# Chimerix 3Q2022 Corporate Presentation





### **Forward-Looking Statements**

These slides contain 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, consummation of the Transaction, including, as a result of failing to satisfy the closing conditions to the Transaction; the satisfaction of any closing conditions in a timely manner or at all, including, without limitation; the execution of a procurement contract for TEMBEXA; the timing of the initiation of the Phase 3 clinical development of ONC201; 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 that the Transaction will not be completed as planned; Chimerix will not obtain a procurement contract for TEMBEXA in a timely manner, on favorable terms, or at all; risks that the initial delivery or any subsequent deliveries of TEMBEXA will not occur as planned, or at all; 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, or may not be predictive of real-world results or of results in subsequent trials; 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.



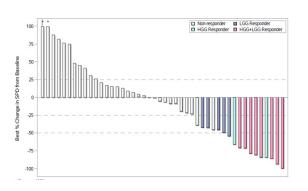
# Proceeds from pending sale of TEMBEXA® to Emergent BioSolutions to fund oncology development



Pending Emergent BioSolutions transaction likely provides immediate non-dilutive capital

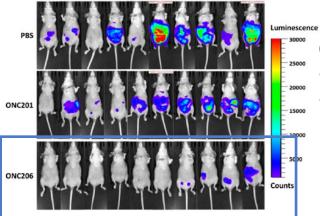
- CMRX to participate in future economics and upside potential
- Reduces spend associated with maintaining supply chain
- Leverages Emergent's government contracting process to maximize future value

## Focus on oncology areas of high unmet need supported by strong data



#### **ONC201**

- Ph 3 trial (ACTION study) planned to initiate 4Q22
- Positive Phase 2 ORR data in recurrent H3 K27M-mutant glioma
- New indications

