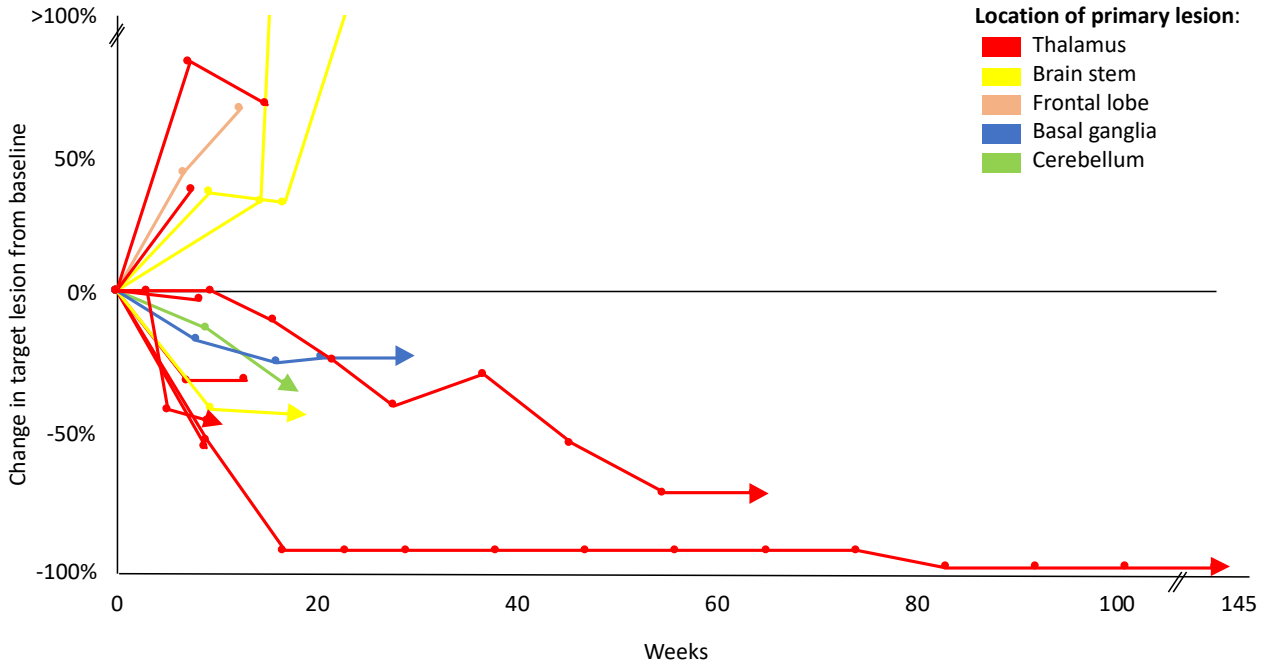
Enrollment cutoff: 12/15/2018

Adult Recurrent H3 K27M-Mutant Glioma Trials: Change in Tumor Size Over Time

Contrast-enhancing assessment

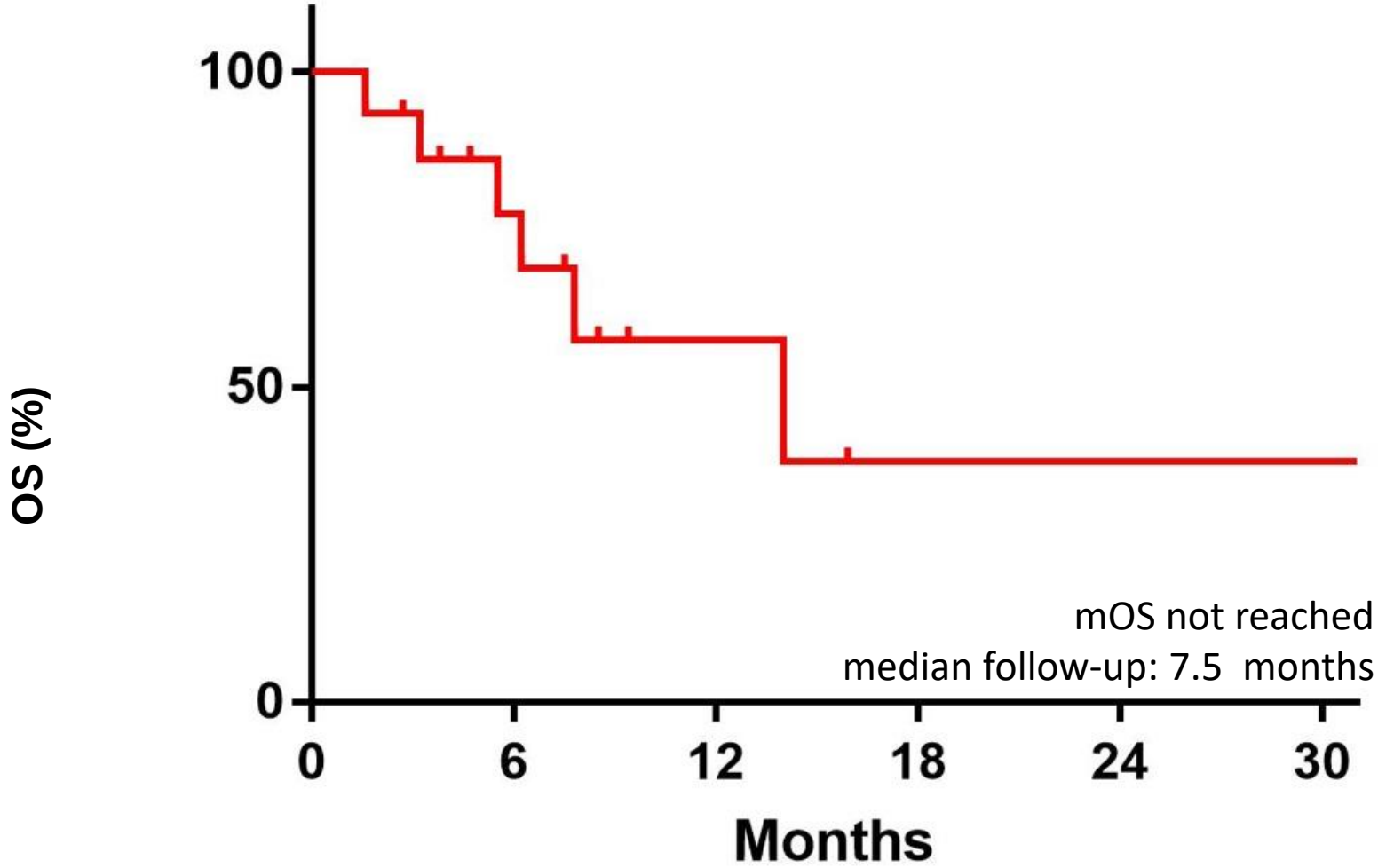


Non-contrast-enhancing assessment



Enrollment cutoff: 12/15/2018

Adult Recurrent H3 K27M-Mutant Glioma Trials: OS



Enrollment cutoff: 12/15/2018

Well Tolerated at Weekly Oral Recommended Phase II Dose

Very well tolerated at 625mg Q1W PO in neoadjuvant or recurrent settings

Consistent with experience in >350 advanced cancer patients who have received ONC201

AEs in Recurrent Glioblastoma Patients (n=20)

	All Adverse Events		Possibly/Probably-Related	
Adverse Events, N (%)	All Grades	Grade 3-4	All Grades	Grade 3-4
Nervous system disorders				
Dizziness	4 (20%)	0 (0%)	1 (5%)	0 (0%)
Metabolism and nutrition disorders				
Hypophosphatemia	9 (45%)	0 (0%)	7 (35%)	0 (0%)
Anorexia	4 (20%)	0 (0%)	3 (15%)	0 (0%)
General disorders and administration site conditions				
Gait disturbance	8 (40%)	1 (5%)	4 (20%)	0 (0%)
Injury, poisoning and procedural complications				
Fall	8 (40%)	1 (5%)	0 (0%)	0 (0%)
Gastrointestinal disorders				
Nausea	7 (35%)	0 (0%)	5 (25%)	0 (0%)
Vomiting	7 (35%)	0 (0%)	5 (25%)	0 (0%)
Diarrhea	5 (25%)	0 (0%)	5 (25%)	0 (0%)
Investigations				
Platelet count decreased	6 (30%)	0 (0%)	1 (5%)	0 (0%)
Psychiatric disorders				
Confusion	5 (25%)	0 (0%)	1 (5%)	0 (0%)

All AEs reported in >10% of patients with at least one event attributed by investigator as a least possibly-related to study drug

