Serial plasma and CSF cell-free tumor DNA (cf-tDNA) tracking in diffuse midline glioma patients undergoing treatment with ONC201

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Disclosures

- Nothing to disclose

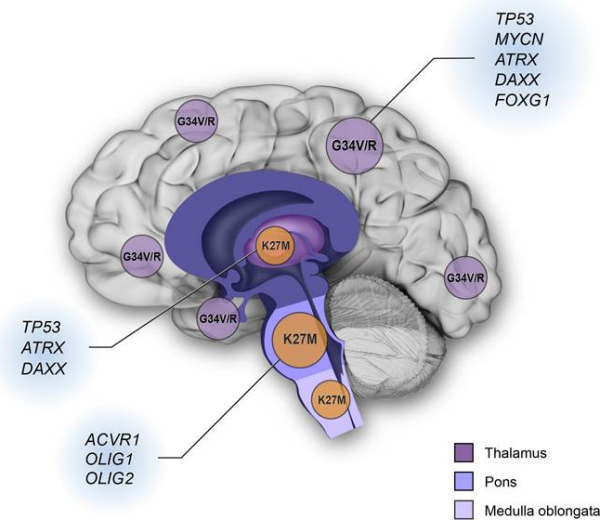
DMG is pathologically defined but driven by mutations in H3

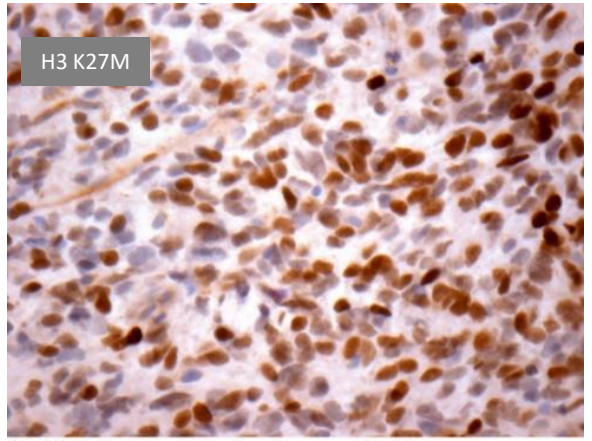
Glioma – grade 2-4 (i.e., infiltrates healthy brain)

- Any part of the midline of the brain (brainstem, thalamus, and spinal cord)
- Most common in younger patients

Behavior, prognosis, and treatments are driven by the H3 K27M mutation

- 75% of H3 K27M occur in the H3F3A gene
- OS of H3 K27-mutant DMG: ~12 m





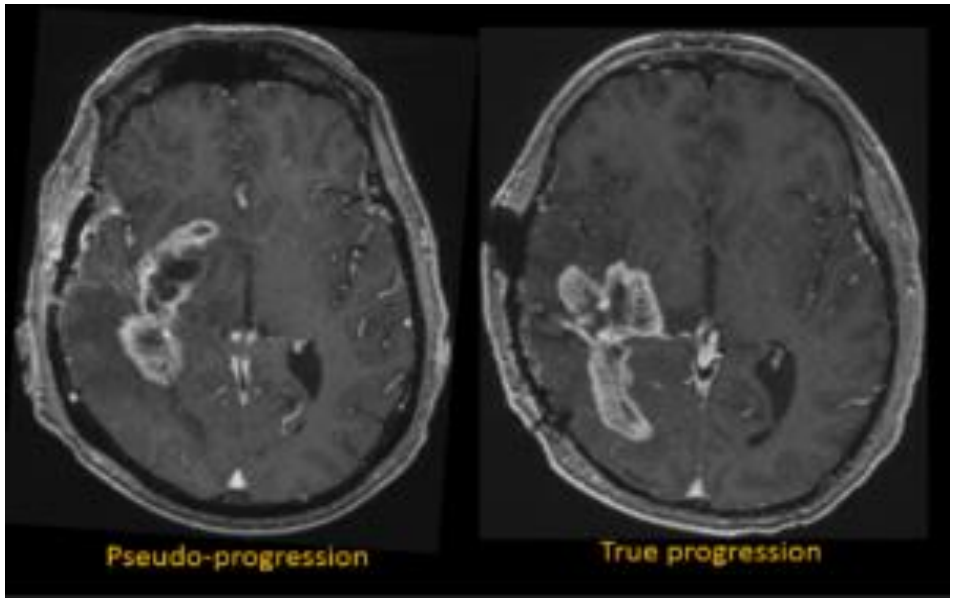
H3 K27M immunohistochemistry: positive in tumors harboring the *H3F3A* mutation (75% of cases)

ACVR1, activin A receptor type 1; ATRX, ATRX chromatin remodeler; DAXX, death domain associated protein; DMG, diffuse midline glioma; FOXG1, forkhead box G1; H3, Histone 3; *H3F3A*, Histone 3 F3A; H3 K27M, Histone 3 lysine to methionine substitution at residue 27; m, months; OLIG1, oligodendrocyte transcription factor 1; OLIG2, oligodendrocyte transcription factor 2; OS, overall survival; TP53, tumor protein p53.

