

# Chimerix Corporate Presentation



# Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks and uncertainties that could cause actual results to differ materially from those projected. Forward-looking statements include those relating to, among other things: the timing of initiation, progress and completion of ONC201 Phase 3 clinical development; the timing and outcomes of any FDA interactions; the probability of success of our ONC201 development program, and Chimerix's financial strength. Among the factors and risks that could cause actual results to differ materially from those indicated in the forward-looking statements are risks associated with the sale of TEMBEXA to Emergent; the anticipated benefits of the sale of TEMBEXA may not be realized; the anticipated benefits of the acquisition of Oncoceutics may not be realized; risks that Chimerix's reliance on a sole source third-party manufacturer for drug supply; risks that ongoing or future trials may not be successful or replicate previous trial results; results from historical studies may not be predictive of real-world results or of results in subsequent trials; risks that the benefits from our planned workforce reduction may not be realized; risks and uncertainties relating to competitive products and technological changes that may limit demand for our drugs; risks that our drugs may be precluded from commercialization by the proprietary rights of third parties; and additional risks set forth in the Company's filings with the Securities and Exchange Commission. These forward-looking statements represent the Company's judgment as of the date of this release. The Company disclaims, however, any intent or obligation to update these forward-looking statements.

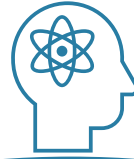


# Investment highlights



## High probability of success for Phase 3 ACTION study of ONC201

- Phase 2 study designed to isolate single agent activity in difficult treatment setting
- Durable responses associated with OS and other forms of clinical benefit
- Numerous independent and natural disease history studies support potential survival advantage
- Genetically selected patient population limits patient heterogeneity



## Low barriers to commercial potential for ONC201

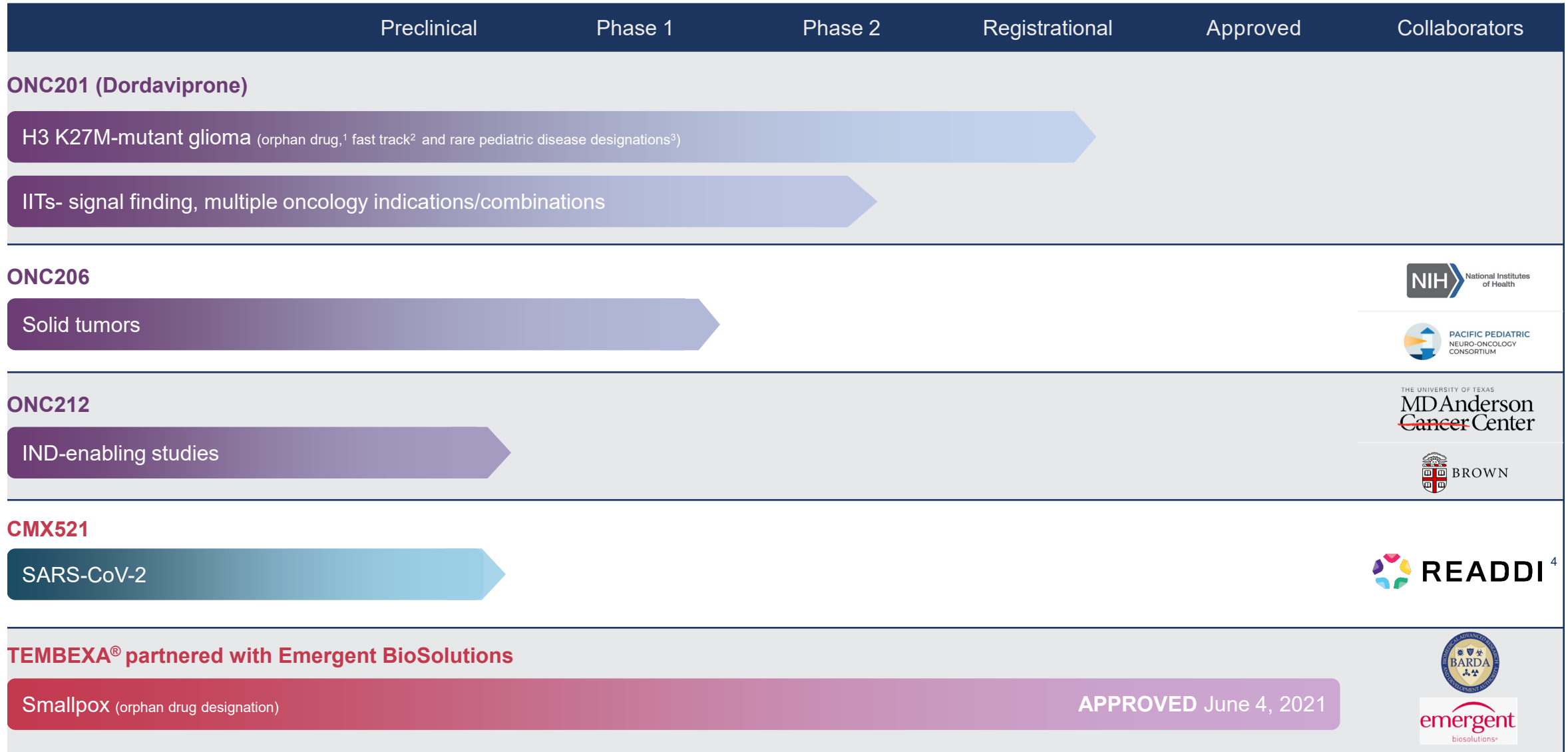
- Terminal disease with no effective therapeutic options
- High awareness for program within neuro-oncology community
- U.S. patent exclusivity through at least 2037
- Global revenue potential of ~\$750m in first indication alone



## Corporate capability and financial flexibility

- Leadership team successfully executed large scale studies and regulatory approvals
- Strong balance sheet fully funds ACTION study, leveraged external funding to support pipeline
- Opportunity for continued non-dilutive TEMBEXA milestones and royalties adds flexibility
- Track record of objectivity in creating paths to capture value

# Deep pipeline across all development stages



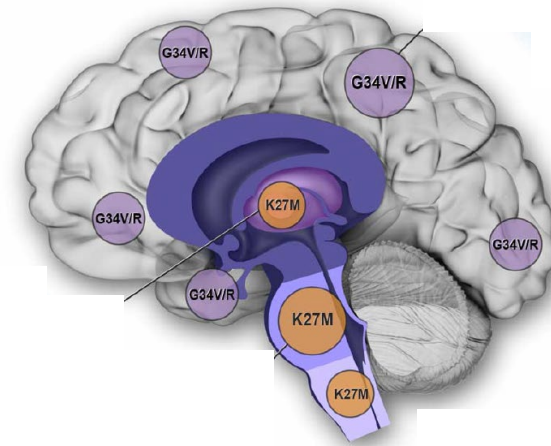
1 Malignant glioma  
 2 Adult recurrent H3 K27M-mutant high-grade glioma  
 3 H3 K27M-mutant glioma  
 4. Rapidly Emerging Antiviral Drug Development Initiative