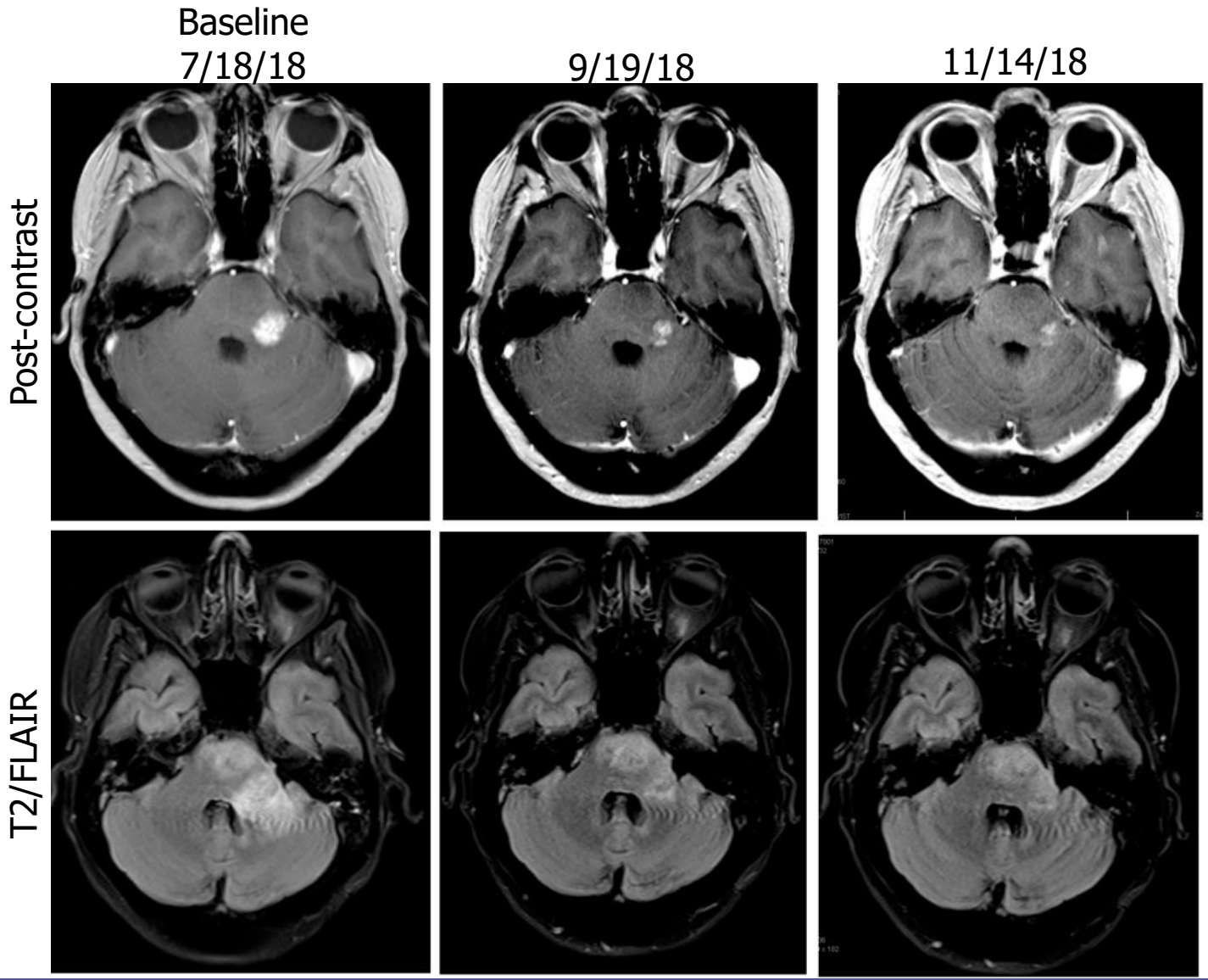
Adult Recurrent H3 K27M-Mutant Glioma Trials: Case Study 2

55yo female enrolled to NCT03295396 at recurrence following TMZ + RT

Objective response associated with normalization of neurological deficits by NANO within two cycles

- -Gait
- -Facial Strength
- -Language

Radiographic response and neurological improvements remain durable



Ongoing and Planned Pediatric Clinical Trials

Sabine Mueller, MD, PhD, UCSF

Phase I Pediatric DIPG and H3 K27M-mutant Glioma Trial: Endpoints

Open-label, multi-arm, multi-center, Phase I dose escalation and dose expansion trial (NCT03416530) in pediatric H3 K27M-mutant glioma and/or DIPG

Primary Endpoint:

Determine RP2D of ONC201 (single agent and + RT)

Secondary Endpoints:

- Safety/tolerability
- PK, PD, CSF Tumor DNA
- PFS, ORR, Duration of Response, Overall Survival
- Cranial nerve palsy scoring
- Clinical benefit/symptom scores

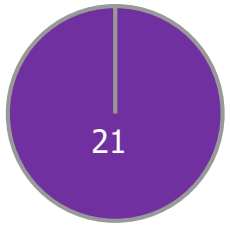
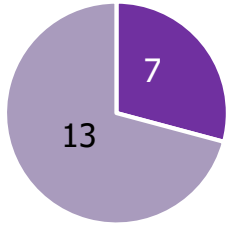
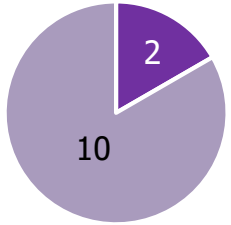
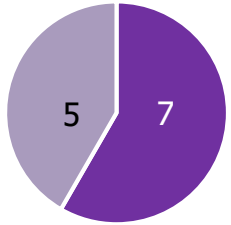
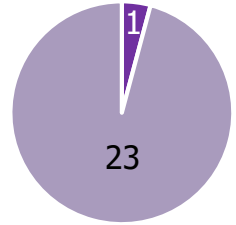
Exploratory Endpoints:

- Association of outcomes w/ tumor markers
- Association of outcomes w/ circulating markers
- Correlation between H3 K27M in tumor and CSF

List of Clinical Trial Sites	
New York University	Children's Healthcare of Atlanta / Emory University School of Medicine
MD Anderson Cancer Center	University of California, San Francisco
Miami Cancer Institute	Cincinnati Children's Hospital
University of Michigan	

Cranial palsy score developed based on first DIPG patient treated 6 weeks post-RT treated on compassionate use

Phase I Pediatric DIPG and H3 K27M+ Glioma Trial: Arms and Accrual

Arm A	Arm B	Arm C	Arm D	Arm E
Post-radiation H3 K27M+ Glioma	Newly Diagnosed DIPG	DIPG Tumor Biopsy	Post-radiation H3 K27M+ Glioma CSF	Post-radiation H3 K27M+ Glioma OraSweet Formulation
ONC201	ONC201 + RT	ONC201 -/+ RT	ONC201	ONC201
Enrollment				
				
Level 2: n=6 → n=12 Level 1: n=3 Level -1	Level 2: n=6 → n=12 Level 1: n=3 Level -1: n=3	Level 2: n=12	Level 2: n=12	Level 2: n=6 → n=12 Level 1: n=3 Level -1: n=3

Phase I Pediatric DIPG and H3 K27M-Mutant Glioma Trial: Safety

Single agent equivalent of adult RP2D confirmed with scaling by body weight

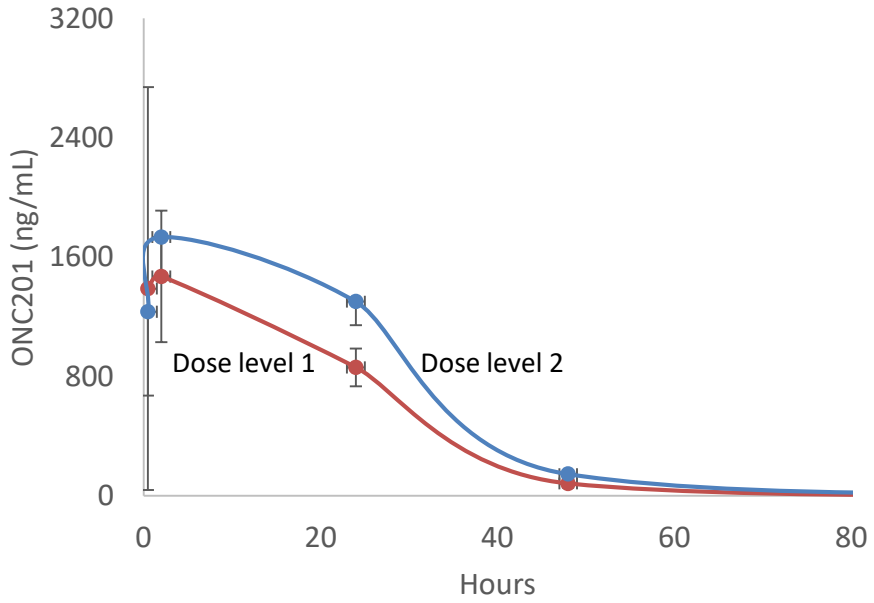
N=21	All Attributions		Possibly or Probably Related	
Adverse Events, N (%)	**All Grades %**	**Grade 3-4%**	**All Grades %**	**Grade 3-4%**
Nervous system disorders				
Headache	52%	0%	14%	0%
Nausea	43%	0%	24%	0%
6th nerve palsy	24%	0%	0%	0%
Ataxia	24%	0%	5%	0%
Dizziness	24%	0%	5%	0%
Vomiting	14%	0%	10%	0%
Dysarthria	10%	0%	0%	0%
Dysphagia	10%	0%	0%	0%
General disorders and administration site conditions				
Fatigue	19%	0%	10%	0%
Gait disturbance	10%	0%	5%	0%
Musculoskeletal and connective tissue disorders				
Muscle weakness right-sided	14%	5%	0%	0%
Right hemiparesis	10%	0%	0%	0%
Investigations				
Alanine aminotransferase elevated	10%	0%	10%	0%
Aspartate aminotransferase elevated	10%	5%	5%	5%
Eye disorders				
Diplopia	10%	0%	0%	0%
Respiratory, thoracic and mediastinal disorders				
Cough	10%	0%	0%	0%
Infections and infestations				
Pharyngitis	10%	0%	0%	0%