Mackay et al, *Cancer Cell,* 2017; Lulla et al, *Science Advances*, 2016

Monitoring treatment response in DMG is complicated by pseudoprogression

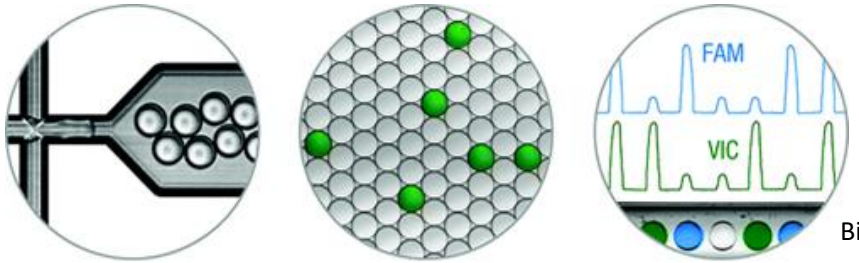
- Tumors often increase in size early in the course of treatment
  - May be tumor progression
  - May be “pseudo-progression” – radiation-related swelling/necrosis
- Some non-CNS tumors displaying multi-pronged clinical responses are tracked by molecular analyses of plasma
- For brain tumors (glioma), MRI is the only approved diagnostic
  - Serial biopsy in HGG carries significant risk



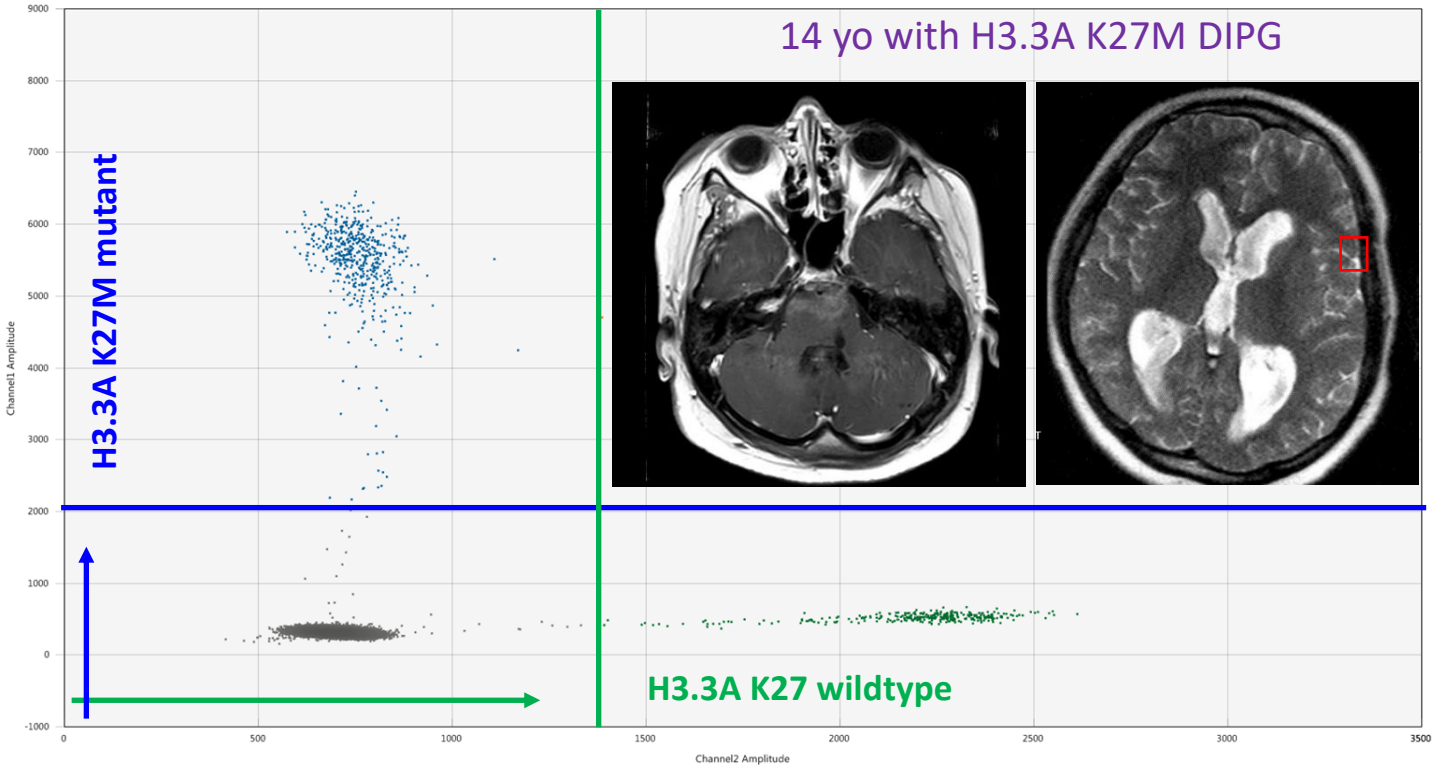
Tiwari et al, *Cleveland Clinic Consult QD*, 2019