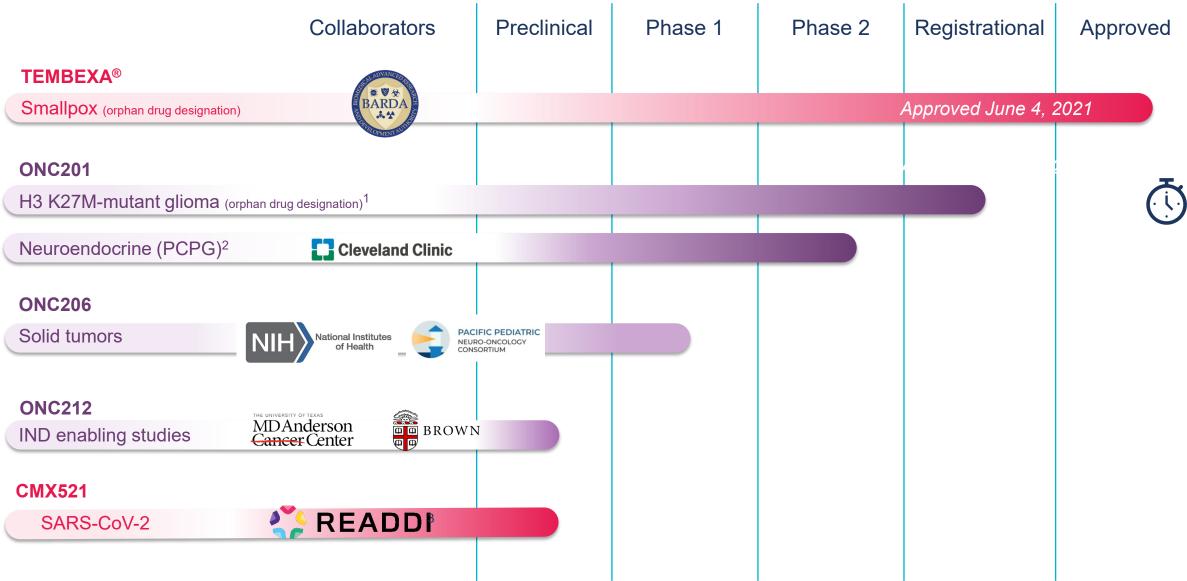


#### **ONC206**

- Phase 1 dose escalation
- Efficacy in tumor xenografts



### Deep pipeline across all development stages







Pheochromocytoma/paraganglioma



<sup>3</sup> Rapidly Emerging Antiviral Drug Development Initiative

# TEMBEXA® Approved for Treatment of Smallpox as a Medical Countermeasure





# The value of preparedness has never been more evident

- Highly infectious virus with ~30% mortality<sup>1</sup>
- Population is unvaccinated since early '70s
- Considered a Class A security threat by PHEMCE<sup>2</sup>, CDC and NIAID
- Weaponized virus could be engineered to increase transmission and resistance, TEMBEXA impairs viral replication with a different mechanism of action than TPOXX<sup>®</sup>, important hurdle to an engineered bioterror attack<sup>3</sup>
- TEMBEXA® approved June 4,2021 for the treatment of smallpox in tablet and oral suspension formulations
- To date, two international contracts of approximately \$35 million signed for TEMBEXA





Two labs in the world keep a live smallpox sample. The one in Russia just had an explosion

N'dea Yancey-Bragg USA TODAY Published 12:46 p.m. ET Sep. 17, 2019





Health » Diet + Fitness | Living Well | Parenting + Family

CDC: Smallpox found in NIH storage room is alive

By Jen Christensen, CNN

(3) Updated 3:07 PM ET, Fri July 11, 2014



How Canadian researchers reconstituted an extinct poxvirus for \$100,000 using mail-order DNA

By Kai Kupferschmidt | Jul. 6, 2017, 5:00 PM

Posted in: **Health, Science and Policy, Scientific Community** doi:10.1126/science.aan7069



- 1. World Health Organization, estimate for the more common variola major form of smallpox (vs variola minor of 1%), January 13, 2014
- 2. Public Health Emergency Medical Counter Measures Enterprise

### **TEMBEXA®** deal term summary

Emergent experienced biodefense company with government agencies to protect public health.

Terms summary subject to transaction closure:

- \$225 million upfront at closing<sup>1</sup>
- Up to an additional \$100 million in future milestones with the execution of additional CLINs from BARDA<sup>1</sup>
- 20% royalty on future U.S. gross profit with volumes above 1.7 million courses of therapy
- 15% royalty of all international gross profit



10 mg/mL oral suspension | 100 mg tablets





# **ONC201 Phase 2 Primary Efficacy Analysis**

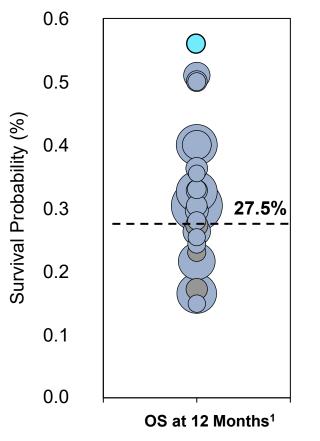


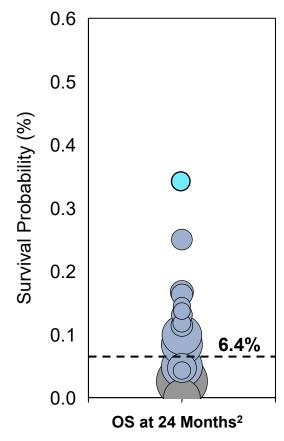


### Recurrent glioma remains a high unmet need

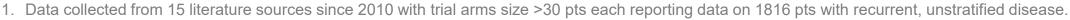
- FDA has acknowledged available therapy in recurrent setting is palliative
  - Often not possible to resect
  - Recurrence inevitable after first-line radiation
  - Chemotherapy ineffective; objective responses rare by RANO-HGG
- Survival in grade II-IV recurrent glioma reported to be 27.5% at 12 months<sup>1</sup> and 6.4% at 24 months<sup>2</sup>
- Survival in pediatric recurrent H3 K27M DMG reported to be 0% at 24 months<sup>3</sup>
- Survival in ONC201-treated recurrent H3 K27M DMG was 57% OS at 12 months and 35% at 24 months







- Grade II-III Glioma GBM (Grade IV) Ph 2 50 Patient Primary Efficacy Analysis by BICR



- 10 literature sources that describes OS with 1279 patients
- 3. Koschmann et al, 2020; DOI:10.21203/rs.3.rs-69706/v1



### Topline results 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% by RANO HGG and/or LGG by dual reader BICR
  - RANO-HGG criteria assessed by dual reader BICR
    - ORR 20% (95% CI: 10 34%)
    - Median 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