Gardner et al, *Society of Neuro-oncology*, 2018

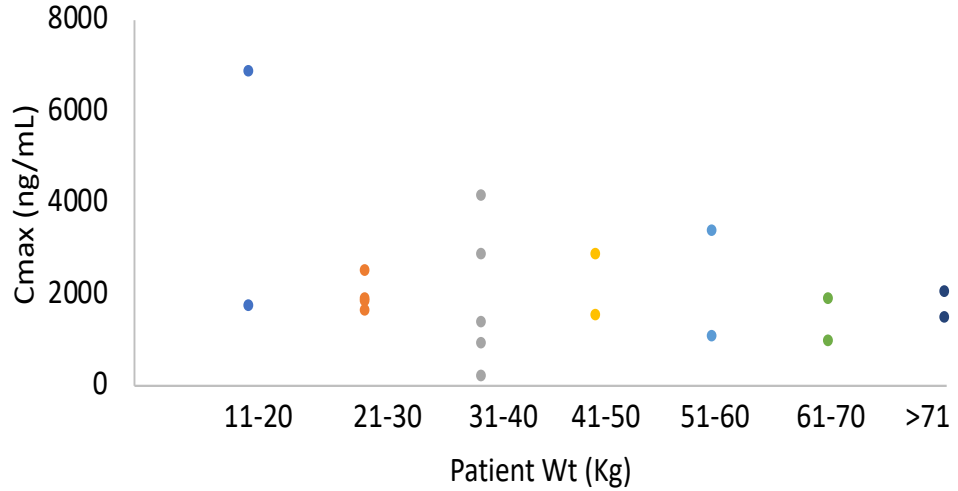
Phase I Pediatric DIPG and H3 K27M-Mutant Glioma Trial: Pharmacokinetics

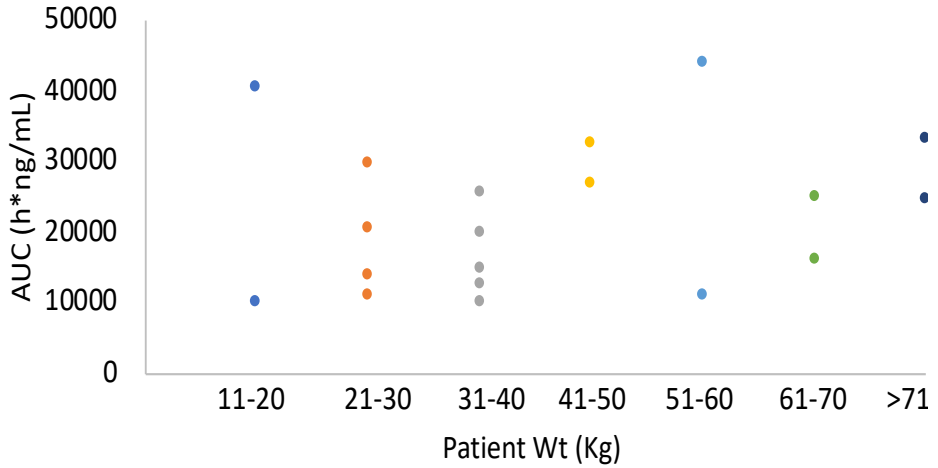
Preliminary pharmacokinetics similar to adults

- C_{max}~2.1ug/mL (6uM)
- T_{max}~2.1h
- AUC~2.3h*ug/mL
- $T_{1/2}$~8 h



Exposure consistent across body weights

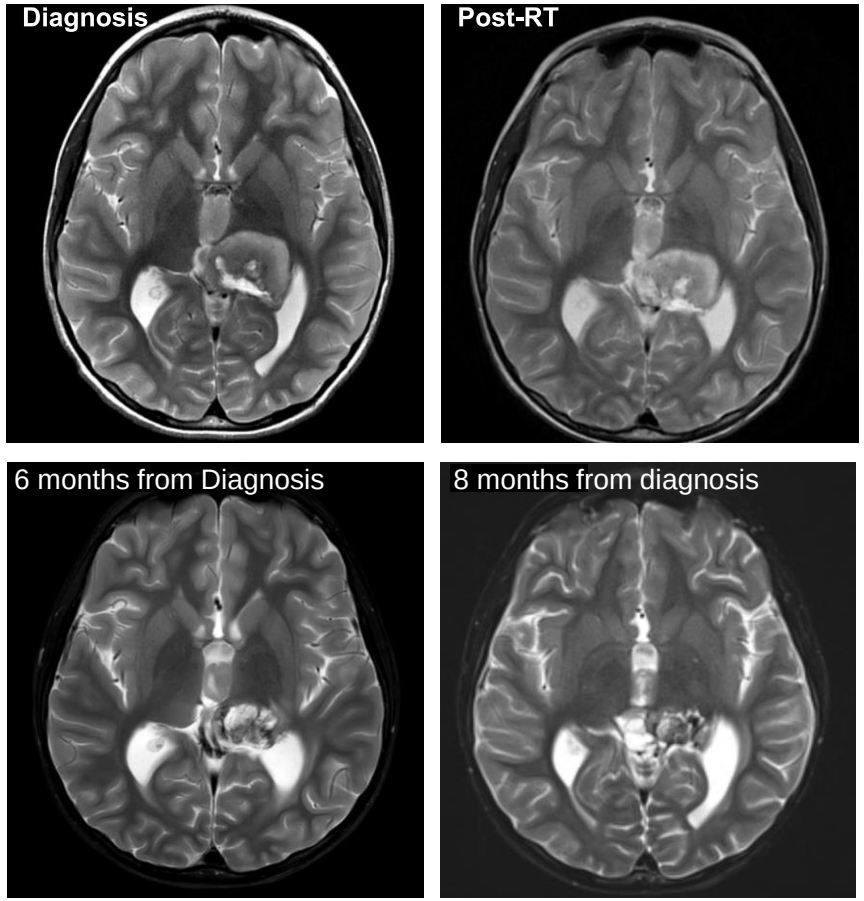




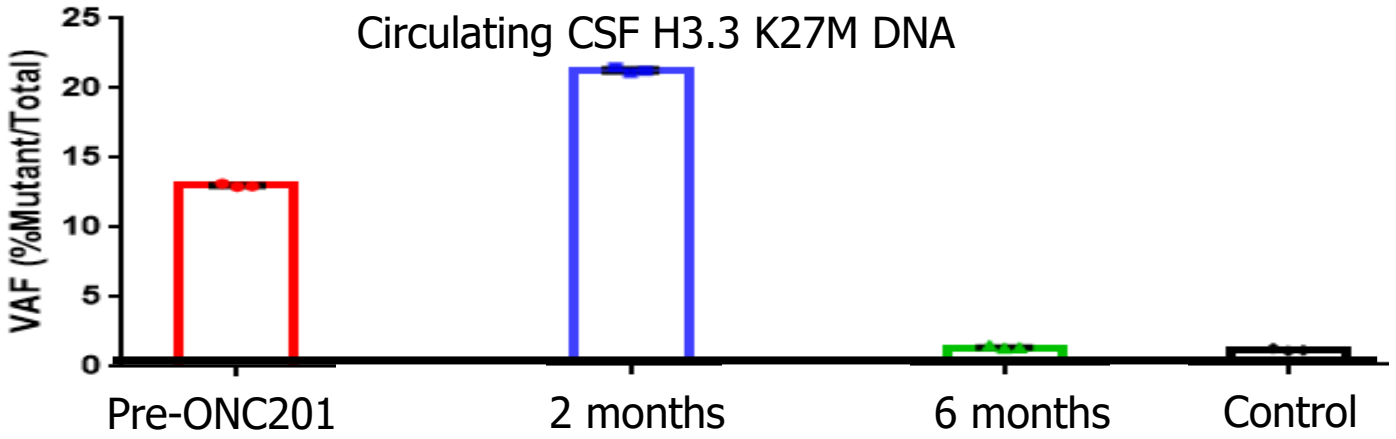
Phase I Pediatric DIPG and H3 K27M-Mutant Glioma Trial: Case Study 3/4

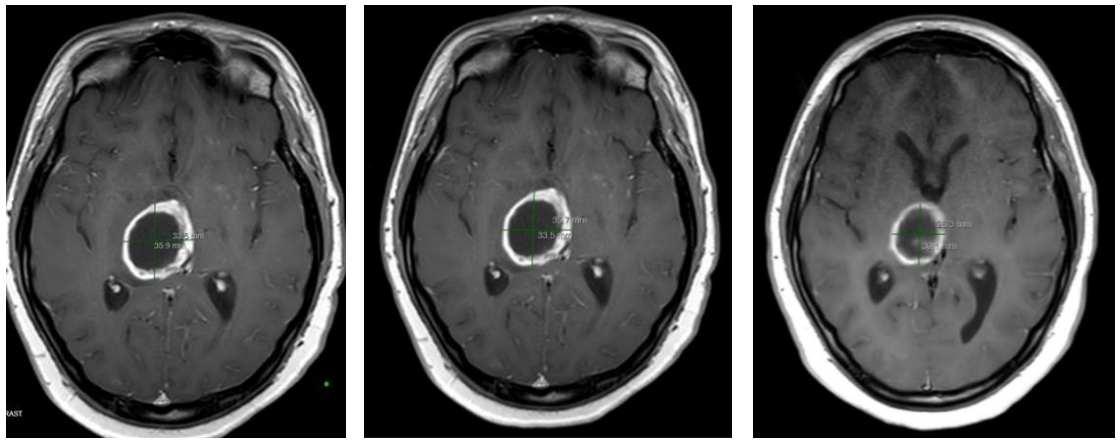
Tumor regressions and ctDNA depletion in H3 K27M-mutant glioma patients who initiated ONC201 after RT