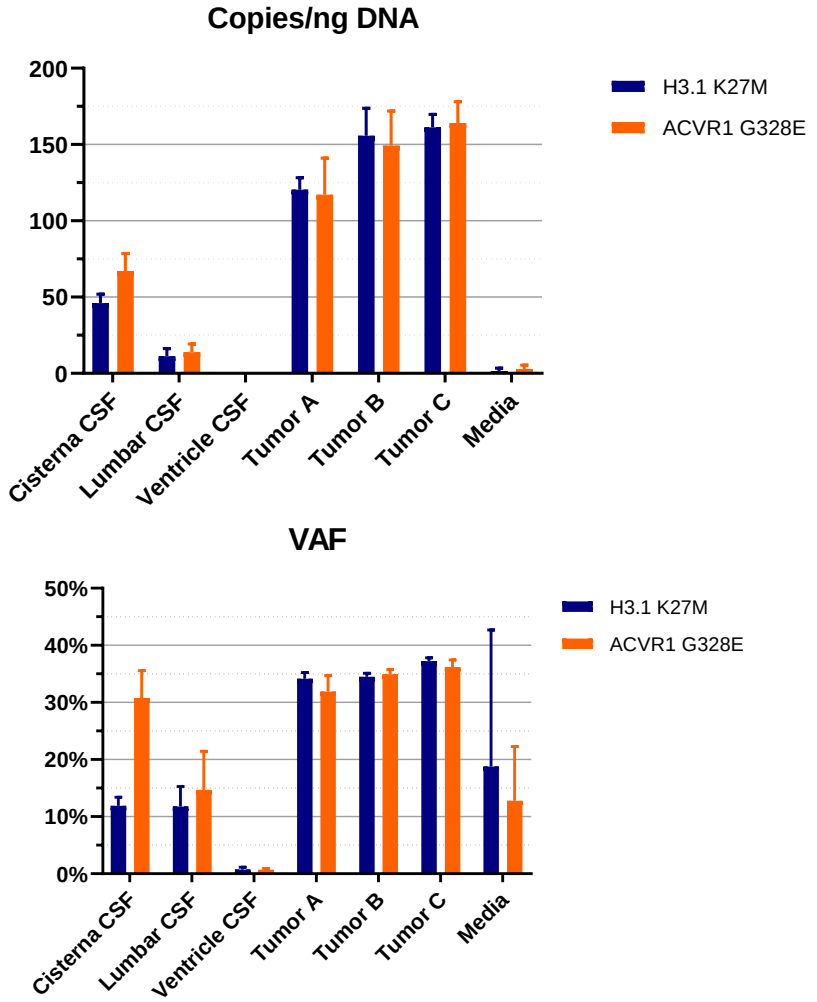
CNS, central nervous system; DMG, diffuse midline glioma; HGG, high grade glioma; MRI, magnetic resonance imaging.

Droplet digital PCR to diagnosis and quantify H3K27M cf-tDNA



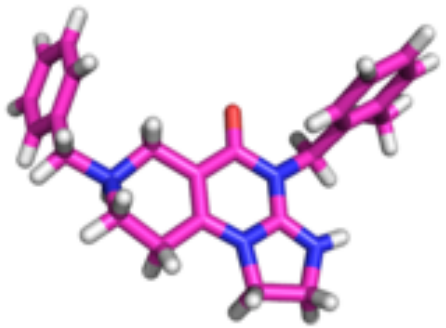
Biorad





Stallard et al (Koschmann), *Acta Neuropath Comm*, 2018
Bruzek et al (Koschmann), *Clinical Cancer Research*, 2020