# **ONC201 (Dordaviprone) Phase 2 Efficacy Analysis**



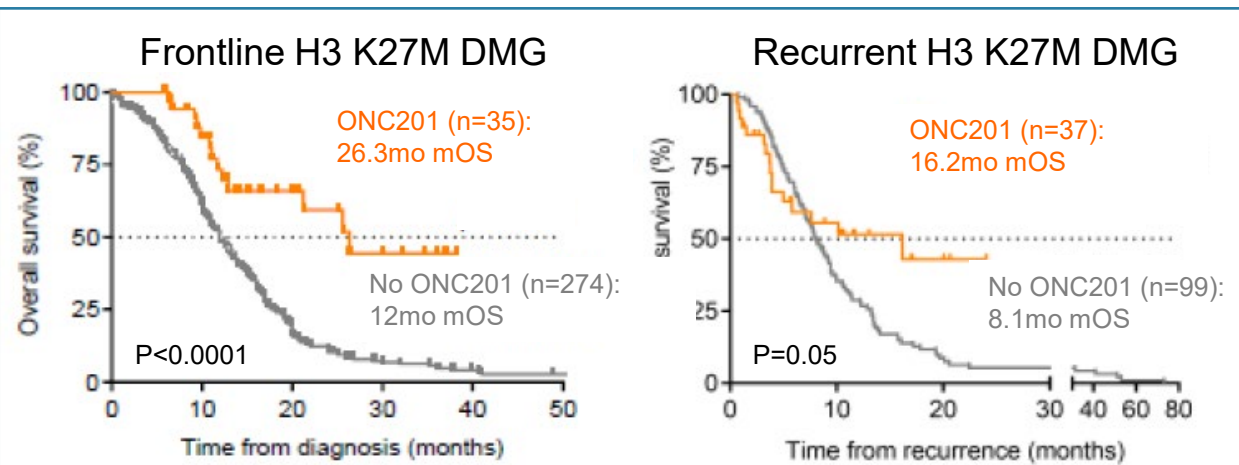
# H3 K27M-mutant diffuse glioma: high unmet need

- H3 K27M mutation is predominantly found among diffuse midline gliomas (DMGs) in young adults and children
- Frontline radiotherapy remains standard of care with transient benefit; resection often not feasible
- DMGs harboring the H3 K27M mutation are WHO Grade IV; historically invariably lethal
- Studies consistently indicate longer OS of ONC201-treated glioma patients relative to diverse external controls



Histone H3 Mutations in CNS Tumors<sup>1</sup>

## External analysis reported at SNO 2022<sup>2</sup>



## Company Sponsored Studies

	Natural Disease History: Recurrent H3 K27M and/or DMG <sup>3</sup> (n=43)	ONC201 Phase 2: Recurrent H3 K27M DMG (n=50)
Median OS, mo (95% CI)	5.1 (3.9-7.7)	13.7 (8-20.3)
OS @ 12mo (95% CI)	23.6% (11.7-37.9)	57% (41-70)
OS @ 24mo (95% CI)	11.1% (3.3-24.2)	35% (21-49)



<sup>1</sup> Lulla RR et al. Sci Adv. 2016;2(3):e1501354

<sup>2</sup> Sunjong Ji, B.S. et al, "Clinical efficacy and predictive biomarkers of ONC201 in H3 K27M-mutant diffuse midline glioma", Society of Neuro-oncology 2022

<sup>3</sup> The median OS was 5.1 months for the subset of patients with H3 K27M-mutant diffuse glioma excluding DIPG, CSF dissemination, spinal or leptomeningeal disease (N=12), OS at 12 mos was 25.0%, OS at 24 mos was 16.7%

## Phase 2 efficacy for ONC201 in recurrent H3 K27M DMG

- ONC201 monotherapy exhibited durable, clinically meaningful efficacy in recurrent H3 K27M-mutant DMG
  - Overall Response Rate (ORR) of 30% (95% CI: 18 - 45%) by RANO HGG and/or LGG dual reader BICR
  - RANO-HGG criteria assessed by dual reader BICR
    - ORR 20% (95% CI: 10 – 34%)
    - Median Duration of Response (DOR) 11.2 months (95% CI: 3.8 – not reached)
    - Median time to response 8.3 months (range 1.9 – 15.9)
    - Disease control rate 40% (95% CI: 26 – 55%)
    - PFS at 6 months 35% (95% CI: 21 – 49%); PFS at 12 months 30% (95% CI: 17 – 44%)
  - RANO-LGG criteria assessed by dual reader BICR
    - ORR 26% (95% CI: 15 – 40%)
  - Overall survival
    - 12 months: 57% (95% CI: 41 – 70%)
    - 24 months: 35% (95% CI: 21 – 49%)
- Improvements observed in performance status and reduction in corticosteroid use
- All SAEs considered not related to ONC201 by sponsor

# FDA-aligned criteria for Phase 2 efficacy analysis to isolate ONC201 single agent activity

## Objective

- To evaluate monotherapy efficacy of ONC201 in recurrent H3 K27M-mutant diffuse midline glioma

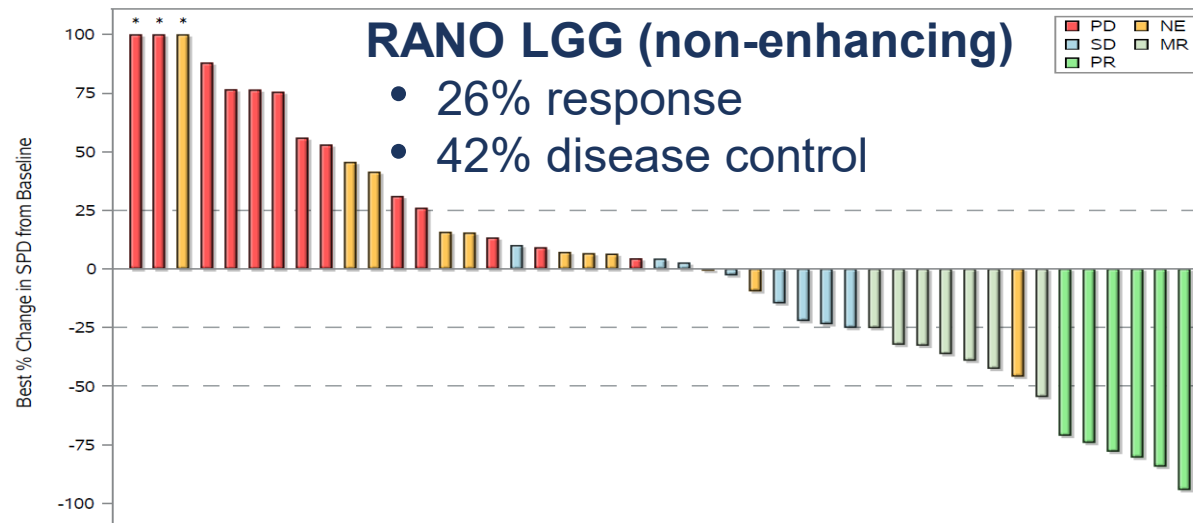
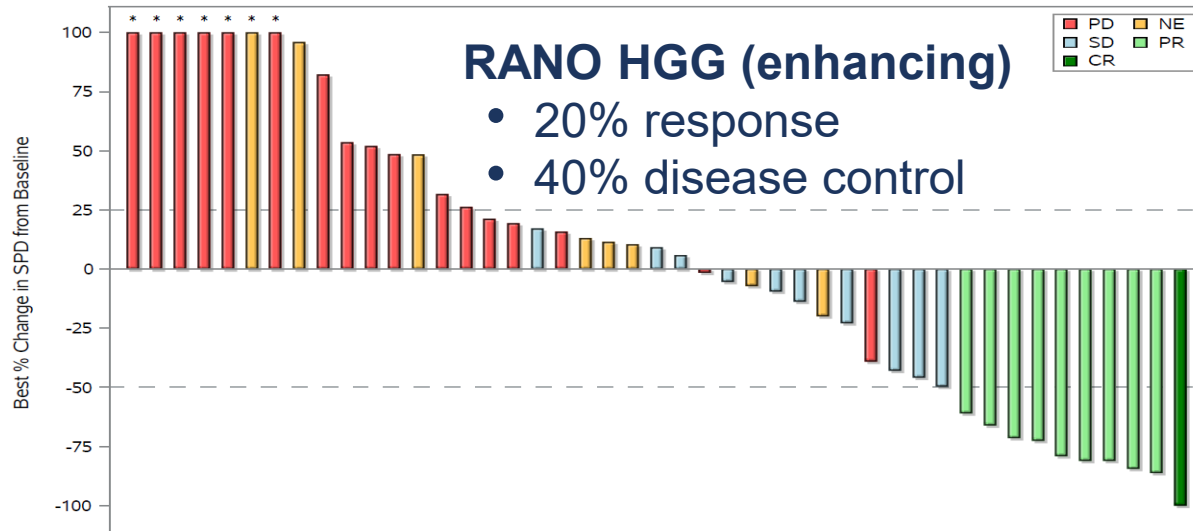
## Eligibility