6 year-old patient



17 year-old patient

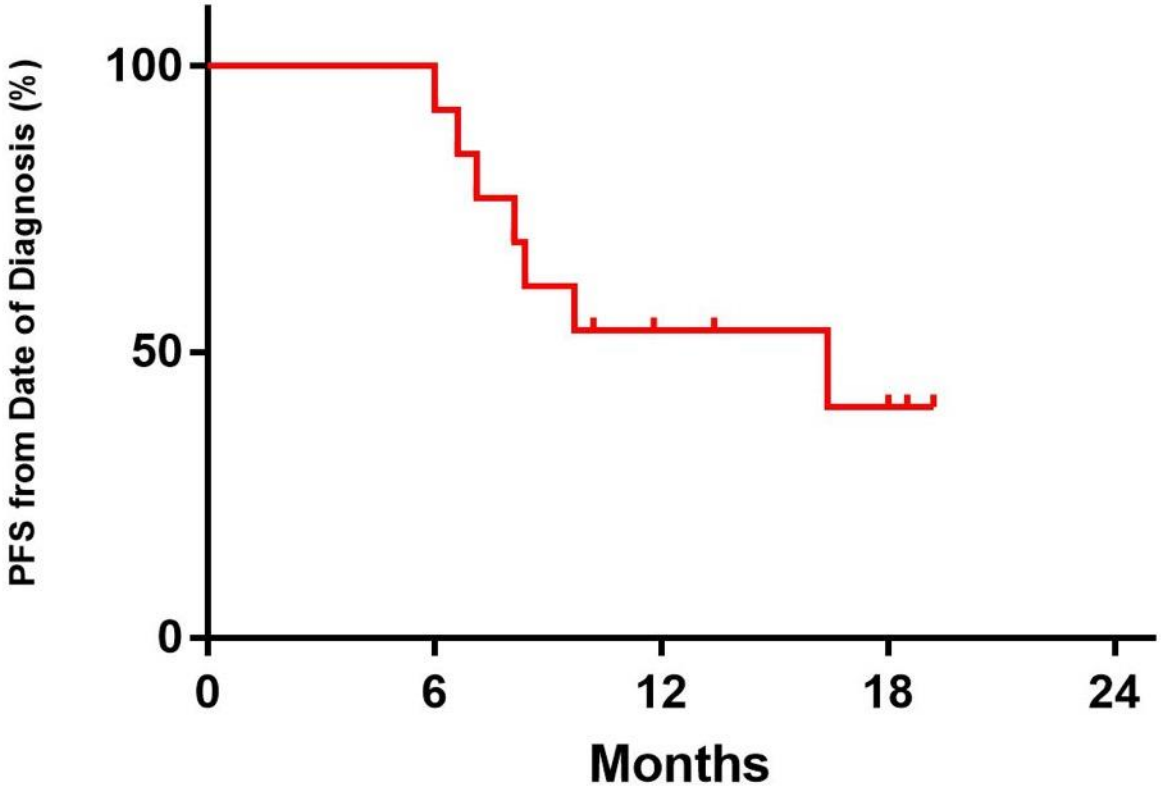


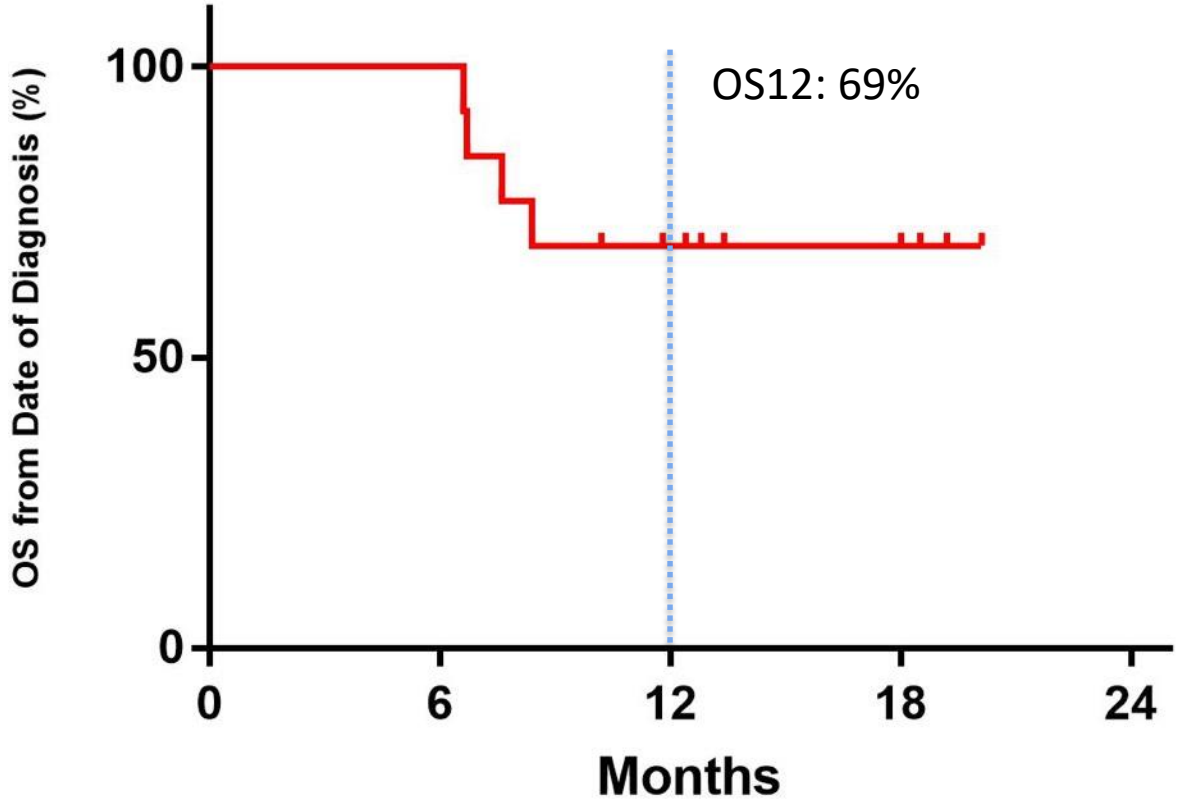


Pediatric DIPG and H3 K27M-Mutant Glioma: Post-Radiation DIPG

13 DIPG patients treated following radiation, prior to recurrence is most mature cohort

Median follow-up: 13.2 months





Enrollment cutoff: 12/15/2018

Summary of Pediatric Glioma Trials With Efficacy Readouts

Ongoing

Oncoceutics-sponsored trial: Sharon Gardner, MD
- -Newly diagnosed DIPG (OS)
- -Progressive non-DIPG H3 K27M-mutant glioma (ORR)

Intermediate-size expanded access protocol (ORR in non-DIPG H3 K27M; OS in DIPG)

In Development

NRG/COG: Yazmin Odia, MD, MS; Sharon Gardner, MD
- -Newly diagnosed DIPG (OS)
- -Newly diagnosed non-DIPG H3 K27M-mutant glioma (OS)

BIOMEDE 2.0: Jacques Grill, MD, PhD, and Gilles Vassal, MD
- -Newly diagnosed H3 K27M and/or H3K27me3-negative diffuse midline glioma

PNOC: Sabine Mueller, MD, PhD
- -Newly-diagnosed diffuse midline glioma (PD)
- -Previously-treated diffuse midline glioma (PD)

Supplementary Slides

Well Tolerated at Weekly Oral Recommended Phase II Dose

Safety profile consistent across age and tumor type

Pediatric H3 K27M-mutant Glioma Patients (n=21)

	All Attributions		Possibly or Probably Related	
Adverse Events, N (%)	**All Grades %**	**Grade 3-4%**	**All Grades %**	**Grade 3-4%**
Nervous system disorders				
Headache	52%	0%	14%	0%
Nausea	43%	0%	24%	0%
6th nerve palsy	24%	0%	0%	0%
Ataxia	24%	0%	5%	0%
Dizziness	24%	0%	5%	0%
Vomiting	14%	0%	10%	0%
Dysarthria	10%	0%	0%	0%
Dysphagia	10%	0%	0%	0%
General disorders and administration site conditions				
Fatigue	19%	0%	10%	0%
Gait disturbance	10%	0%	5%	0%
Musculoskeletal and connective tissue disorders				
Muscle weakness right-sided	14%	5%	0%	0%
Right hemiparesis	10%	0%	0%	0%
Investigations				
Alanine aminotransferase elevated	10%	0%	10%	0%
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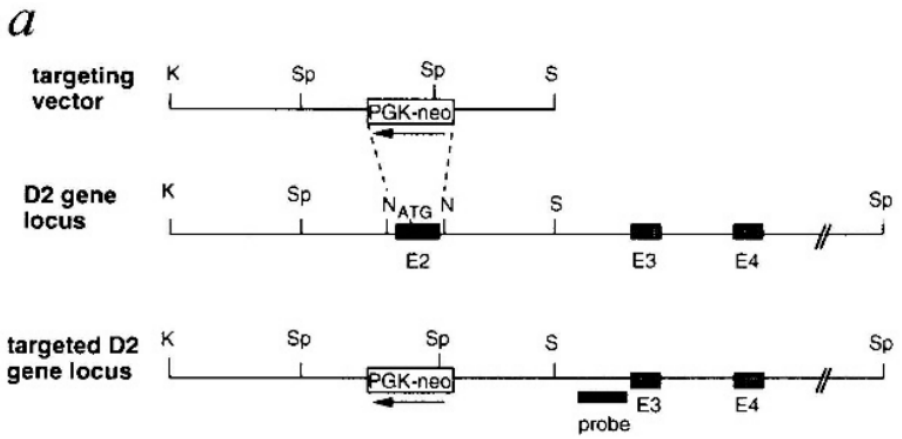
Eye disorders				
Diplopia	10%	0%	0%	0%
Respiratory, thoracic and mediastinal disorders				
Cough	10%	0%	0%	0%
Infections and infestations				
Pharyngitis	10%	0%	0%	0%