ONC201: DRD2 antagonist and ClpP agonist



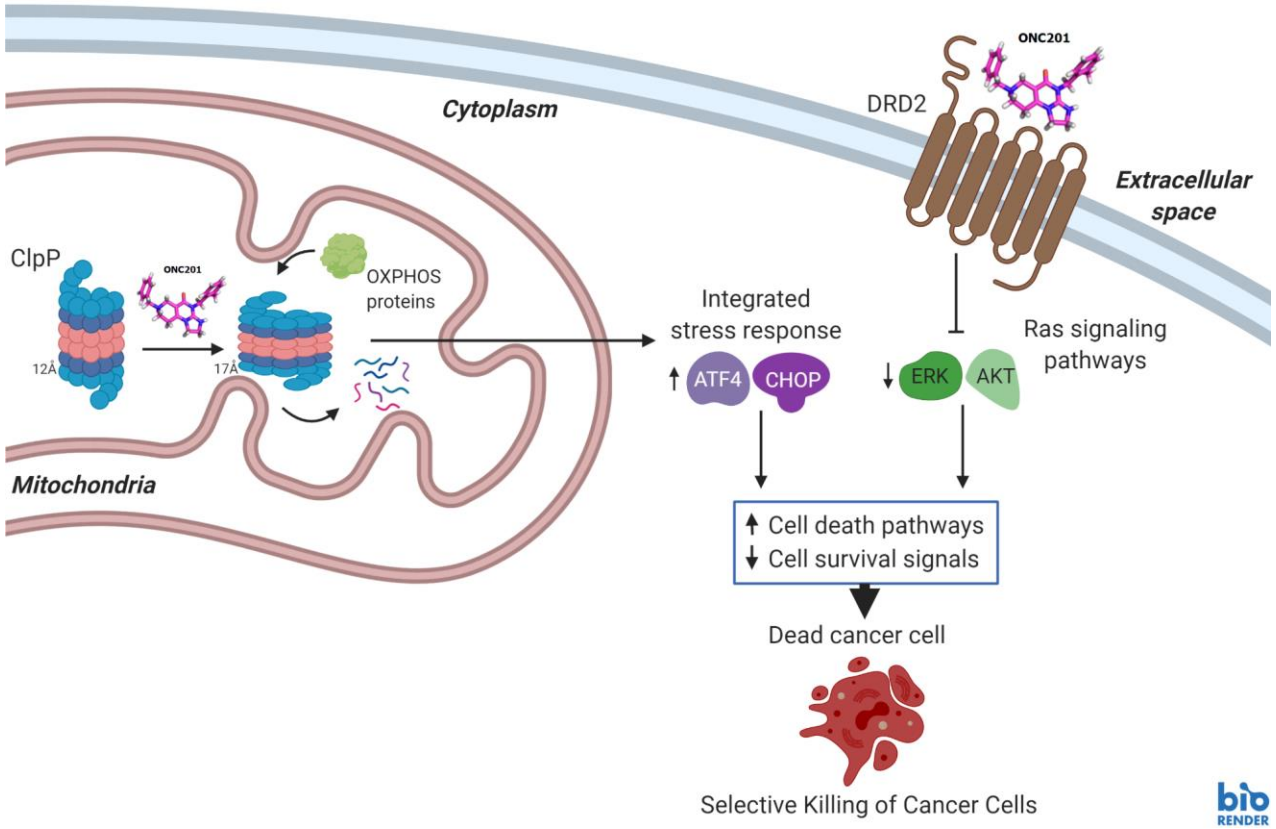
ONC201

DRD2/3 antagonist
ClpP agonist

Oral capsules, administered weekly

Pharmacodynamic-based dose without DLT

Crosses blood-brain barrier



Chimerix.com

AKT, protein kinase B; ATF4, activating transcription factor 4; CHOP, C/EBP-homologous protein; ClpP, caseinolytic protease P; DLT, dose-limiting toxicity; DRD2/3, dopamine receptor D2/D3; ERK, extracellular-regulated kinase.

Allen et al, *Science Translational Medicine,* 2013; Ishizawa et al, *Science Signaling*, 2016; Kline et al, *Science Signaling*, 2016; Ishizawa et al, *Cancer Cell*, 2019; Prabhu et al, *Neoplasia*, 2020

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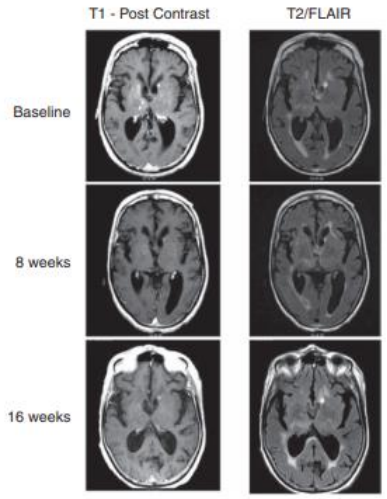
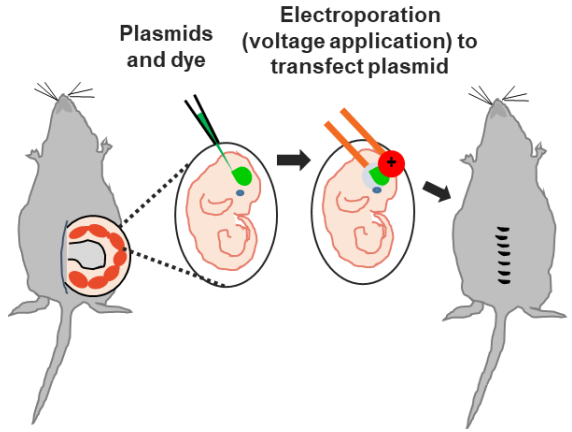
H3 K27M-mutant gliomas exhibit sensitivity to ONC201

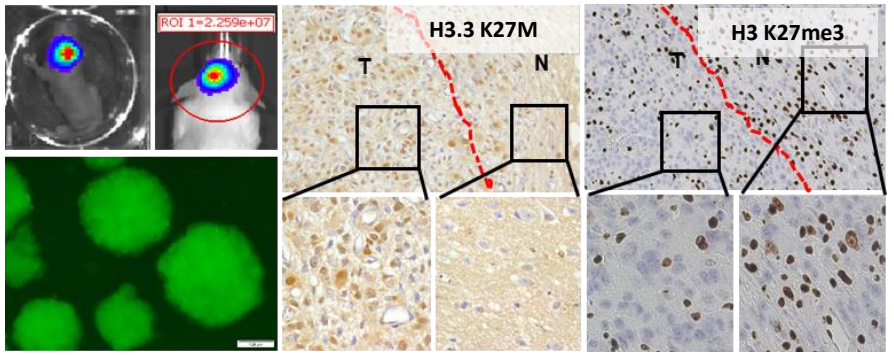
Adult phase 2 study in recurrent GBM – ONC201 (NCT02525692)

