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

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

GPCRs are selectively hijacked by malignant cells

Therapeutic opportunity to reverse dysregulation via specific targeting
The H3 K27M mutation predominantly occurs in young patients with gliomas located in midline brain structures.
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:

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>DAT</th>
<th>D1 receptor</th>
<th>D2 receptor</th>
<th>D3 receptor</th>
<th>D4 receptor</th>
<th>D5 receptor</th>
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<tbody>
<tr>
<td>L293</td>
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<tr>
<td>Bc-1</td>
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<td>K322</td>
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<td>CG-1</td>
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<td>PRI</td>
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<tr>
<td>NCEB1</td>
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<td>JVM2</td>
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<tr>
<td>DOHH2</td>
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<tr>
<td>K106</td>
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</tbody>
</table>

DRD2 Induced Volume Change:

- **Dox-** (red line) shows a significant decrease in volume over 6 weeks.
- **Dox+** (blue line) shows a significant increase in volume over 6 weeks.


Meredith et al, *PNAS*, 2006

Li et al, *Oncotarget*, 2014
ONC201: First Clinical Bitopic DRD2 Antagonist

ONC201 selectivity antagonizes DRD2 via orthosteric and allosteric residues

Enables selective and unique DRD2 antagonism

Orthosteric Residues

DR Conservation of ONC201-critical residues

20% 40% 60% 80% 100%

Adapted from PDB 6C38; Wang et al, Nature, 2018

Prabhu et al, Society of Neuro-Oncology, 2018
Effective in Preclinical Models of High Grade Glioma

Achieves biologically active brain concentrations

Active in preclinical models of high grade glioma

Allen et al, Science Translational Medicine, 2013
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

H3 K27M-mutant gliomas respond to ONC201

Morgan and Shilatifard, Science, 2013

Morgan and Shilatifard, Pediatric SNO, 2019

Koschmann et al, Pediatric SNO, 2019

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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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>57 (22-74) y/o</td>
</tr>
<tr>
<td>Male : Female</td>
<td>9 : 8</td>
</tr>
<tr>
<td>KPS, median (range)</td>
<td>90 (70-100)</td>
</tr>
<tr>
<td>Number of baseline lesions, median (range)</td>
<td>1 (1-3)</td>
</tr>
<tr>
<td>Prior low grade</td>
<td>4</td>
</tr>
<tr>
<td>Prior TMZ/RT</td>
<td>17</td>
</tr>
</tbody>
</table>

**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

Arrillaga et al, Oncotarget, 2017
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

<table>
<thead>
<tr>
<th>All Patients</th>
<th>ONC006</th>
<th>ONC013</th>
<th>Expanded Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=15</td>
<td>N=5</td>
<td>N=9</td>
<td>N=1</td>
</tr>
</tbody>
</table>

**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

**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%) -

**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 (1-3)

**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

<table>
<thead>
<tr>
<th>Best RANO Response (N=15)</th>
<th>CE*</th>
<th>NCE**</th>
<th>CE* or NCE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Partial Response</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Minor Response</td>
<td>-</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Progress Disease</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Unevaluable</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

| 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

Location of primary lesion:
- Thalamus
- Brain stem
- Frontal lobe
- Basal ganglia
- Cerebellum

Best change in target lesion

SD – stable disease; PD – progressive disease
*patient remains on study

Arrillaga et al., ASCO, 2019
Adult Recurrent H3 K27M-Mutant Glioma Trials: Change in Tumor Size Over Time

Contrast-enhancing assessment

Non-contrast-enhancing assessment

Location of primary lesion:
- Thalamus
- Brain stem
- Frontal lobe
- Basal ganglia
- Cerebellum

Change in target lesion from baseline

Arrillaga et al., ASCO, 2019

Enrollment cutoff: 12/15/2018
Adult Recurrent H3 K27M-Mutant Glioma Trials: OS

Enrollment cutoff: 12/15/2018

Arrillaga et al., ASCO, 2019
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

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

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

Arrillaga et al., ASCO, 2019
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