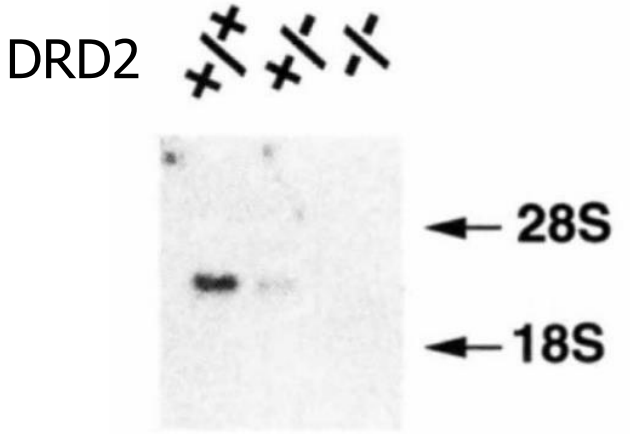
Adult Recurrent Glioblastoma Patients (n=20)

	All Adverse Events		Possibly/Probably-Related	
Adverse Events, N (%)	**All Grades**	**Grade 3-4**	**All Grades**	**Grade 3-4**
Nervous system disorders				
Dizziness	4 (20%)	0 (0%)	1 (5%)	0 (0%)
Metabolism and nutrition disorders				
Hypophosphatemia	9 (45%)	0 (0%)	7 (35%)	0 (0%)
Anorexia	4 (20%)	0 (0%)	3 (15%)	0 (0%)
General disorders and administration site conditions				
Gait disturbance	8 (40%)	1 (5%)	4 (20%)	0 (0%)
Injury, poisoning and procedural complications				
Fall	8 (40%)	1 (5%)	0 (0%)	0 (0%)
Gastrointestinal disorders				
Nausea	7 (35%)	0 (0%)	5 (25%)	0 (0%)
Vomiting	7 (35%)	0 (0%)	5 (25%)	0 (0%)
Diarrhea	5 (25%)	0 (0%)	5 (25%)	0 (0%)
Investigations				
Platelet count decreased	6 (30%)	0 (0%)	1 (5%)	0 (0%)
Psychiatric disorders				
Confusion	5 (25%)	0 (0%)	1 (5%)	0 (0%)

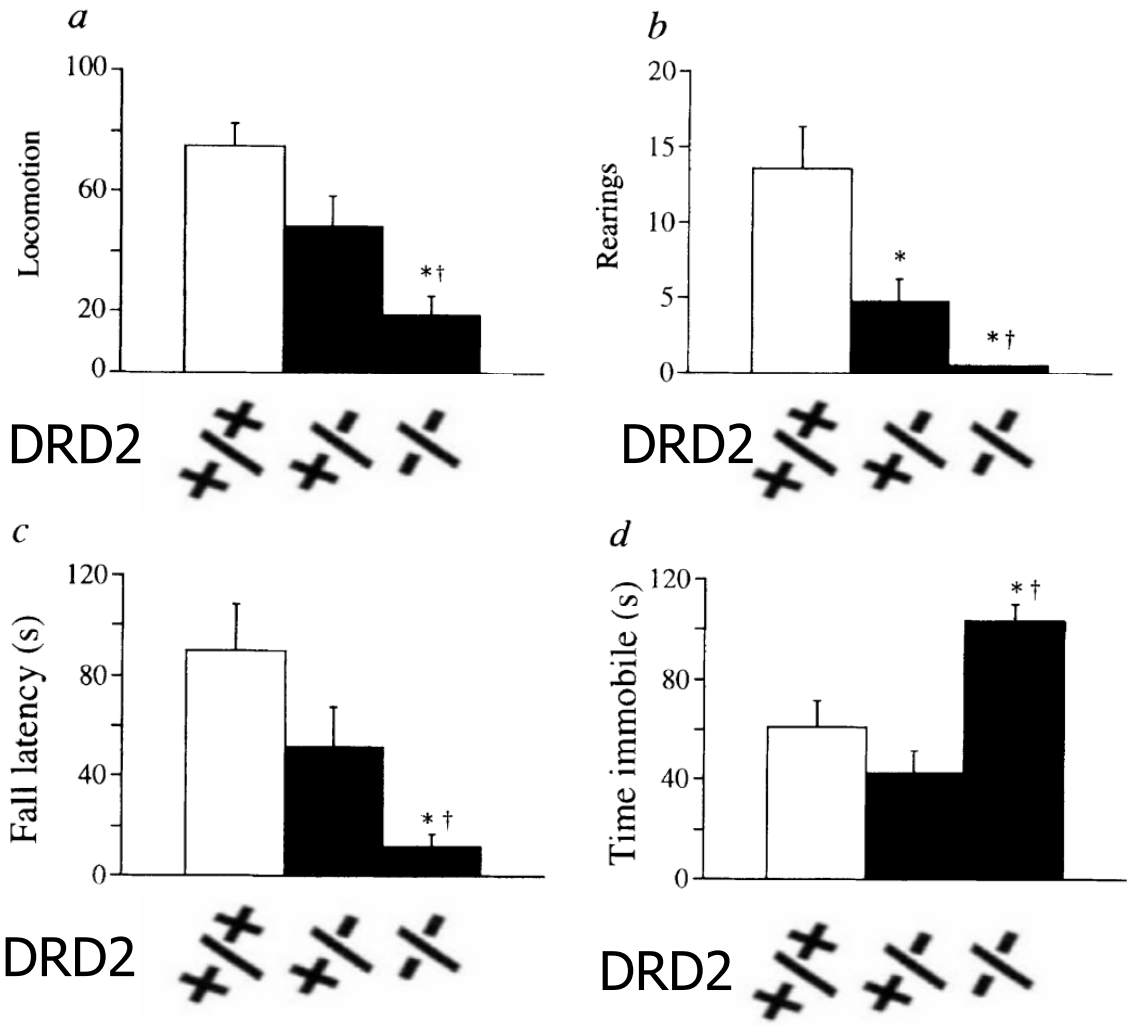
DRD2 Knockout Mice Exhibit Locomotor Deficits

DRD2 knockout mice





Locomotor deficits with DRD2 knockout



Receptor Binding Kinetics Define DRD2 Antagonism Without EPS

ONC201 exhibits a slow on-rate and fast off-rate with DRD2, which are defining features of DRD2 antagonists without extrapyramidal side effects

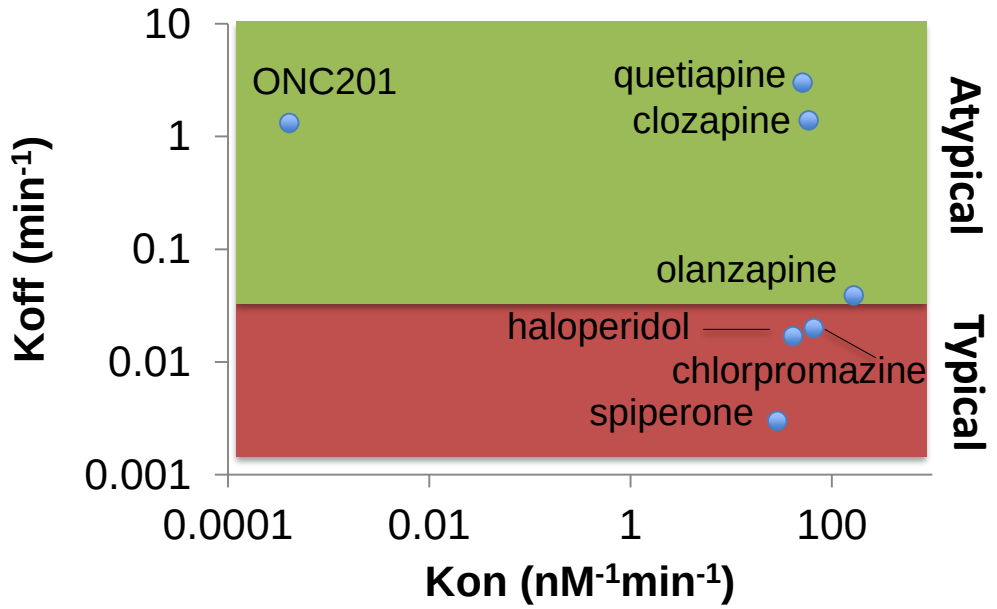
ARTICLE

DOI: 10.1038/s41467-017-00716-z OPEN

Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D_2 receptors

David A. Sykes[1], Holly Moore[2,3], Lisa Stott[1], Nicholas Holliday[1], Jonathan A. Javitch[2,4,5], J. Robert Lane[6] & Steven J. Charlton[1]

Molecular Psychiatry (1998) 3, 123–134



PERSPECTIVE

Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors

P Seeman[1,2] and T Tallerico[1]