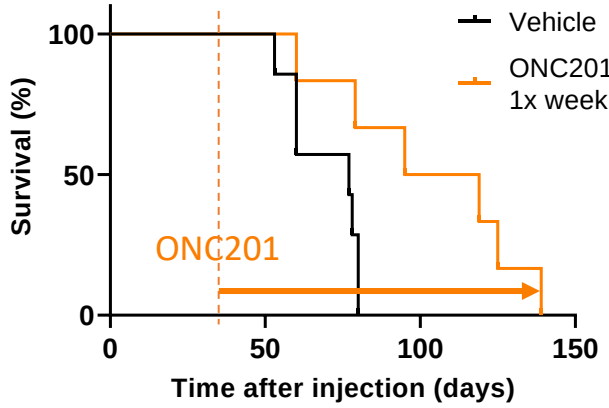
- Well tolerated, achieved intratumoral concentrations that exceeded preclinical efficacy thresholds
- Primary endpoint of PFS6 at 5% by RANO was not achieved
- However, 1 patient enrolled with the H3 K27M mutation had a complete regression of enhancing multifocal lesions that remained durable for >1.5 years



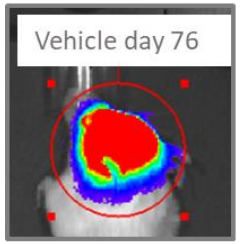
Arrillaga-Romany et al, *Neuro-Oncology*, 2020

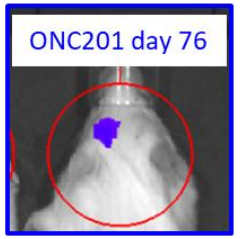






Median Survival:
Vehicle: 77 days
ONC201: 107 days
p=0.02

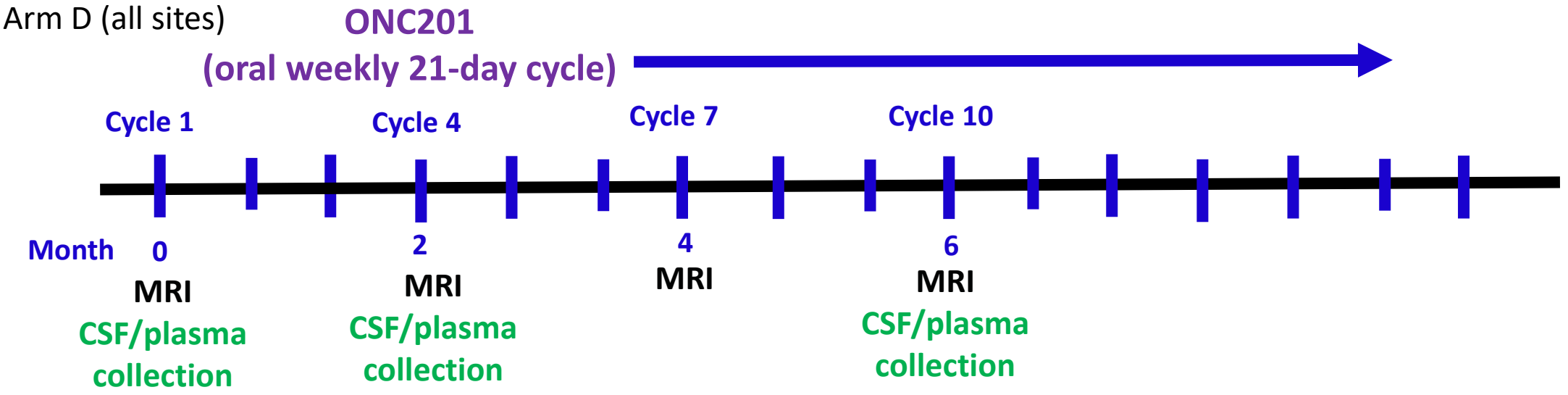




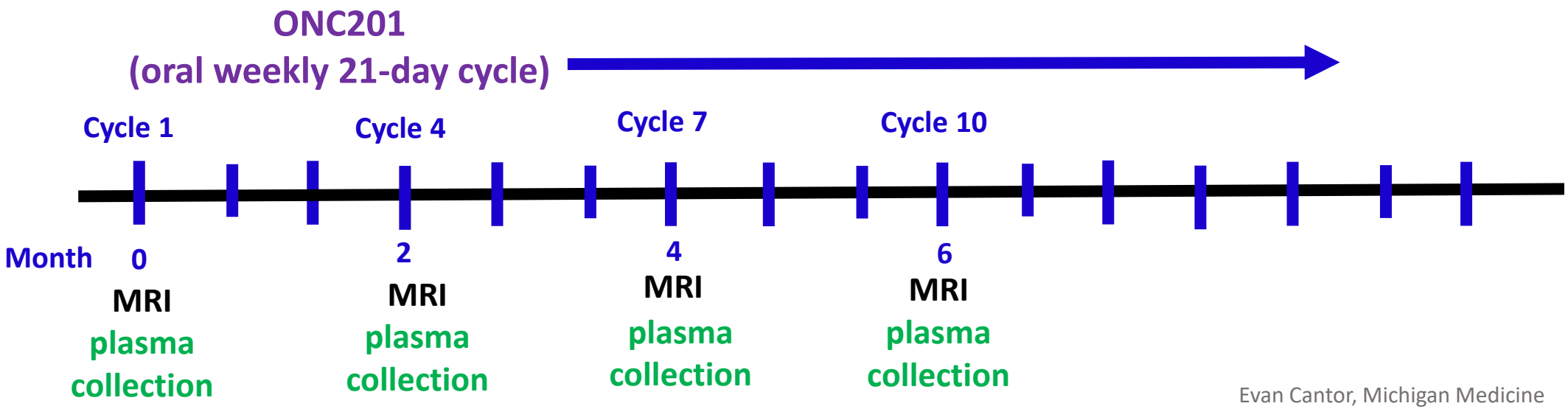
GBM, glioblastoma multiforme; H3.3, H3 histone variant; H3 K27M, Histone 3 lysine to methionine substitution at residue 27; H3 K27m3, Histone 3 residue lysine 27 tri-methylation; PFS6, progression-free survival at 6 months; RANO, Response Assessment in Neuro-Oncology.