- Age  $\geq 2$ yo and received ONC201 under studies ONC006, ONC013, ONC014, ONC016, or ONC018
- Diffuse glioma with a known H3 K27M mutation and involvement of a midline structure of the brain
- Progressive and measurable disease on contrast-enhanced brain MRI by RANO-High Grade Glioma (HGG) criteria
- Prior therapy with at least radiation
- Washouts prior to first ONC201 dose:
  - Radiation: 90 days
  - Temozolomide: 23 days / Antibodies (e.g., bevacizumab): 42 days / Other anticancer therapies: 28 days
- Baseline Performance Status  $\geq 60$
- Corticosteroids stable or decreasing for at least 3 days prior to baseline scan
- Excluded: DIPG, primary spinal tumors, atypical and non-astrocytic hist., leptomeningeal spread, CSF dissemination



# ONC201 waterfall plot – 30% RANO HGG / LGG response

ONC201 Ph 2 Efficacy Analysis by BICR in Recurrent H3  
K27M-mutant Diffuse Midline Glioma



- Strict selection criteria to ensure responses attributable to single agent treatment
- Responses require both imaging and clinical criteria
- Dual reader blinded independent central review (BICR)
- Growing consensus that assessment of enhancing and non-enhancing disease (RANO-HGG and RANO-LGG criteria) is needed for diffuse midline glioma

# RANO-HGG responses observed across age groups

## Responses by age group:

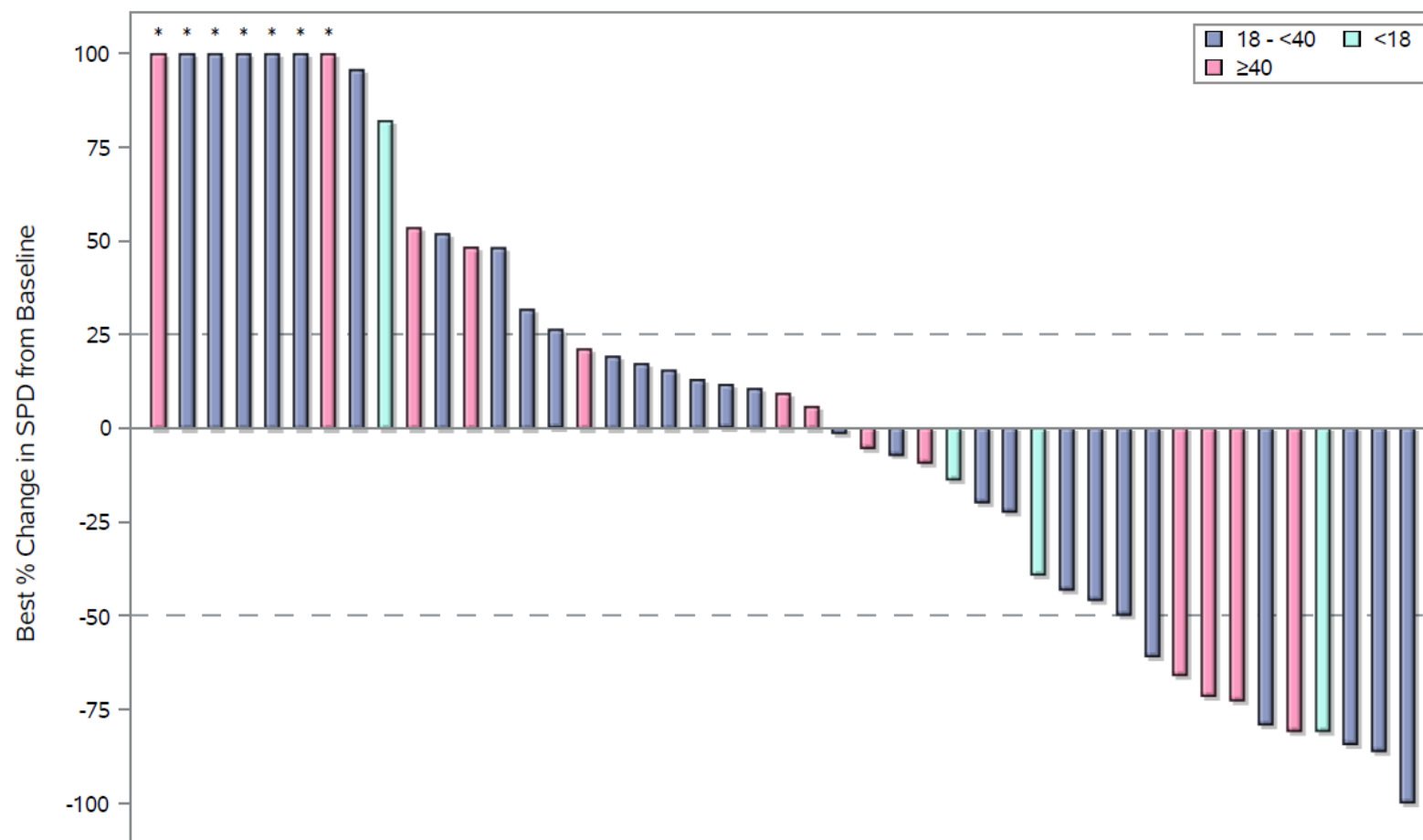
<18 years: 1/4 (25%)

18-40 years: 5/32 (16%)

≥40 years: 4/14 (29%)

RANO-HGG response of 8-year-old subject suggests activity in this population

## ONC201 Ph 2 Efficacy Analysis by BICR in Recurrent H3 K27M-mutant Diffuse Midline Glioma



\* Change > 100%, SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR)  
Only patients with measurable target enhancing lesions at both baseline and post-baseline are included.