### Efficacy analysis of ONC201 in recurrent H3 K27M DMG

### **Objective**

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

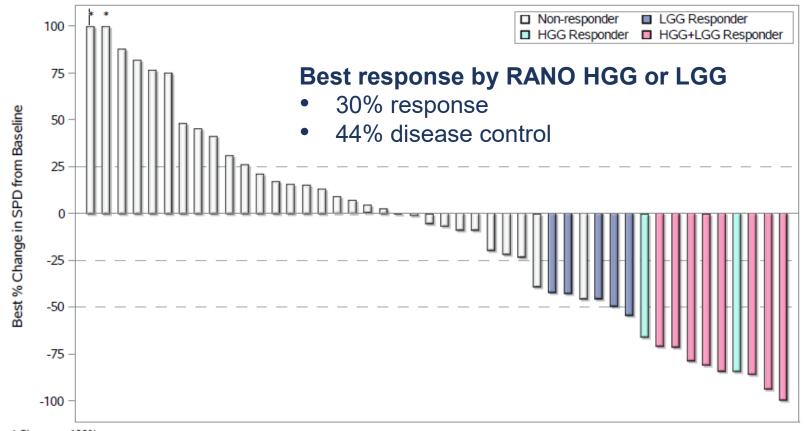
### **Eligibility**

- Age ≥2yo and received ONC201 under studies ONC006, ONC013, ONC014, ONC016, or ONC018
- Diffuse glioma with a known H3K27M 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 ≥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

- Strict inclusion to ensure responses attributable to single agent treatment
- Responses require both imaging and clinical criteria
- Blinded independent central review (BICR)
- Growing consensus that both RANO HGG and RANO LGG are meaningful measures of patient benefit





<sup>\*</sup> Change > 100%



SPD=sum of products of perpendicular diameters (target lesions per BICR)
Only patients with measurable target lesions at both baseline and post-baseline are included.
Best change in enhancing or non-enhancing lesions reflected on y-axis.

# RANO-HGG responses observed across age groups

### Responses by age group:

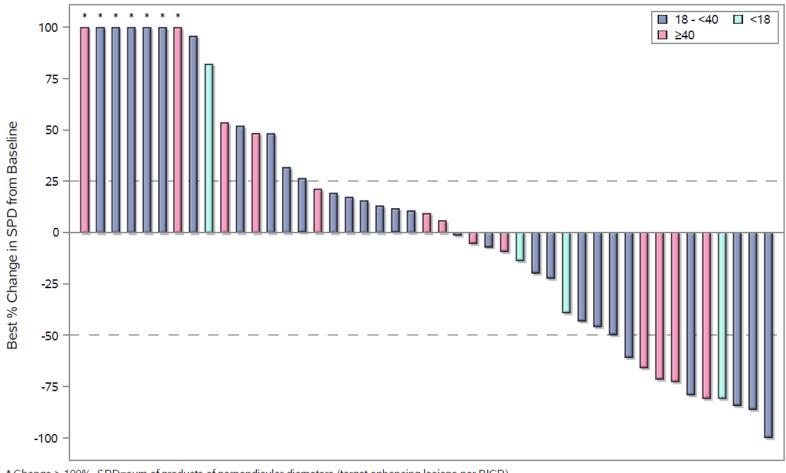
- <18 years: 1/4 (25%)

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

- <u>></u>40 years: 4/14 (29%)

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

Ph 2 50 Patient Primary Efficacy Analysis by BICR in H3 K27M-mutant Recurrent Diffuse Midline Glioma



<sup>\*</sup> 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 supports early-line trial

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

- 100: 1/2 (50%)

- 90: 4/14 (29%)

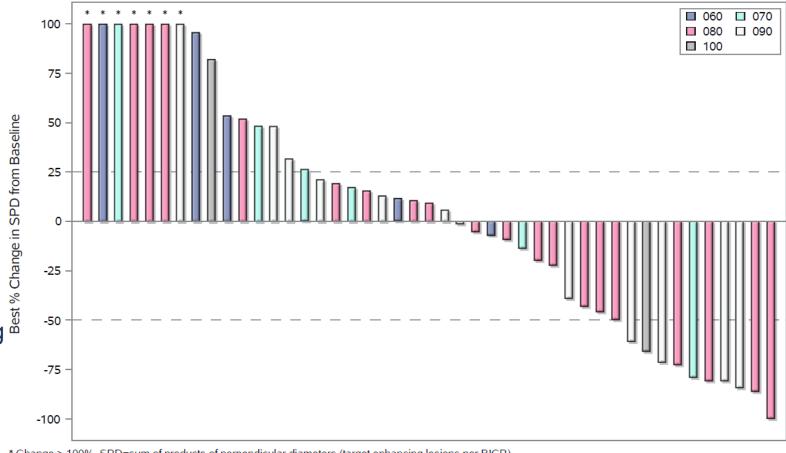
- 80: 4/20 (20%)