Kawakibi et al, Society of Neuro-Oncology, 2019, *Unpublished*

Arm D (all sites)



Other arms (UM patients only)



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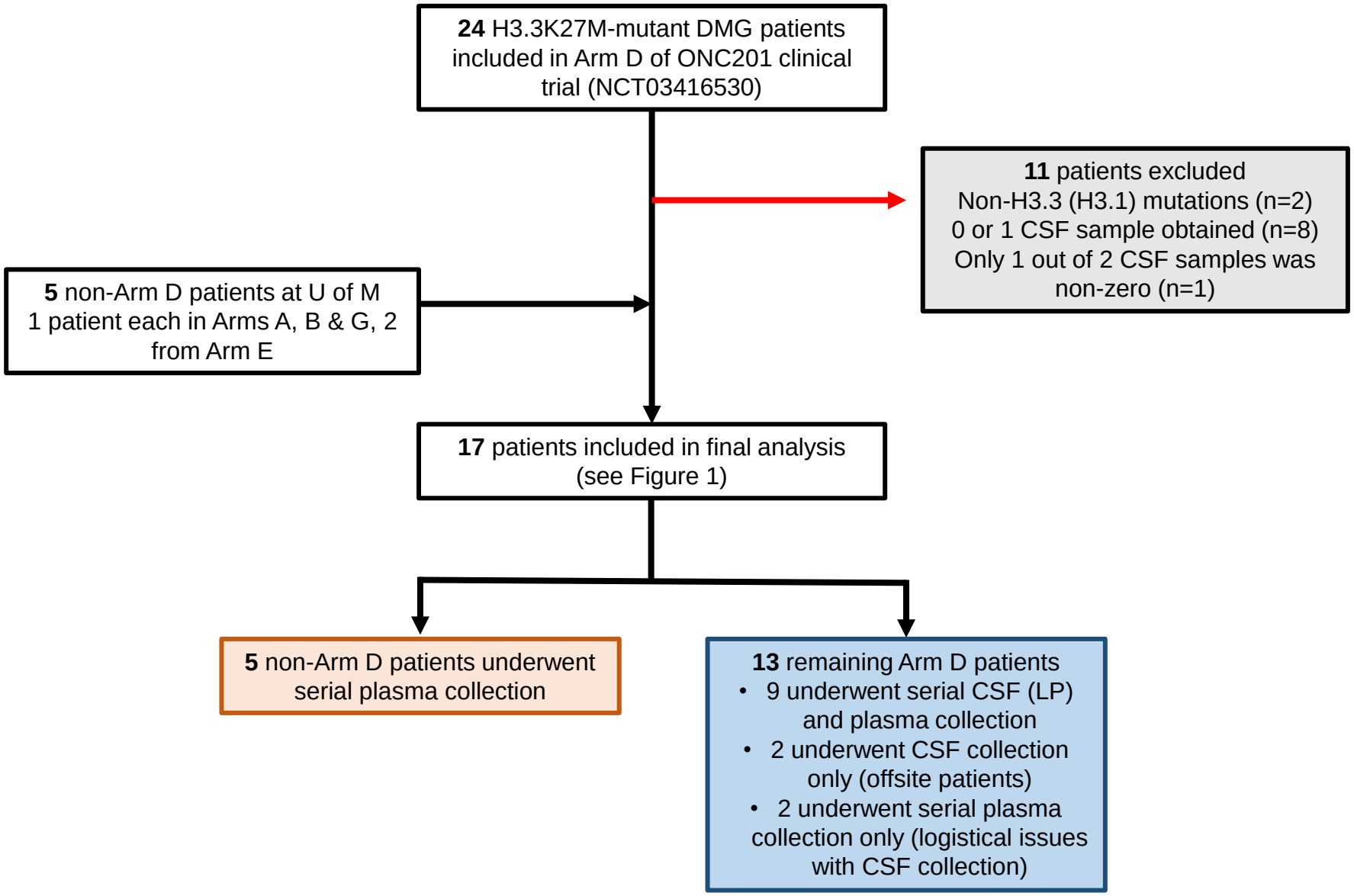
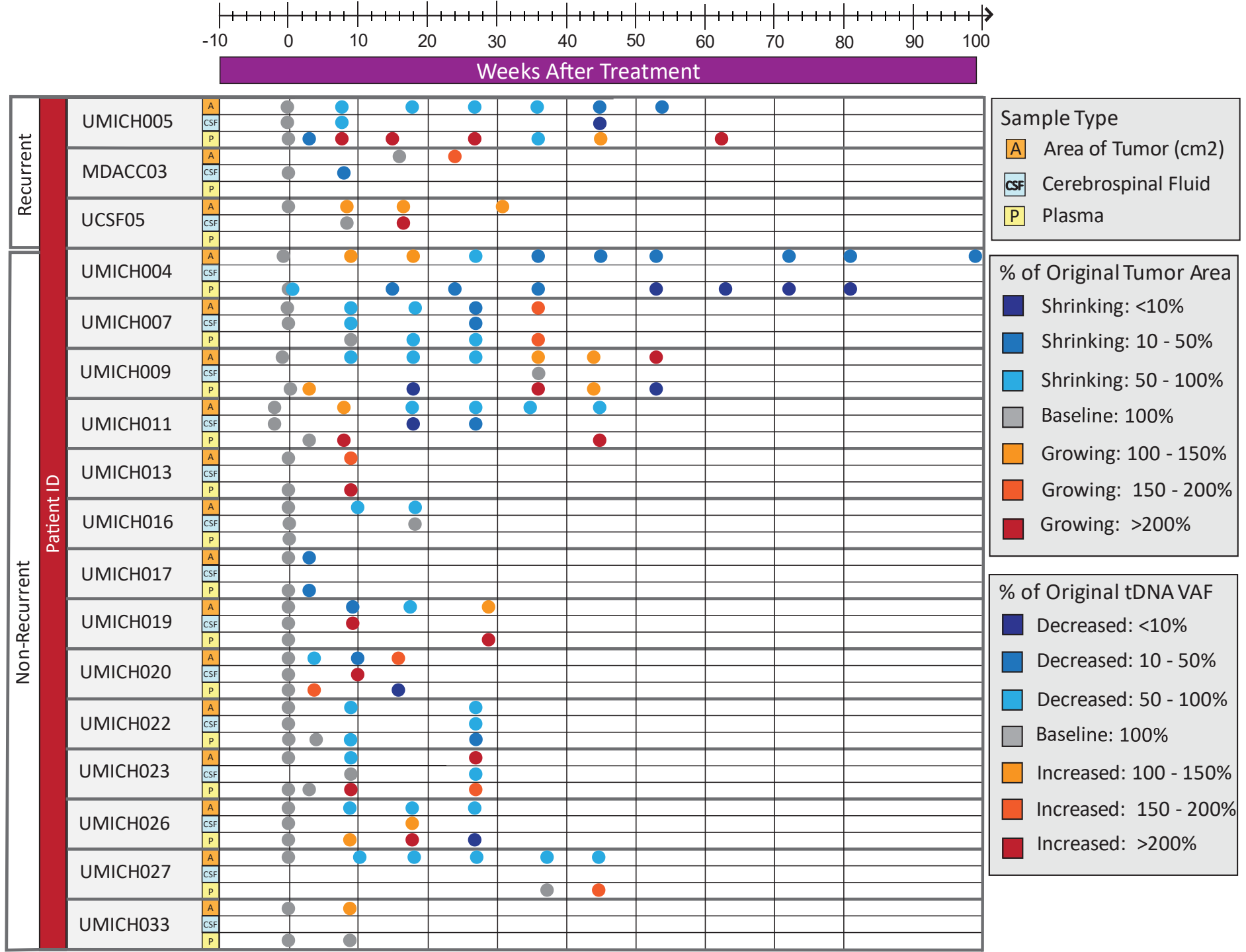