# RANO HGG response correlation to performance status (PS) supports early-line trial

Predictably, patients with higher PS were more likely to respond to treatment

100: 1/2 (50%)

90: 4/14 (29%)

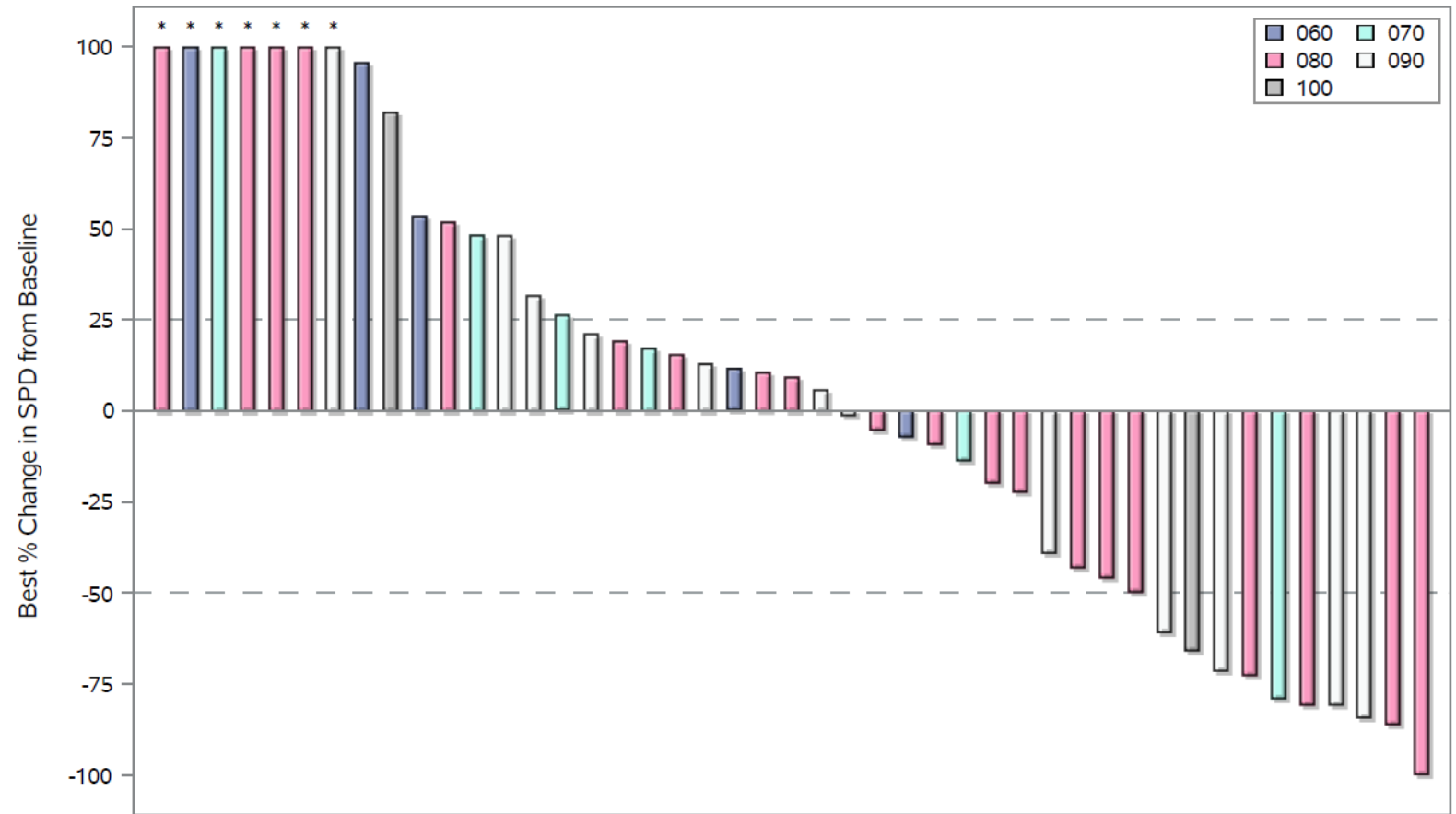
80: 4/20 (20%)

70: 1/7 (14%)

60: 0/7 (0%)

Supports hypothesis that treating earlier in disease course may enhance efficacy

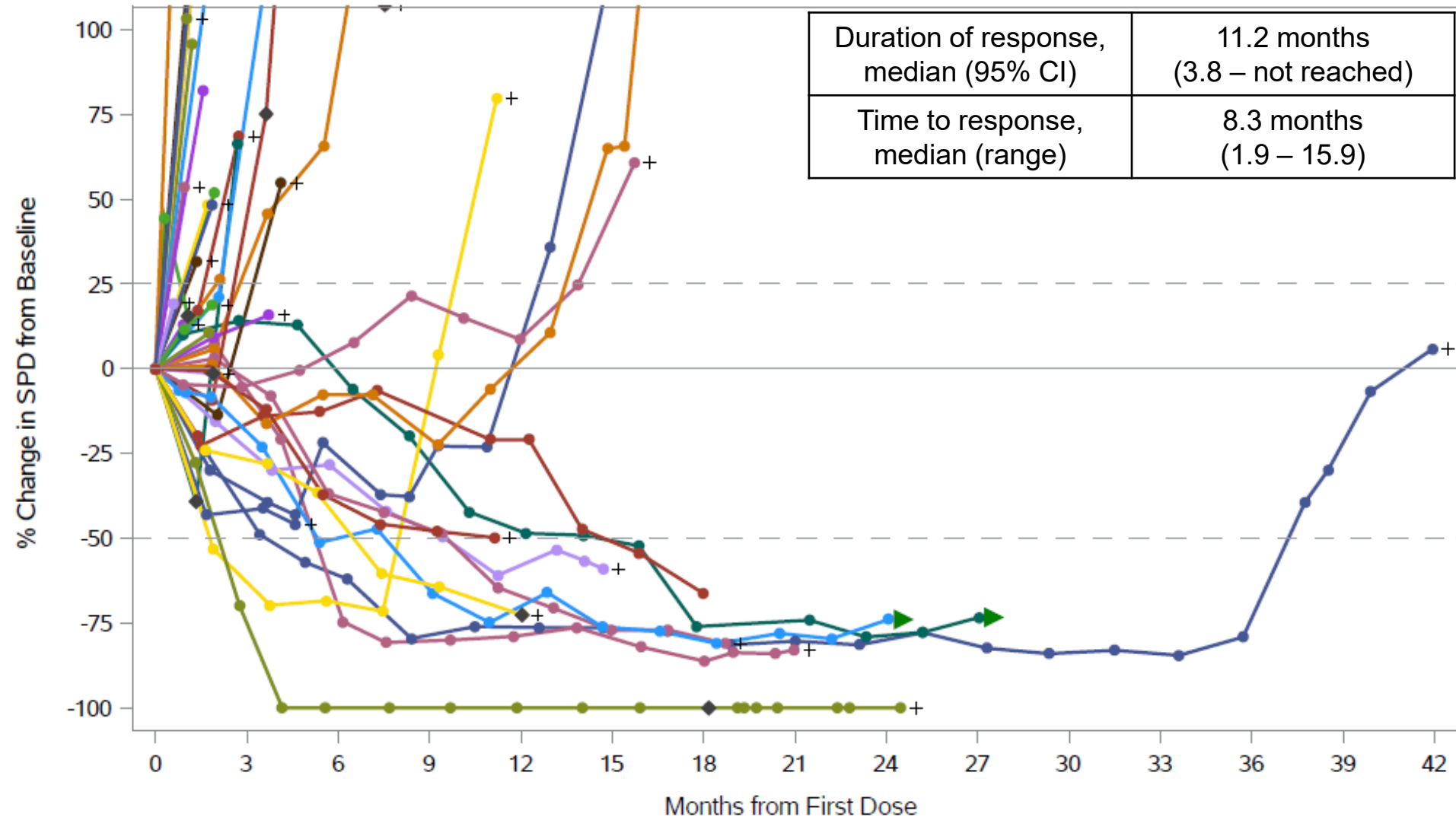
ONC201 Ph 2 Efficacy Analysis by BICR in Recurrent H3 K27M-mutant Diffuse Midline Glioma



\* Change > 100%, SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR)  
Only patients with measurable target enhancing lesions at both baseline and post-baseline are included.

# Clinically meaningful and durable RANO-HGG responses

ONC201 Phase 2 Efficacy Analysis by BICR in Recurrent H3 K27M-mutant Diffuse Midline Glioma



SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR)

Only patients with measurable target enhancing lesions by BICR at baseline and with post-baseline evaluations are included.

Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI ; one patient did not have measurable target lesion.

# ONC201 Safety

## Treatment-related Adverse Events in $\geq 3\%$ patients

Treatment-related Adverse Events, Integrated Safety Data Set, (N=211 glioma patients) <sup>1</sup>	Related TEAEs	
	All grades	Grade > 3
Any Treatment-related AE	55.5%	11.8%
Fatigue	21.8%	2.8%
Nausea	20.4%	0
Vomiting	14.2%	0.5%
Headache	8.5%	0.5%
Lymphocyte count decreased	6.6%	0.5%
Decreased appetite	5.7%	0
White blood cell count decreased	4.7%	0.5%
ALT increased	4.3%	0.5%
Hypophosphataemia	4.3%	0
Neutrophil count decreased	3.8%	0.5%
Anaemia	3.3%	0
Diarrhea	3.3%	0

## Healthy Adult Study<sup>2</sup> Incidence of ONC201-related Adverse Events

	125 mg N=33	375 mg N=15	625 mg N=45
Any treatment-related AE	33.0%	20.0%	49.0%
Grade 1	33.0%	20.0%	49.0%
Grade 2	0	0	0
Grade 3-5	0	0	0

- Dose modifications / discontinuations uncommon
- Most common events: headache, fatigue, nausea and vomiting
- Treatment-related AEs generally Grades 1 & 2
- Most common treatment-related event was fatigue



# RANO responses correspond with survival & clinical benefit

ONC201 Ph 2 Efficacy Analysis by BICR in Recurrent H3 K27M-mutant DMG

- No patients who experienced a RANO-HGG response had died at 24 months<sup>2</sup>
- RANO response strongly associated with reduction in steroid use and improvement in performance status

	All patients	RANO HGG Responders	RANO HGG and/or LGG Responders
N	50	10	15
PFS at 12 months (number of patients censored)	30% <sup>1</sup>	90% (0)	67% (2)
OS at 24 months (number of patients censored) <sup>2</sup>	35% <sup>1</sup>	80% (2)	53% (5)
Corticosteroids response <sup>3</sup> (number of patients evaluable)	47% (15)	100% (4)	100% (5)
Performance status response <sup>4</sup> (number of patients evaluable)	21% (34)	60% (5)	67% (9)



1. Kaplan-Meier median Progression-Free Survival or Overall Survival

2. Censored patients include those who are lost to follow-up or have withdrawn prior to the time point, as well as those who have not yet reached the time point. These patients are counted in the denominator but not counted as survivors (i.e., imputed as failure)

3. Corticosteroid response: ≥50% reduction in average daily corticosteroid dose compared to baseline with stable or improved KPS/LPS. Must be confirmed at next analysis timepoint. Corticosteroids converted into a dexamethasone equivalent dose. Baseline ≥4mg dexamethasone at baseline were evaluable.

4. Performance status response: increase in KPS/LPS compared to baseline with stable or reduced corticosteroid use. Must be confirmed at next analysis timepoint. Baseline KPS/LPS ≤80 were evaluable.

# Strong rationale for phase 3 success relative to recent GBM trials

Experimental Agent	Ph2 Design	Biomarker	Response criteria	Confounded by anti-angiogenic pseudo response	ORR	Duration of response	6 month PFS	Approved?
<i>ONC201– Ph2 rDMG</i>	Single agent	H3 K27M	RANO BICR	No	20-30%	11.2	35%	To be determined
 <b>Temodal®</b> temozolomide	Single agent	-	Levin	No	5%	?	21%	Yes (OS)
 <b>AVASTIN®</b> bevacizumab	Various	-	Various	Yes	20-70%	4-6	18-50%	Yes (AA per ORR, PFS)
<i>Cediranib</i>	Single agent	-	MacDonald	Yes	27%	?	26%	No
<i>Rindopepimut</i>	Combo + Avastin	EGFRv3	RANO	Yes	30%	7.8	28%	No
<i>Depatuxizumab mafodotin</i>	Single agent	-	RANO	No	7%	6.7	29%	No
<i>Enzastaurin</i>	Combo + Avastin	-	RANO	Yes	22%	?	21%	No



# ONC201 Phase 3 ACTION Study Summary





# Pivotal Phase 3 ACTION trial design

*Now enrolling, a randomized, double-blind, placebo-controlled, multicenter international study in 450 newly diagnosed diffuse glioma patients whose tumor harbors an H3 K27M-mutation.*

## Key Patient Inclusion

- H3 K27M-mutant diffuse glioma<sup>1</sup>
- Radiation therapy recently completed
- KPS  $\geq$  70 at time of randomization
- Stable steroid dose
- No prior bevacizumab
- No temozolomide within three weeks

## Treatment

ONC201 twice weekly  
(625mg ONC201 day 1 +  
day 2)

ONC201 weekly  
(625mg ONC201 day 1  
+ placebo day 2)

Placebo  
(Placebo day 1  
+ placebo day 2)

## Endpoints

- Primary: Overall Survival
- PFS (alpha-allocated)
- Secondary: steroid response, performance status, QoL, neurologic function

# Multiple unique aspects to ONC201 data support translation to phase 3 success



## Isolated, durable single agent activity

- Responses not confounded by combination treatments
- Responses were gradual, durable, and multi-focal
- Responses observed via most stringent criteria in blinded assessment



## Consistency across multiple endpoints

- Responses highly associated with other forms of clinical benefit
- PFS and OS favorable to historical benchmarks
- Multiple separate analyses suggest longer survival of patients who received ONC201



## Enhanced activity not required, but likely

- Earlier setting associated with higher response rate (performance status, tumor volume)
- Addition of higher-dose study arm
- Biomarker selection supports patient homogeneity

# Design provides multiple paths for success

*Interim data expected in early 2025 and final data in 2026*

Independent comparisons for each ONC201 arm versus control will be made at each timepoint.

## First OS<sup>(1)</sup> Interim

- ~164 events
- Success at HR<sup>(3)</sup>=0.52

## PFS by RANO HGG<sup>(2)</sup>

- ~286 events
- Success at HR=0.68

## Second OS Interim

- ~246 events
- Success at HR=0.64

## Final OS

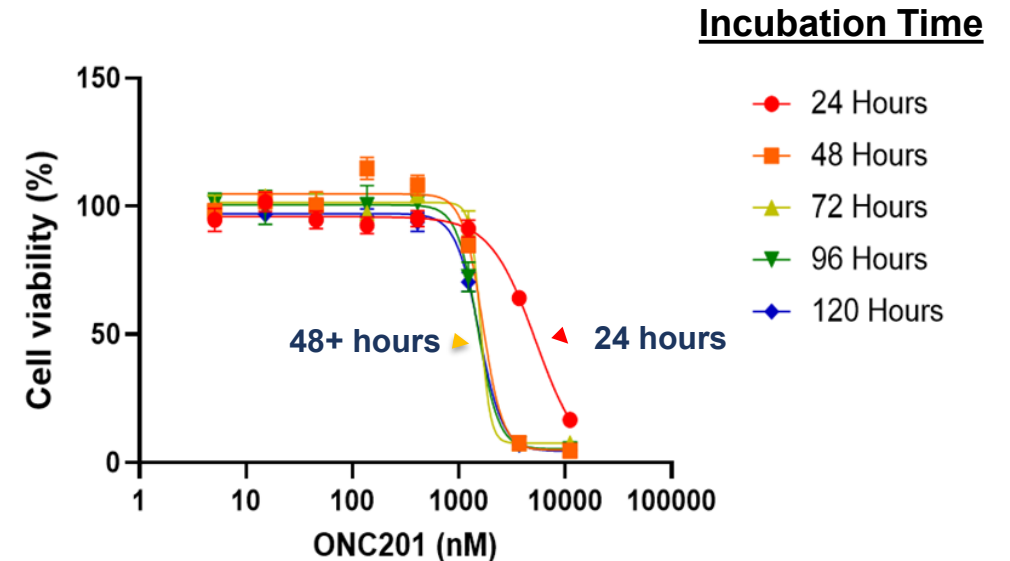
- ~327 events
- Success at HR=0.73

Powering assumptions 0.65 expected HR for OS and 0.60 expected HR for PFS

1. Overall Survival (OS)  
2. Progression-free survival (PFS). PFS may provide valuable data for regulatory discussions.  
3. Hazard Ratio