- 70: 1/7 (14%)

- 60: 0/7 (0%)

• Supports hypothesis that treating earlier in disease course may enhance efficacy

Ph 2 50 Patient Primary Efficacy Analysis by BICR in H3 K27M-mutant Recurrent Diffuse Midline Glioma

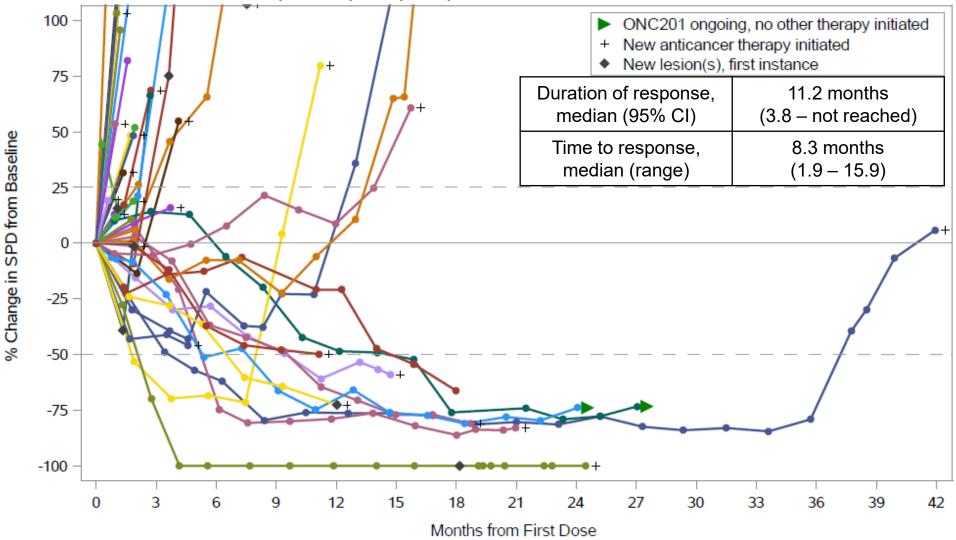


<sup>\*</sup> Change > 100%, SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR) Only patients with measurable target enhancing lesions at both baseline and post-baseline are included.



### **Spider plot (RANO-HGG by BICR)**

Ph 2 50 Patient Primary Efficacy Analysis by BICR in H3 K27M-mutant Recurrent Diffuse Midline Glioma





### **ONC201 Safety**

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

Treatment-related Adverse Events,	Related TEAEs		
Integrated Safety Data Set, (N=211 patients) <sup>1</sup>	All grades	<b>Grade</b> ≥ 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

- Most common events were headache, fatigue, nausea and vomiting
- Treatment-related AEs generally Grades 1 & 2
- Most common treatment-related event was fatigue

<sup>&</sup>lt;sup>1</sup>Reported in ONC201 Investigator Brochure

<sup>&</sup>lt;sup>2</sup> Preliminary results from ONC201-101, Part A

### **RANO Reponses Correspond with Survival & Clinical Benefit**

Ph 2 50 Patient Primary Efficacy Analysis by BICR in H3 K27M-Mutant Recurrent Diffuse Midline Glioma

	All patients	RANO HGG Responders	RANO HGG and/or LGG Responders	All Other Patients
N	50	10	15	35
PFS at 12 months (number of patients censored)	30%1	90% (0)	67% (2)	0% (8)
OS at 24 months (number of patients censored) <sup>2</sup>	35% <sup>1</sup>	80% (2)	53% (5)	0% (8)
Corticosteroids response <sup>3</sup> (number of patients evaluable)	47% (15)	100% (4)	100% (5)	20% (10)
Performance status response <sup>4</sup> (number of patients evaluable)	21% (34)	60% (5)	67% (9)	4% (25)