Drug Schedule Rationale

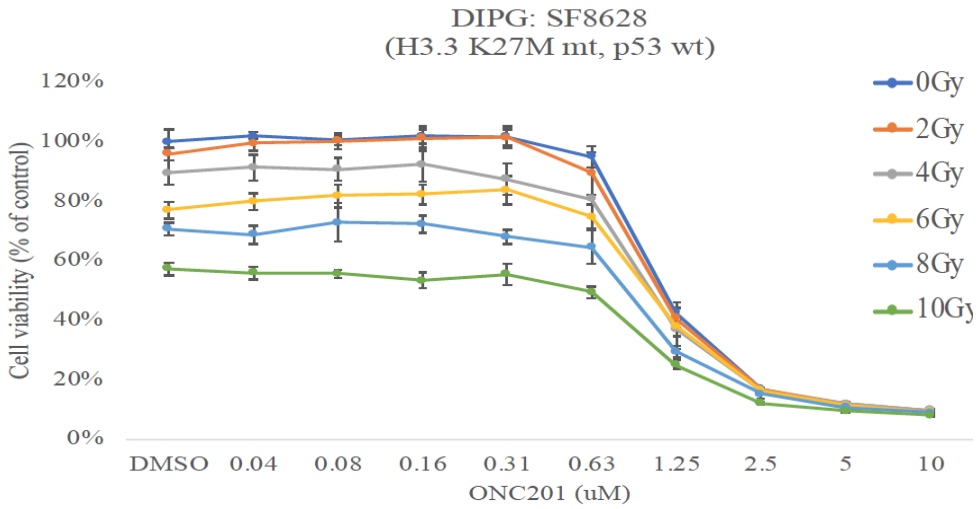
- Adult recommended phase 2 dose selected as 625mg orally once per week selected based on:
  - Saturation of preclinical pharmacodynamics and efficacy at adult equivalent of 125mg
  - No additional preclinical efficacy benefit with dose intensification beyond weekly dosing in solid tumor models
  - Pharmacokinetics in humans consistent with those association with preclinical efficacy
  - Pharmacodynamics in humans consistent with saturated and sustained target engagement
- Corroborated by radiographic regressions (including objective responses), intratumoral drug concentrations, and pharmacodynamic responses observed in patients with every 1 or 3 week dosing

ONC201 Collaboration with NCI PPTC Consortium

- ONC201 efficacy in pediatric oncology preclinical models will be evaluated by the NCI Pediatric Preclinical Testing Consortium (PPTC) in vitro with follow-on in vivo studies
  - Glioblastoma
  - Ependymoma
  - Medulloblastoma
  - Neuroblastoma
  - Ewing sarcoma
  - Rhabdomyosarcoma
- PPTC sites: Children's Hospital of Philadelphia for neuroblastoma, the Greehey Children's Cancer Research Institute for sarcoma, and Northwestern University for brain cancers

Synergy with Radiation In Preclinical Models

ONC201 combines synergistically with radiation in DIPG

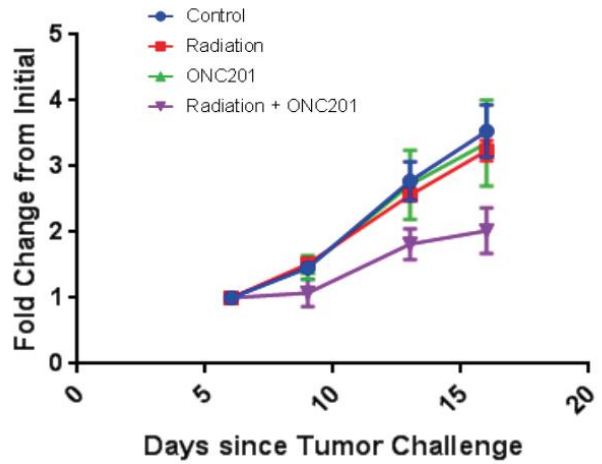


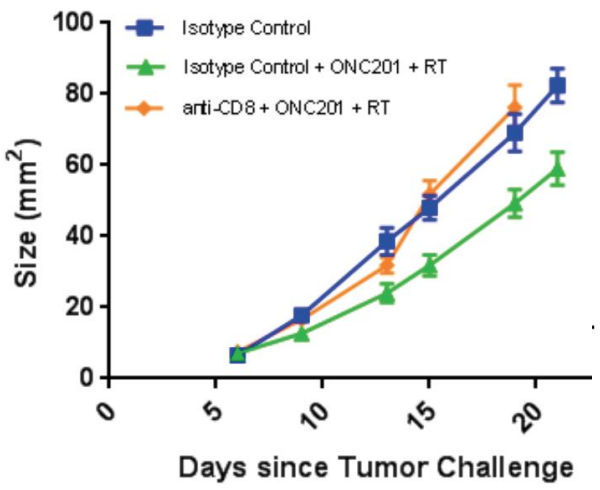
CI Data for Non-Constant Combo: Combo (ONC+RT)

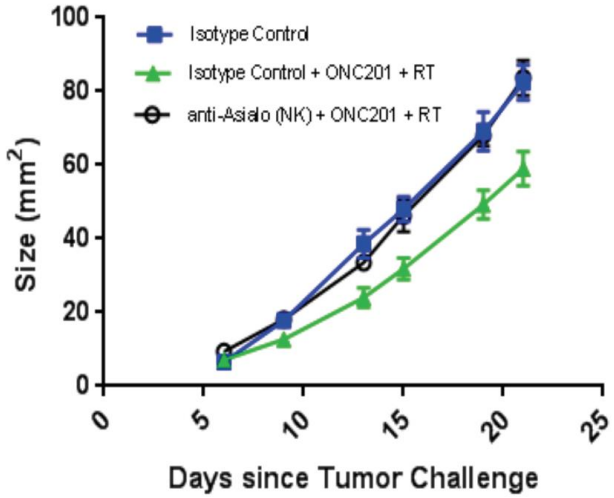
(RT-Gy) \ (ONC201-uM)	0.04	0.08	0.16	0.31	0.63	1.25	2.5	5	10
2	2.49504	NA	NA	NA	1.73155	0.71106	0.63854	0.95793	1.54829
4	1.28205	1.36905	1.66008	1.47768	1.5657	0.76506	0.67565	1.0103	1.70248
6	1.11211	1.25196	1.36177	1.69938	1.58138	0.9065	0.73891	1.00422	1.63563
8	1.0521	1.21512	1.26003	1.26352	1.39693	0.81596	0.76779	1.05376	1.67931
10	0.952	0.9783	0.96259	1.10387	1.14182	0.81328	0.71463	0.97067	1.59992