# Potential to increase ONC201 efficacy with dose schedule

- Once per week ONC201 dosing effective as monotherapy in Phase 2 studies
- Twice per week dosing on two consecutive days expected to increase duration of therapeutic exposure
  - Increased exposure time can increase glioma sensitivity to ONC201 in vitro
  - Generally well tolerated in Phase 1 without dose limiting toxicity or AEs leading to dose modification
- Phase 3 ACTION study will evaluate once per week and twice per week dosing schedules at 625mg (or body weight equivalent)



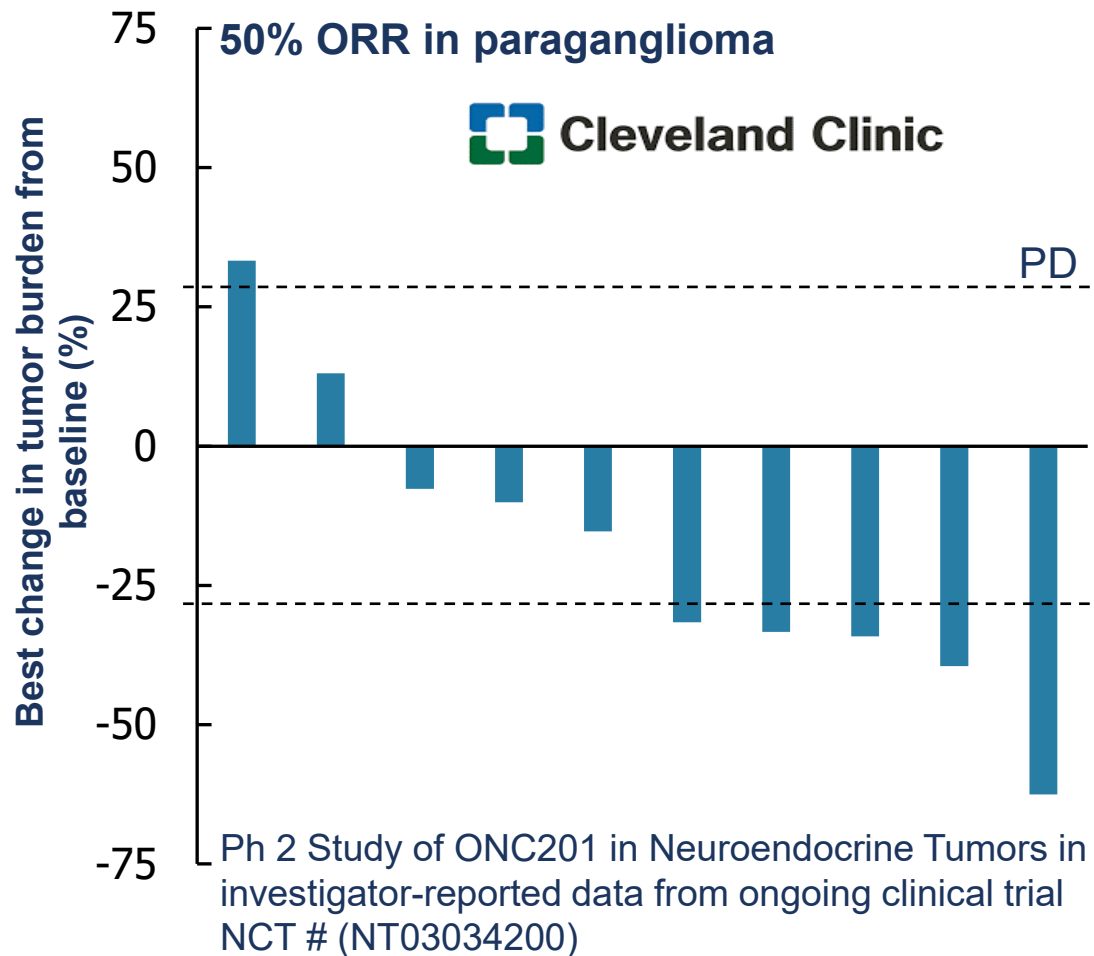
# ONC201 Market Opportunity Assessment



## H3 K27M-mutant glioma: rapid ramp to peak revenue expected

- No approved therapies for H3 K27M mutant glioma, ONC201 is the leading program targeting this mutation globally
- Potential market opportunity up to ~\$750 million
- Approximately 5,000 patients in top seven markets
- Ultra-orphan indication drug pricing
- H3 K27M mutations most often in children / young adults (little to no exposure to Medicare)
- Low barriers to adoption
  - No effective alternative therapies
  - High unaided awareness among neuro-oncologists
  - Mutation routinely identified by existing diagnostics
  - Longer-term, potentially combinable with other glioma therapies
- Patent protection for lead indication into 2037 - potential U.S. patent term extension (up to five years)

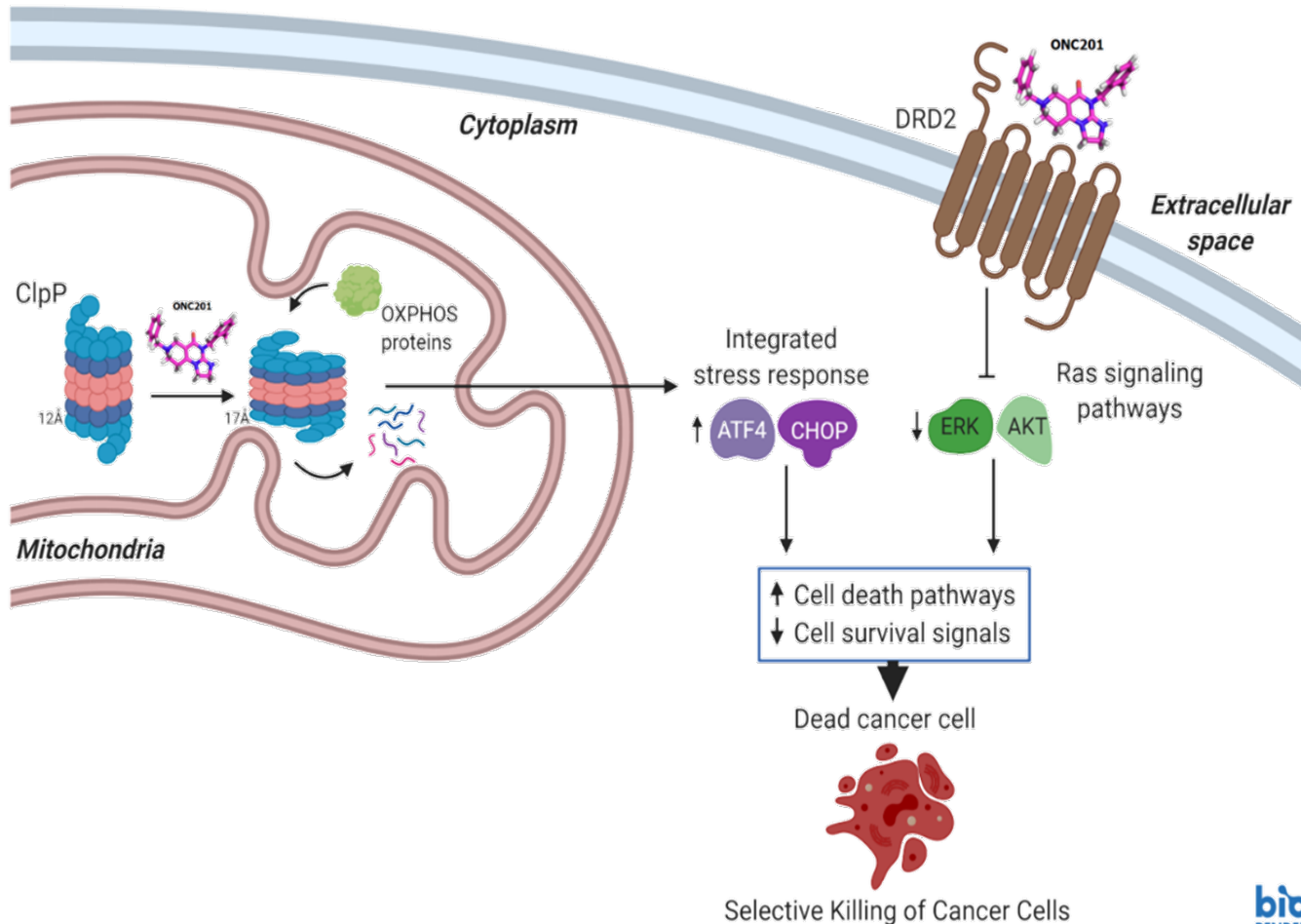
# ONC201 interim efficacy results in dopamine-secreting tumors outside the brain