Arrillaga et al., ASCO, 2019
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

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

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

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

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Arm B</th>
<th>Arm C</th>
<th>Arm D</th>
<th>Arm E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-radiation H3 K27M+ Glioma</td>
<td>Newly Diagnosed DIPG</td>
<td>DIPG Tumor Biopsy</td>
<td>Post-radiation H3 K27M+ Glioma CSF</td>
<td>Post-radiation H3 K27M+ Glioma OraSweet Formulation</td>
</tr>
<tr>
<td>ONC201</td>
<td>ONC201 + RT</td>
<td>ONC201 -/+ RT</td>
<td>ONC201</td>
<td>ONC201</td>
</tr>
<tr>
<td>n=6</td>
<td>n=12</td>
<td>n=12</td>
<td>n=12</td>
<td>n=12</td>
</tr>
<tr>
<td>Level 2</td>
<td>Level 1</td>
<td>Level -1</td>
<td>Level 2</td>
<td>Level 1</td>
</tr>
<tr>
<td>n=6</td>
<td>n=3</td>
<td>n=3</td>
<td>n=6</td>
<td>n=3</td>
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<tr>
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<td>n=3</td>
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<tr>
<td>n=21</td>
<td>n=13</td>
<td>n=10</td>
<td>n=5</td>
<td>n=7</td>
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</table>
Single agent equivalent of adult RP2D confirmed with scaling by body weight

<table>
<thead>
<tr>
<th>Adverse Events, N (%)</th>
<th>All Attributions</th>
<th>Possibly or Probably Related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade 3-4%</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>52%</td>
<td>0%</td>
</tr>
<tr>
<td>Nausea</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>6th nerve palsy</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>24%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>10%</td>
<td>0%</td>
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<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>10%</td>
<td>0%</td>
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<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness right-sided</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Right hemiparesis</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase elevated</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Aspartate aminotransferase elevated</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Phase I Pediatric DIPG and H3 K27M-Mutant Glioma Trial: Pharmacokinetics

Preliminary pharmacokinetics similar to adults

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

Exposure consistent across body weights

Gardner et al, Society of Neuro-oncology, 2018
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

Circulating CSF H3.3 K27M DNA

Koschmann et al, unpublished
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

OS12: 69%

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

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

**Safety profile consistent across age and tumor type**

**Adult Recurrent Glioblastoma Patients (n=20)**

<table>
<thead>
<tr>
<th>Adverse Events, N (%)</th>
<th>All Adverse Events</th>
<th>Possibly/Probably-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events, N (%)</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9 (45%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>8 (40%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>8 (40%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (35%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (35%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>6 (30%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion</td>
<td>5 (25%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
DRD2 Knockout Mice Exhibit Locomotor Deficits

DRD2 knockout mice

Locomotor deficits with DRD2 knockout

DRD2

Fall latency (s)

Time immobile (s)

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.

Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D2 receptors

David A. Sykes¹, Holly Moore²,3, Lisa Stott¹, Nicholas Holliday¹, Jonathan A. Javitch²,4,5, J. Robert Lane⁶ & Steven J. Charlton⁷

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 Seeman¹,² and T Tallerico¹
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
ONC201 combines synergistically with radiation in DIPG

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

Tarapore et al., AACR, 2019
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

<table>
<thead>
<tr>
<th>Normalized Coefficient</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRD2</td>
<td></td>
</tr>
<tr>
<td>DRD1</td>
<td></td>
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<tr>
<td>DRD3</td>
<td></td>
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<tr>
<td>DRD4</td>
<td></td>
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<tr>
<td>DRD5</td>
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</tbody>
</table>

**Normalized Coefficient Score**

**GI50 (log)**

**NCI60**

**DRD5 mRNA (log Z-score)**

**Prabhu et al, Clinical Cancer Research, 2018**
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

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

Chi et al., Society of Neuro-Oncology, 2017
Overview of Mechanism of Action of ONC201

Ishizawa et al, Cancer Cell, 2019