(RT-Gy) NA = effect value<=0

ONC201 + radiation synergy in vivo can be mediated by NK and CD8+ T cells

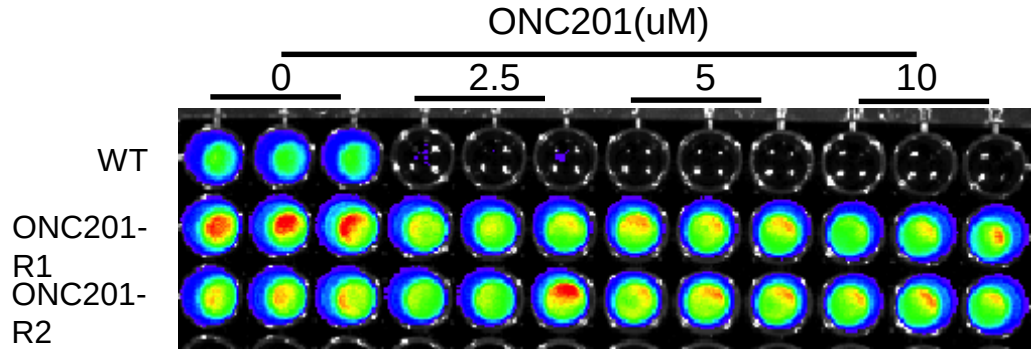


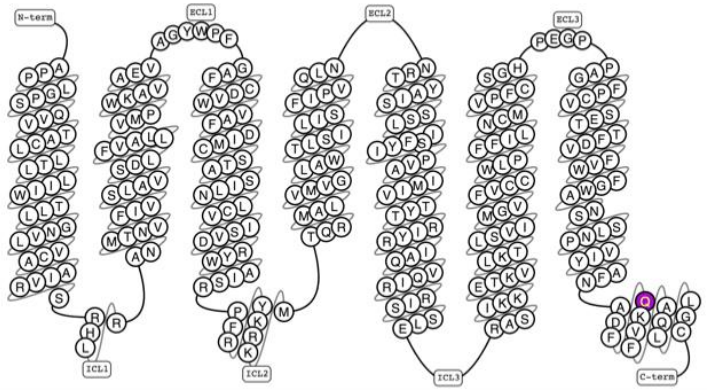


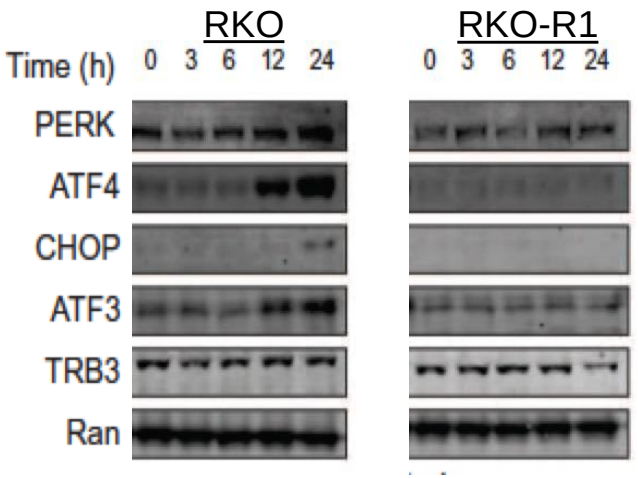


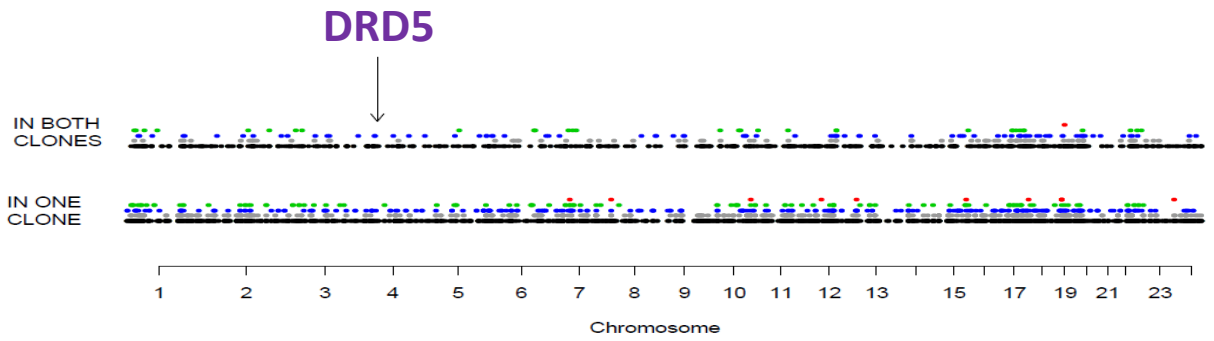
DRD5 Is Involved in Acquired Resistance

- Resistant clones with stable and complete ONC201 resistance exhibited no downstream signaling with ONC201 treatment
- Consensus Q366R missense mutation identified in ONC201-resistance cells in DRD5 gene





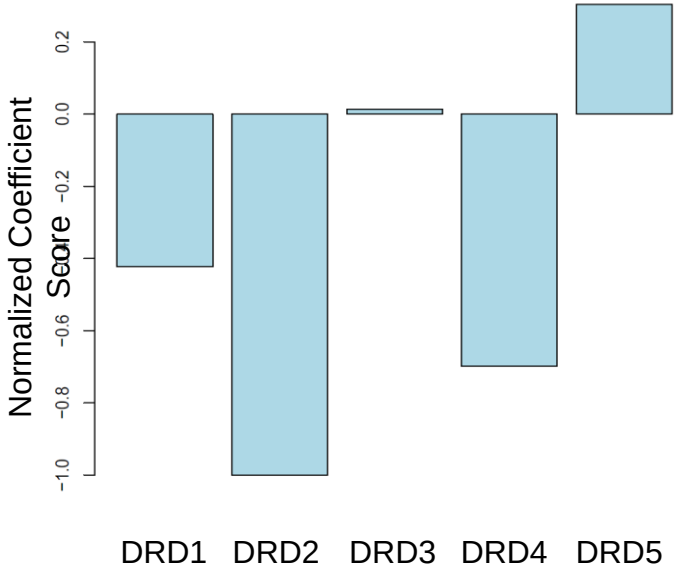




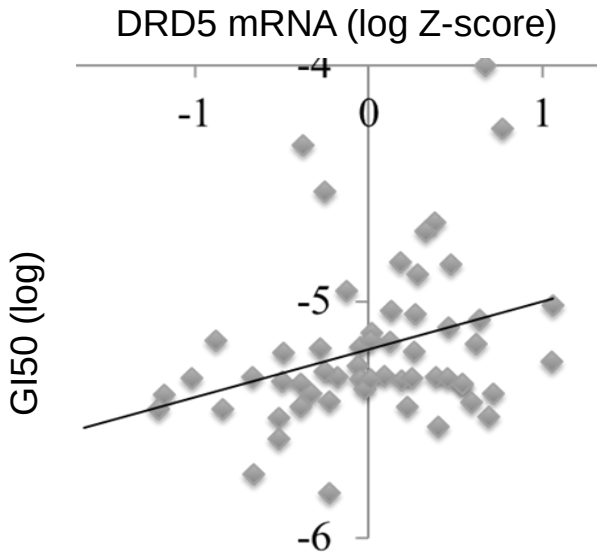
Dopamine Receptor Expression Signature is a Predictive Biomarker

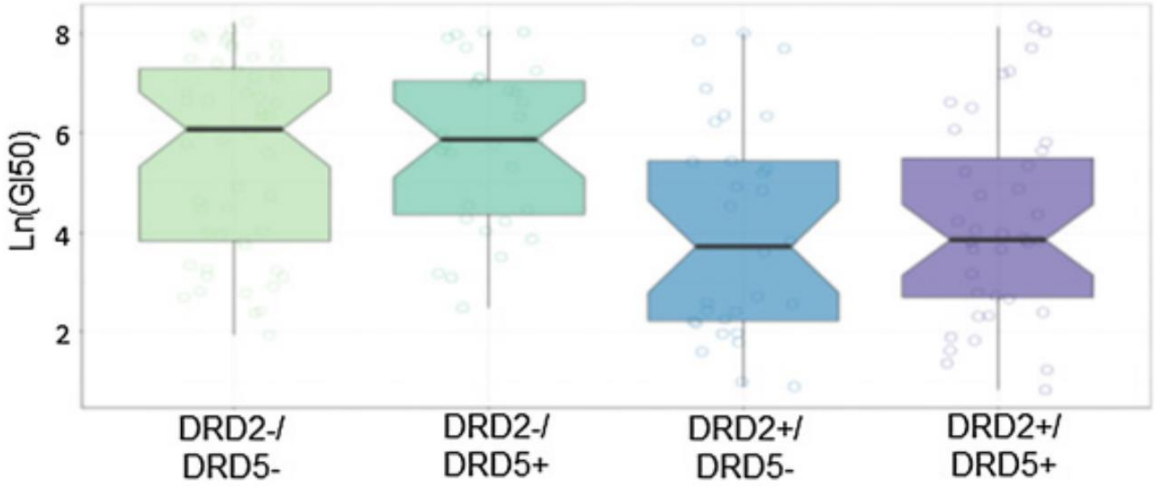
- Expression of the 5 dopamine receptors were evaluated as predictive biomarkers across the GDSC panel
  - DRD2 strongest positive predictor
  - DRD5 strongest negative predictor