- Single agent responses in Ph 2 neuroendocrine trial of ONC201 observed in subset (paraganglioma)
- Paraganglioma are adrenal-related tumors with elevated DRD2 expression
- Five patients have been treated > 1 year
- Fewer short-term and potential long-term toxicities than other paraganglioma therapies

# ONC201 directly engages DRD2 and ClpP

*ONC201 upregulates integrated stress response, inactivates Akt/ERK, selectively inducing tumor cell death*

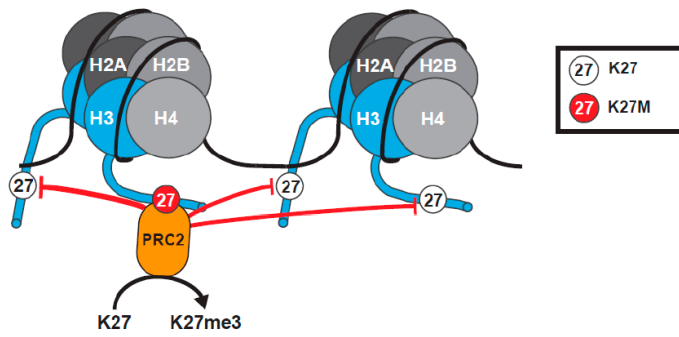


- ONC201 can selectively induce apoptosis in cancer cells by altering activity of two proteins
- DRD2 antagonism
  - DRD2 is a G protein-coupled neuroreceptor that regulates Ras signaling
  - ONC201 antagonizes DRD2, inhibiting Ras signaling pathways
- ClpP agonism
  - ClpP normally degrades misfolded proteins in mitochondria
  - ONC201 modifies ClpP conformation, promoting excess degradation of specific mitochondrial proteins important for cancer cell viability



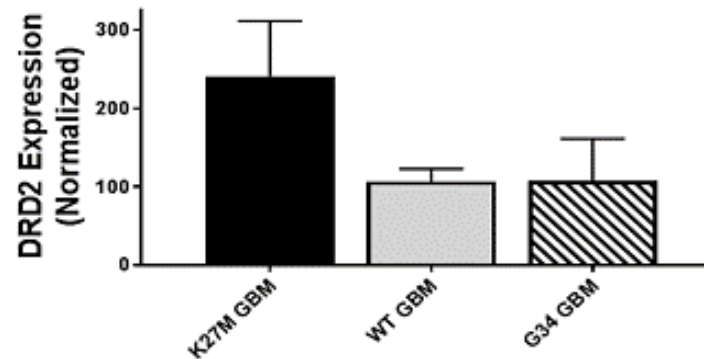
# H3 K27M glioma cell lines exhibit enhanced sensitivity to ONC201

Lysine to methionine (“K-to-M”) histone H3 mutation reduces H3 K27 methylation



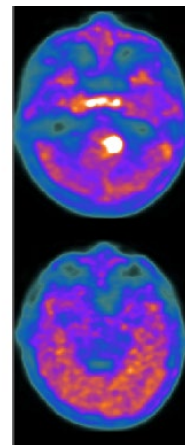
K27M-mutants bind PRC2 which normally methylates H3 K27 via EZH1/2; binding/tethering PRC2 prevents methylation of even nonmutant H3 K27