- 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

Durable and unconfounded single agent responses unique to ONC201

Experimental Agent	Ph2 Design	Biomarker	Response criteria	Confounded by anti-angiogenic pseudo response	ORR	Duration of response	6 month PFS	Approved?
ONC201 – Ph2 rDMG	Single agent	H3K27M	RANO BICR	No	20-30%	11.2	35%	To be determined
Temodar temozolomide	Single agent	-	Levin	No	5%	?	21%	Yes (OS)
AVASTIN° bevacizumab	Various	-	Various	Yes	20-70%	4-6	18-50%	Yes (AA per ORR, PFS)
Cediranib	Single agent	-	MacDonald	Yes	27%	?	26%	No
Rindopepimut	Combo+ TMZ	EGFRv3	RANO	Yes	30%	7.8	28%	No
Depatuxizumab mafodotin	Single agent	-	RANO	No	7%	6.7	29%	No
Enzastaurin	Combo + Avastin	-	RANO	Yes	22%	?	21%	No



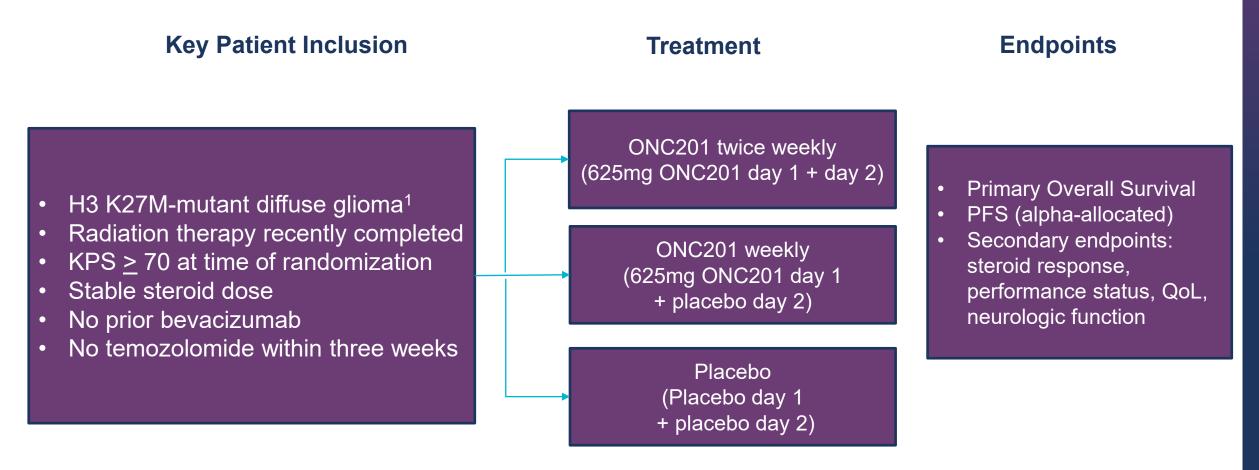
# ONC201 Ph 3 ACTION Study Summary





### **Pivotal Phase 3 ACTION Trial Design**

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





### **Design provides multiple paths for success**

Endpoints 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(1)	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



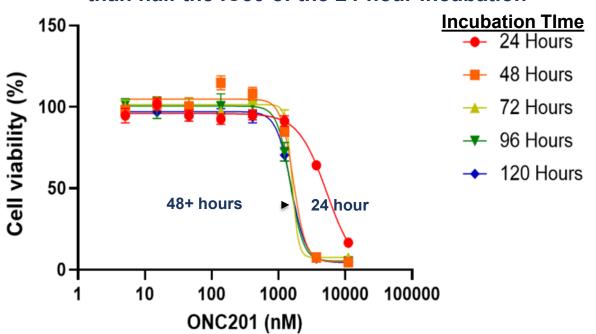
<sup>(1)</sup> Overall Survival (OS)

<sup>(2)</sup> Progression-free survival (PFS). PFS may provide valuable confirmatory data for regulatory discussions.