GDSC



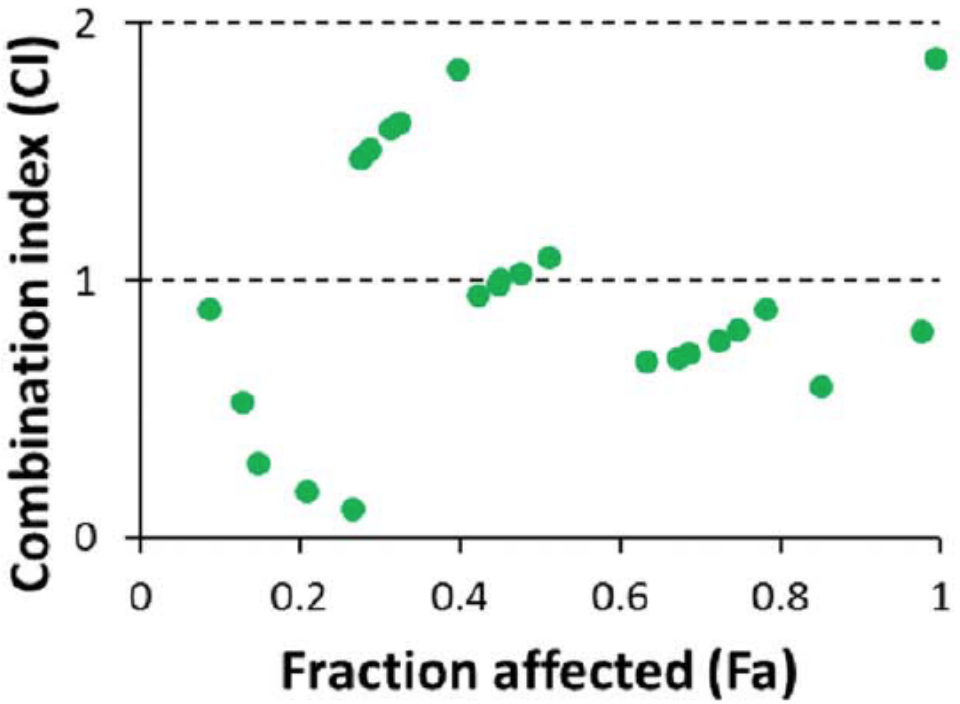
NCI60

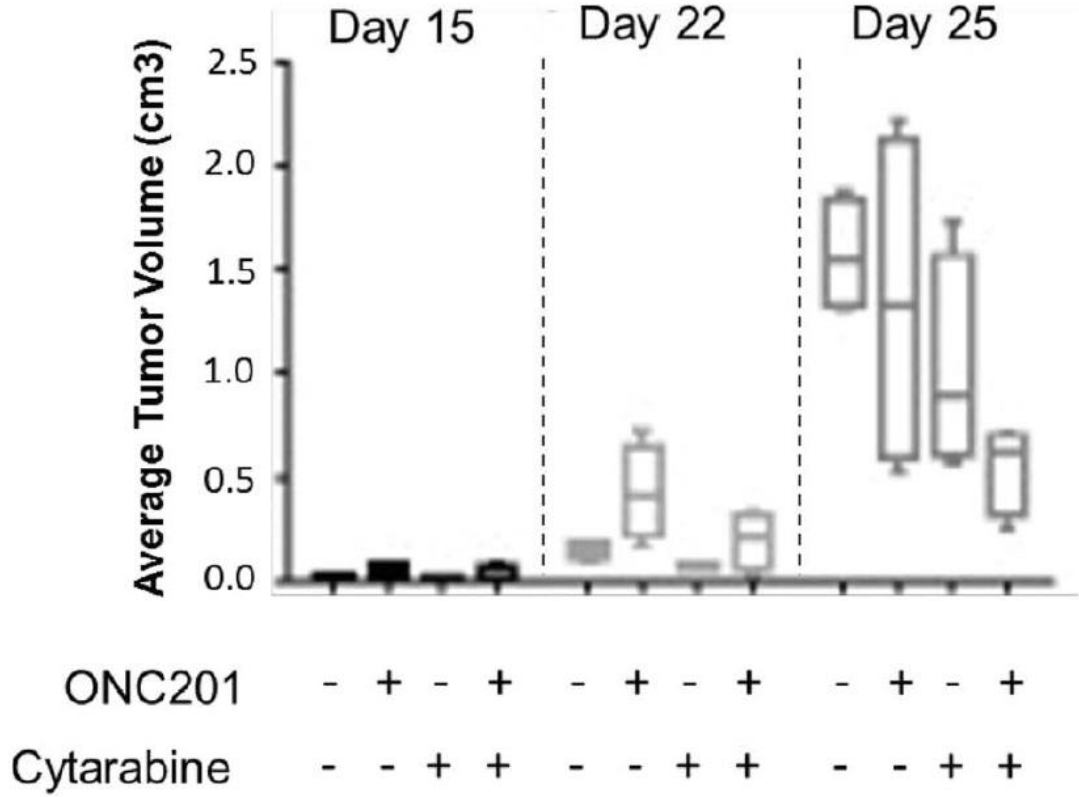




Cytarabine Synergy in Treatment Naïve and Acquired Resistance Settings

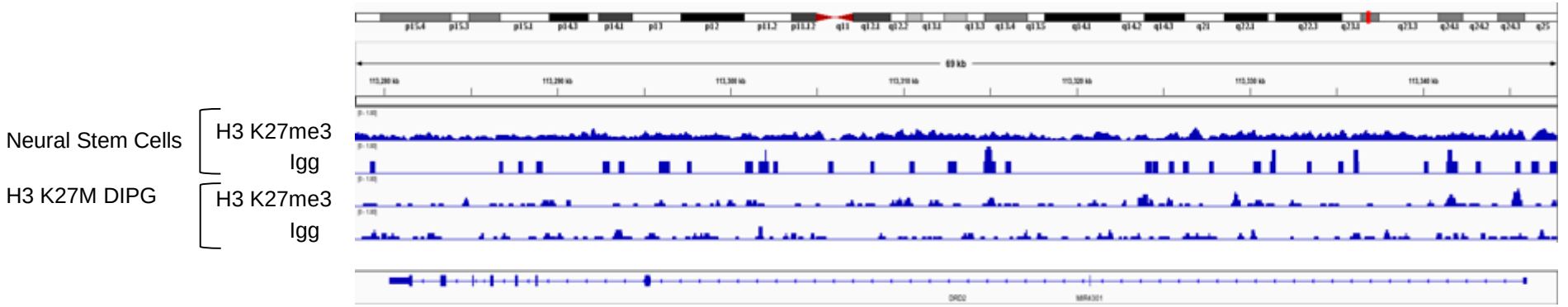
- Synergy screening with FDA-approved oncology drugs in cancer cells with acquired resistance to ONC201 revealed sensitization to cytarabine
- Cytarabine synergy has been validated in treatment-naïve and acquired resistance settings





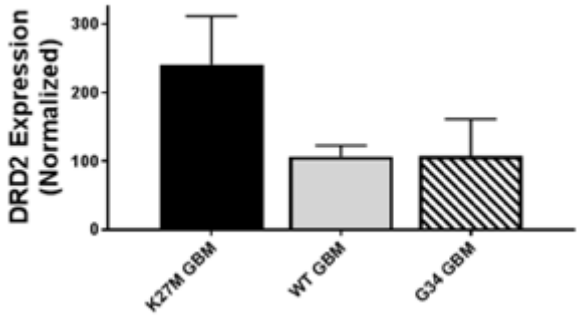
Dopamine Receptor Expression Dysregulation by H3 K27M

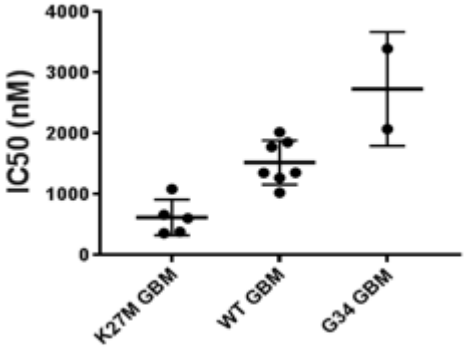
H3 K27me3 repressive mark lost on DRD2 gene in H3 K27M glioma

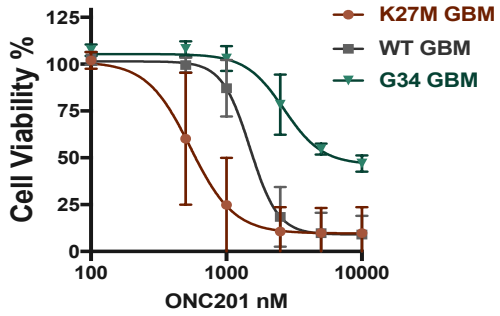


GSE61586

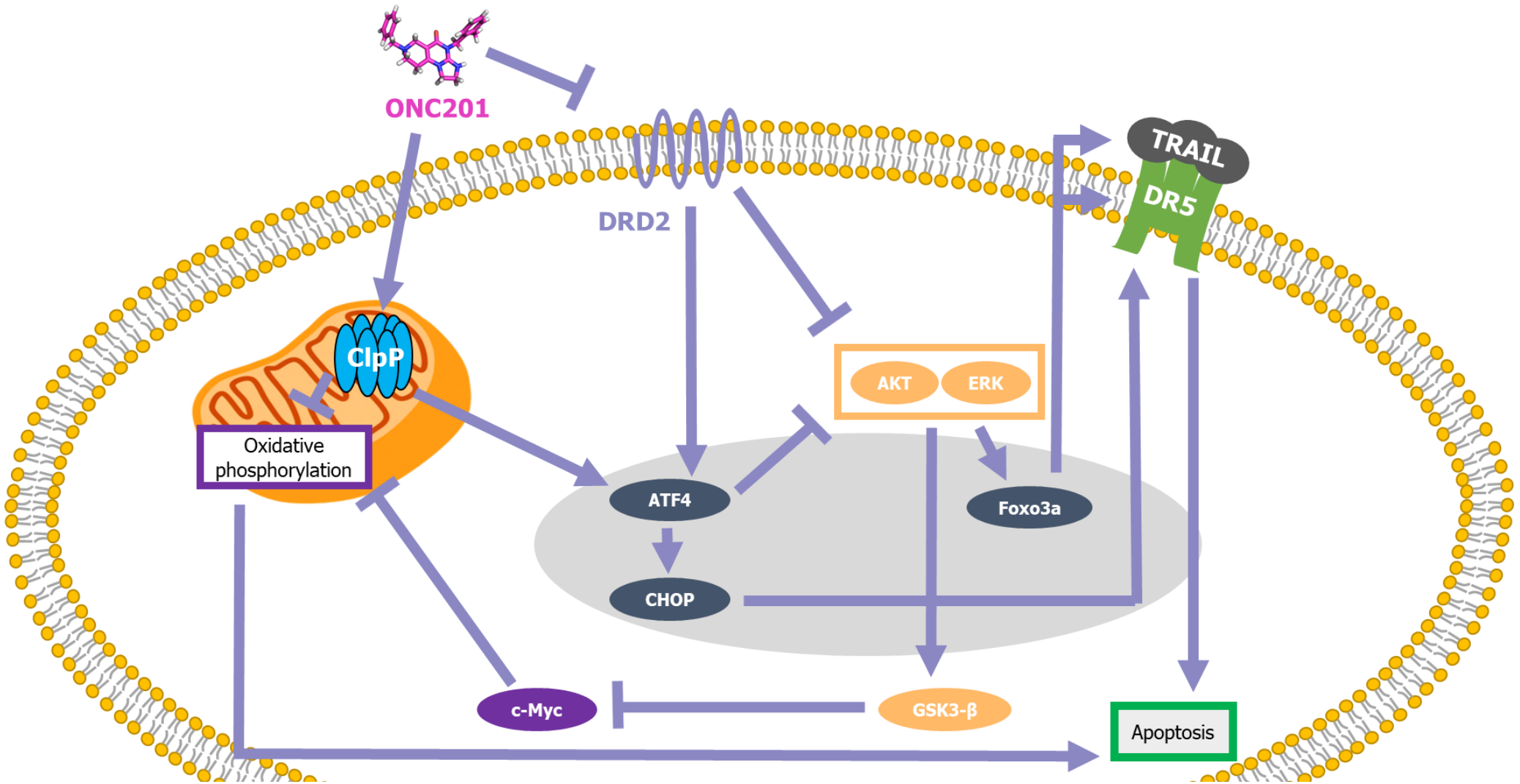
H3 K27M-mutant gliomas overexpress DRD2 and are more ONC201-sensitive







Overview of Mechanism of Action of ONC201



Allen et al., *Science Translational Medicine*, 2013 ; Ishizawa et al, *Science Signaling*, 2016; Kline et al, *Science Signaling*, 2016 ; Ishida et al, *Clinical Cancer Research*, 2018
Ishizawa et al, *Cancer Cell*, 2019