H3 K27M elevates DRD2 expression



H3 K27M  
Grade IV  
DMG

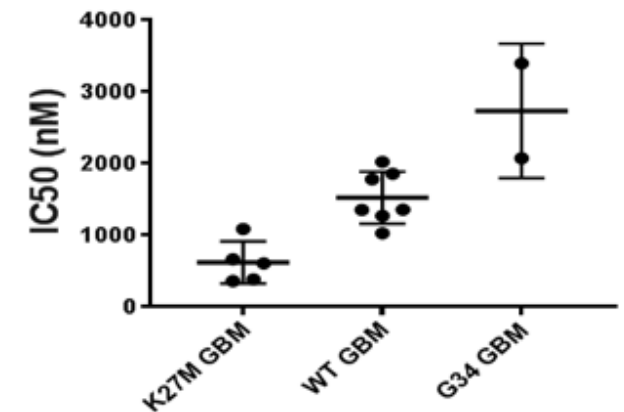
H3 WT  
Grade IV  
DMG



<sup>18</sup>F-DOPA PET

Midline tumors occur in dopamine-rich regions of the brain

High sensitivity to ONC201



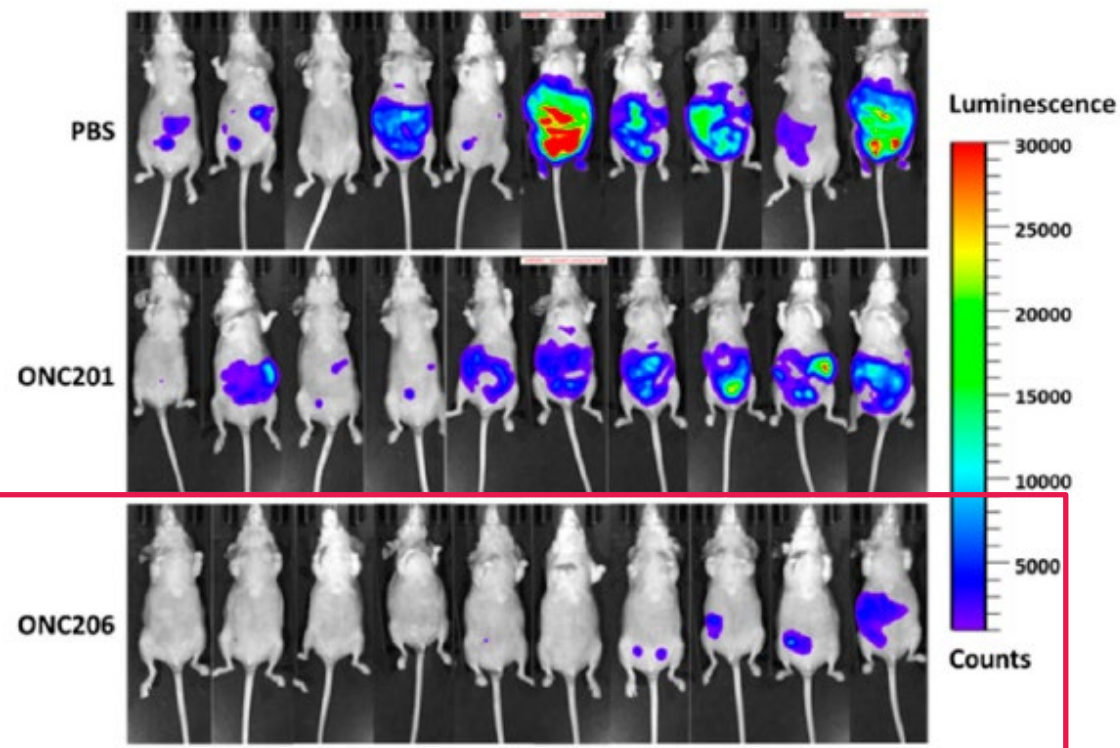
# ONC206 and ONC212



# ONC206: potentially differentiated DRD2 antagonist + ClpP agonist

- Focus in current clinical trials on recurrent central nervous system (CNS) cancers
- Efficacy in preclinical models of central nervous system and other tumors
- Enrolling 2 dose escalation clinical trials for adult and pediatric CNS tumor patients

## ONC206 Efficacy in Tumor Xenografts<sup>1</sup>



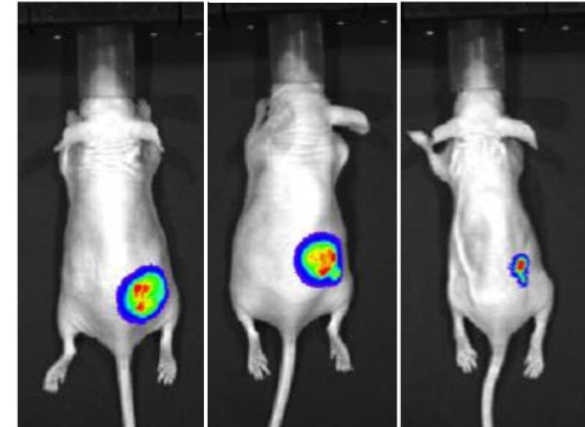
PACIFIC PEDIATRIC  
NEURO-ONCOLOGY  
CONSORTIUM

# ONC212: GPR132 + ClpP Agonist

- Distinct molecular target (GPR132) and efficacy profile relative to ONC201/ONC206
- Efficacy in preclinical models of advanced cancers
- GLP-tox studies ongoing to potentially advance to IND
- Partnerships established for early-stage clinical trials with Brown University and MD Anderson Cancer Center

**Pancreatic cancer model shows the potential of ONC212<sup>1</sup>**

Vehicle    ONC201    ONC212



**BROWN**  
Alpert Medical School

THE UNIVERSITY OF TEXAS  
**MDAnderson**  
**Cancer Center**  
Making Cancer History®

# Legacy antiviral library - CMX521

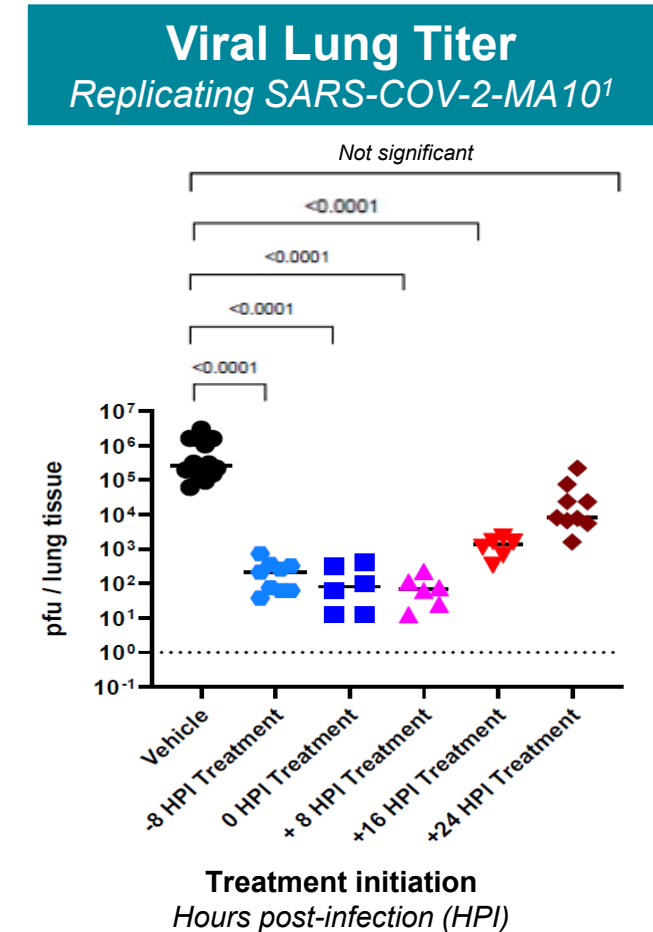




# CMX-521: anti-SARS-CoV-2 preclinical activity

- Ribonucleoside analog that is a viral polymerase inhibitor
  - Inhaled nebulized liquid aerosol formulation; minimal systemic exposure
- Monotherapy efficacy in mouse-adapted SARS-CoV-2-MA10 model across multiple endpoints
  - Lung viral titer
  - Viral RNA parallel viral lung titer (plaque forming unit)
  - Clinical scoring (animal health)
  - Lung pathology
  - Animal weight loss

**\$2 million grant to fund prodrug formulations that could enable oral administration with improved lung delivery**



1. Replicates lung pathology of human infection 4-days post-infection. One day in mouse is 5-7 days in humans (adjusted disease course).

# Corporate Update



# TEMBEXA® deal term summary

Emergent BioSolutions is an experienced biodefense company collaborating with government agencies to protect public health

## Terms summary:

- \$238 million received upfront at closing in Q3 2022
- Up to an additional \$124 million in potential BARDA procurement milestones
- 20% royalty on future U.S. gross profit with volumes above 1.7 million courses of therapy
- 15% royalty of all international gross profit
- Up to an additional \$12.5 million in development milestones

**TEMBEXA®**  
brincidofovir  
10 mg/mL oral suspension | 100 mg tablets





# Financial strength supports development through key catalysts



High probability of  
success for Phase 3  
ACTION study of  
ONC201



Low barriers to  
commercial potential  
for ONC201



Corporate capability  
and financial flexibility

**\$285 million cash balance at September 30, 2022, no debt**

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## **Fully funded Ph 3 program with multiple potential paths to approval**

First-Line H3 K27M-mutant diffuse glioma – The ACTION Study

- ✓ *Trial initiated November 2022*
  - ✓ *Interim OS data expected early 2025*
  - ✓ *Full OS data expected 2026*
- 

## **Early-stage pipeline leverages external capital**

- ✓ *ONC206 dose exploration efficacy signal*
- ✓ *Pre-clinical programs potential to advance to clinic or partner (ONC212, CMX521)*
- ✓ *Robust business development search and evaluation process*

# Chimerix Corporate Presentation