<sup>(3)</sup> Hazard Ratio

# Once per week dosing proven active, Day1/Day2 dosing has potential to further enhance efficacy

ONC201 IC50 at 48 hours of exposure was less than half the IC50 of the 24-hour incubation



### **Preclinical**

Maximum in vitro efficacy achieved with 48 hours of ONC201 incubation in HGG cell viability assays (~2500 to 3000 nM)

### **Clinical**

Human brain tumor samples show 2675nM ONC201 (mean) 24 hours post-dose in range of the in vitro IC50

Day 1/Day 2 dosing has been generally well tolerated

No instances of dose-limiting toxicity

No AEs leading to dose discontinuation or reduction

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

- ✓ Used most robust assessment of response (RANO vs RECIST or McDonald or Levine)
- ✓ Response consistency across distinct imaging assessments (HGG and LGG)
- ✓ Isolation of single agent activity (progression declared, prior therapy washout)
- ✓ Gradual onset of response
- ✓ Durability of response
- ✓ Multi-focal responses
- ✓ Consistency across clinical endpoints (steroid use, performance status, survival)
- ✓ Best outcomes in earlier treatment setting (performance status, tumor volume)
- ✓ Lack of active alternatives
- ✓ Stability and homogeneity of biomarker
- ✓ Definitive single agent activity in mechanistically-related second relapsed cancer indication

# ONC201 Market Opportunity Assessment



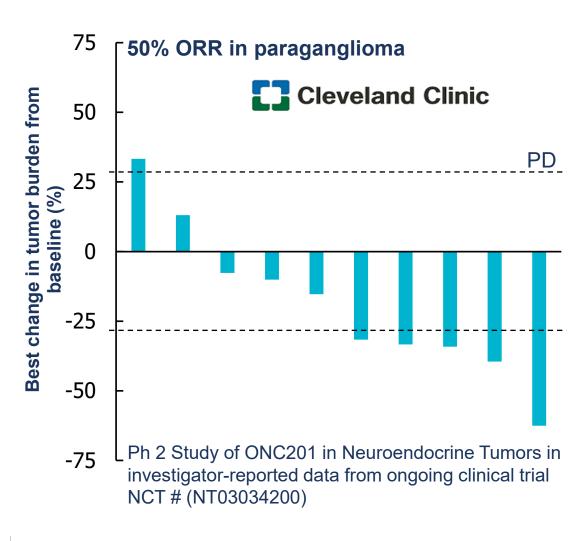


### H3 K27M-mutant glioma: market dynamics and opportunity

- Potential annual revenue opportunity exceeding \$500 million
- U.S. annual incidence of ~2,000
- Market research
  - Nearly all midline glioma patients tested for H3 K27M-mutation
  - ~20% ORR and/or clinically relevant durability deemed clinically meaningful
  - ONC201 use expected in >80% of H3 K27M-mutant glioma patients based on current profile
  - Interest in combination with radiation, if possible, in the front-line setting
- Competitive landscape: chemotherapy and bevacizumab ineffective; targeted agents, vaccines and CAR-T therapies are in early development with limited efficacy analysis available
  - ONC201 most advanced program targeting H3 K27M-mutant glioma
- Low barriers to adoption
  - No approved agents in H3 K27M-mutant glioma treatment options available
  - KOL interest in exploring new front-line therapies (enrollment criteria in ACTION trial)
  - H3 K27M-mutant already on commercial and site-specific NGS panels, oral dosing, safety profile
  - High unaided awareness of ONC201 among neuro-oncologists
  - Longer-term, potential combinable with other glioma therapies



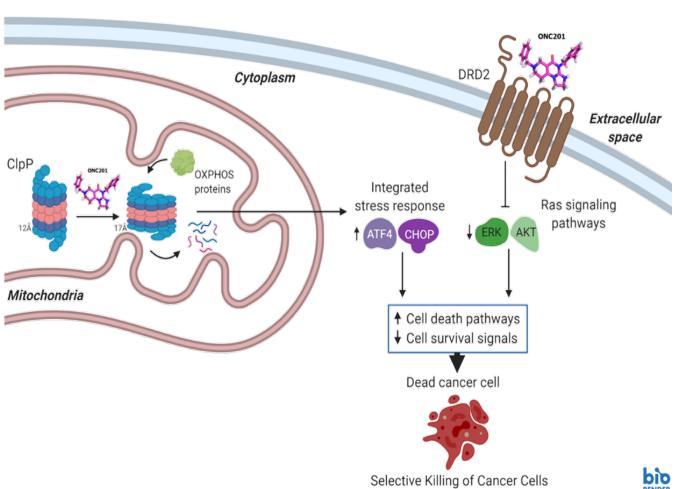
# ONC201 interim efficacy results in dopamine-secreting tumors outside the brain



- 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

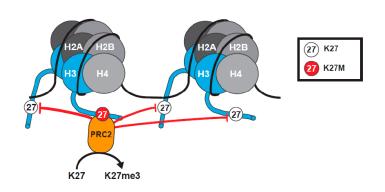


- ONC201 can selectively induce apoptosis in cancer cells by altering activity of two proteins
- DRD2 antagonism
  - DRD2 is a G protein-coupled neuroreceptor that regulates Ras signaling
  - ONC201 antagonizes DRD2, inhibiting Ras signaling pathways
- ClpP agonism
  - ClpP normally degrades misfolded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



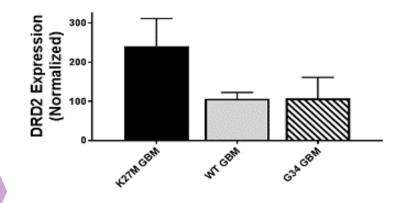
### H3 K27M-mutant gliomas exhibit enhanced sensitivity to ONC201

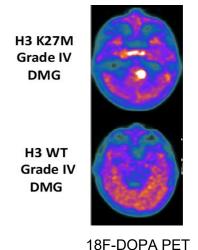
Lysine to methionine ("K-to-M") histone H3 mutation reduces H3 K27 methylation



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

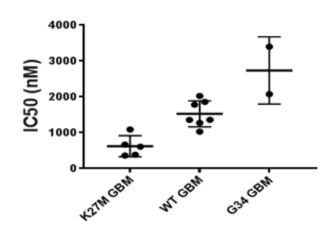




Midline tumors occur in dopaminerich regions of the brain



### High sensitivity to ONC201





### **ONC201 FDA designations**



Orphan Drug Designation (ODD) (treatment of glioblastoma and treatment of malignant glioma)



Fast Track Designation (FTD) for adult recurrent H3 K27M-mutant high-grade glioma



Rare Pediatric Disease Designation for treatment of H3 K27M mutant glioma

Potential to receive rare pediatric voucher<sup>1</sup>

### ONC206 and ONC212





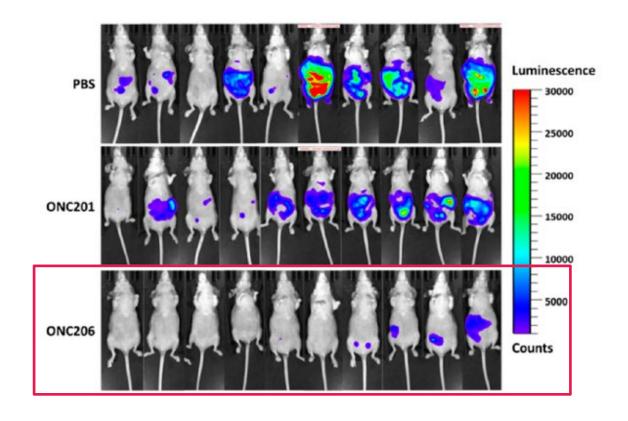
### ONC206: differentiated DRD2 antagonist + ClpP agonist

- 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>





### ONC212 preclinical activity in solid tumor and hematological cancer

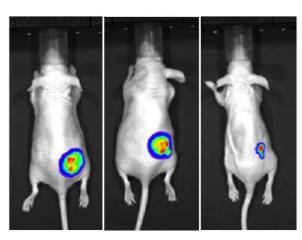
- Distinct molecular target (GPR132) and efficacy profile relative to ONC201/ONC206
- Efficacy in preclinical models of pancreatic cancer and AML
- IND-enabling studies ongoing
- Partnerships established for early-stage clinical trials with Brown and MD Anderson





## Pancreatic cancer model shows the potential of ONC212<sup>2</sup>

Vehicle ONC201 ONC212





### **CMX521**





### CMX521: SARS-CoV-2 antiviral with established safety profile

### **CMX521**

- Ribonucleoside analog known to inhibit viral polymerase
- Uptake and conversion to triphosphate demonstrated in human epithelial cells
- Oral formulation developed through Phase I
- 27 kg of GMP API available for development/ clinical
- COM patent through 2038, with Method of Use through 2040

### Data in SARS-CoV-2

- In vitro activity in human airway epithelial cells (EC50 = 0.3-0.9uM)
- In vivo efficacy with aerosol delivery in SARS-CoV-2-MA10 mouse model established by UNC School of Medicine
- Low µM activity across diverse coronaviruses suggests broad variant activity

### **Safety Profile**

- <u>Not</u> mutagenic, clastogenic, cytotoxic or mitotoxic
- Excellent safety profile in IND enabling tox studies (oral) in rats and dogs
- Inhaled aerosol formulation welltolerated in mice
- Well-tolerated in healthy volunteer Phase I study at ≤ 2400 mg oral

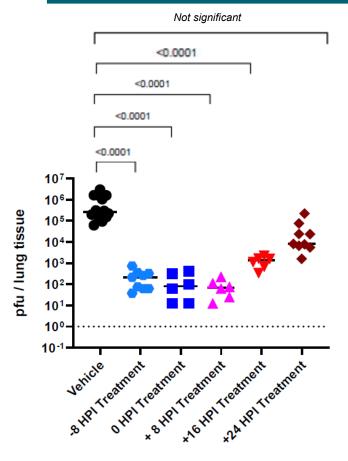
Currently assessing approaches enabling oral administration with improved lung delivery



### Significant antiviral effect demonstrated in nonclinical SARS-CoV-2 model conducted in collaboration with UNC-CH

- Mouse-adapted SARS-CoV-2-MA10 model
  - Replicates lung pathology of human infection 4-days post infection
    - 1 day in mouse = 5-7 days in humans (adjusted disease course)
- CMX521 delivered as inhaled nebulized liquid aerosol
  - 3x daily from initiation through Day 4
- Minimal systemic exposure
- CMX521 treatment significantly decreased lung viral titer
  - 365-fold decrease with treatment initiation 16 hours post-infection
  - 3,000-fold decrease with treatment initiation at time of infection
- Clinical scoring (animal health), lung pathology, animal weight loss and viral RNA parallel viral lung titer (plaque forming unit)
- Dose-range, PK, and combination studies ongoing

### Viral Lung Titer Replicating SARS-COV-2-MA10



Treatment initiation
Hours post-infection (HPI)



### **Corporate Update**





### **Financial summary**

Dollars (millions)	June 30, 2022 (YTD)
Beginning Cash Bal (Jan 1, 2022)	\$ 90.4
R&D (cash)	(28.7)
G&A (cash)	(8.8)
Op Ex (cash)	(37.5)
Debt repayment & other bal sht chgs	(\$10.1)
Cash Balance (June 30, 2022)	42.8
Shares outstanding	87.4

- Pro forma cash balance at June 30, 2022, with proceeds from post-quarter TEMBEXA revenue, is ~\$70M
- Pending Transaction with Emergent BioSolutions yields potential cash runway into 2027
- Cash expected through full data of ACTION study, other pipeline catalysts
- No debt outstanding and no milestone payments owed until potential approval of ONC201

### Continued 2022 execution lays foundation for upcoming catalysts

### **Recent Key Highlights**

### ONC201 ONC206 ONC212

- ✓ 30% response rate by RANO-HGG/LGG in Ph2 recurrent H3 K27M glioma
- ✓ Ph 3 ACTION study in H3 K27M-mutant glioma design announced
- ✓ ONC206 Ph 1 enrolling with NIH and PNOC

#### **TEMBEXA**

- ✓ US Anti-trust clearance for sale of TEMBEXA to EBS
- ✓ ~\$35 million in international procurement agreements
- ✓ Contracting process with BARDA for up to 1.7m treatment courses

#### **CMX521**

#### **COVID-19:**

- ✓ Preclinical inhaled data demonstrates potential efficacy
- ✓ Previous Phase 1 in different indication supports safety profile
- ✓ ICAR late breaker presentation

### 2022 Expected 2H Events

- FDA feedback on accelerated approval for ONC201
- Initiation of the ONC201 ACTION Ph 3 study
- Completion of BARDA procurement contract
- Closing of TEMBEXA sale to EBS
- Completion of ONC212 IND enabling tox studies
- CMX521 animal data on improved oral formulation



# **Chimerix Corporate Presentation**