24 H3.3K27M-mutant DMG patients included in Arm D of ONC201 clinical trial (NCT03416530)
11 patients excluded
Non-H3.3 (H3.1) mutations (n=2)
0 or 1 CSF sample obtained (n=8)
Only 1 out of 2 CSF samples was non-zero (n=1)
5 non-Arm D patients at U of M
1 patient each in Arms A, B & G, 2 from Arm E
17 patients included in final analysis (see Figure 1)
5 non-Arm D patients underwent serial plasma collection
13 remaining Arm D patients
• 9 underwent serial CSF (LP) and plasma collection
• 2 underwent CSF collection only (offsite patients)
• 2 underwent serial plasma collection only (logistical issues with CSF collection)



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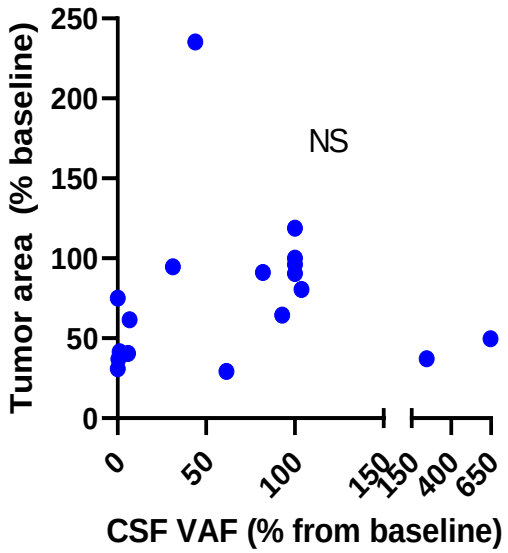
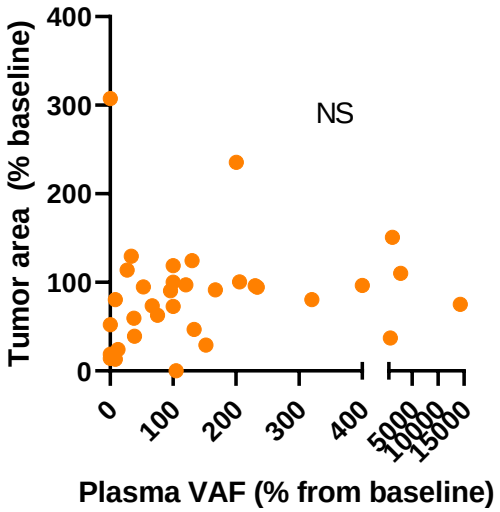
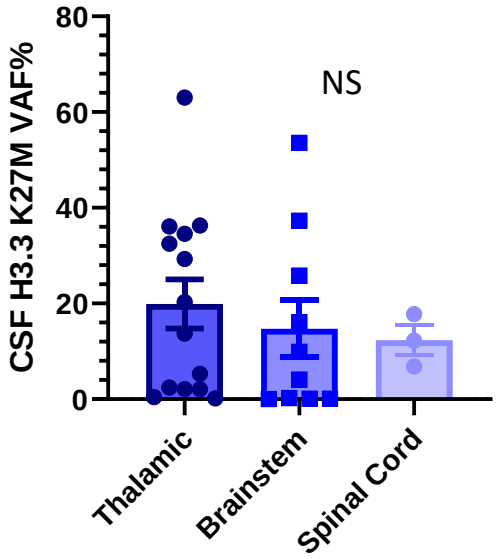
Serial plasma and CSF H3.3 K27M cf-tDNA monitoring on ONC201 treatment

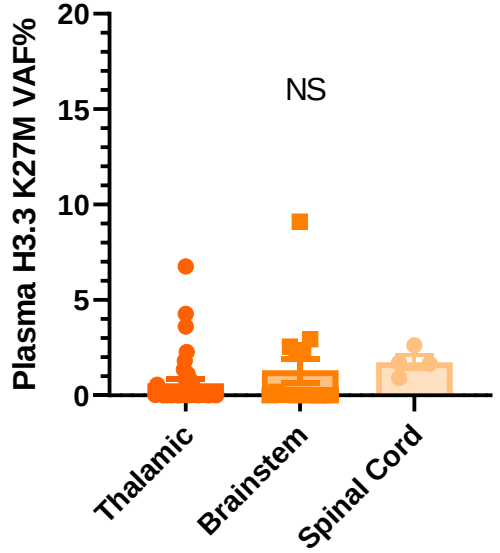
Tumor size v. H3.3K27M VAF





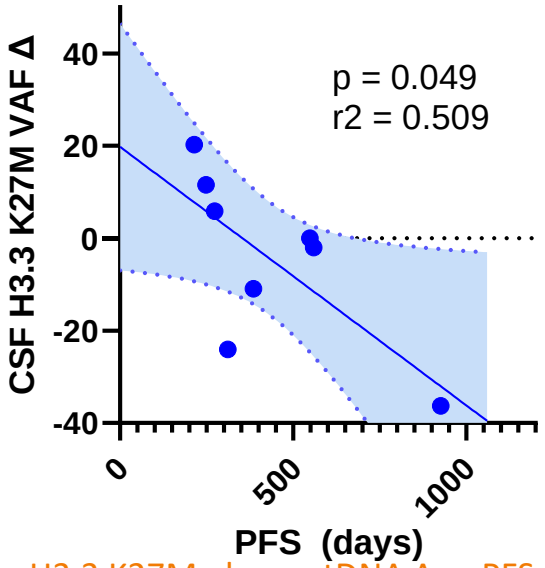
VAF by location



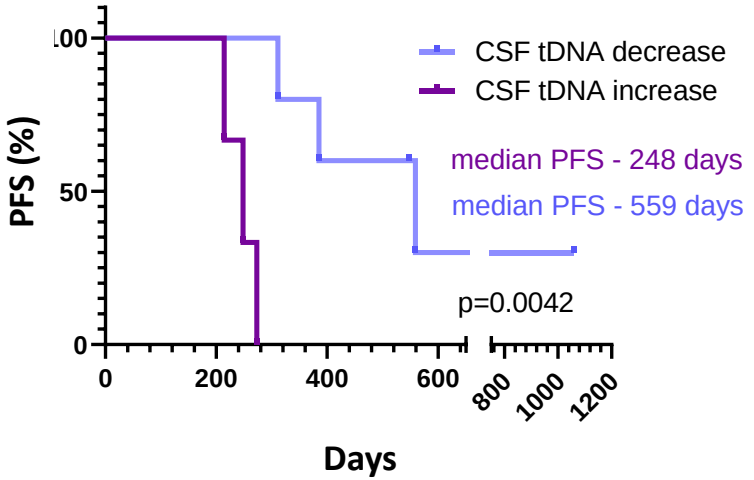


OS/PFS by change in H3.3 K27M VAF

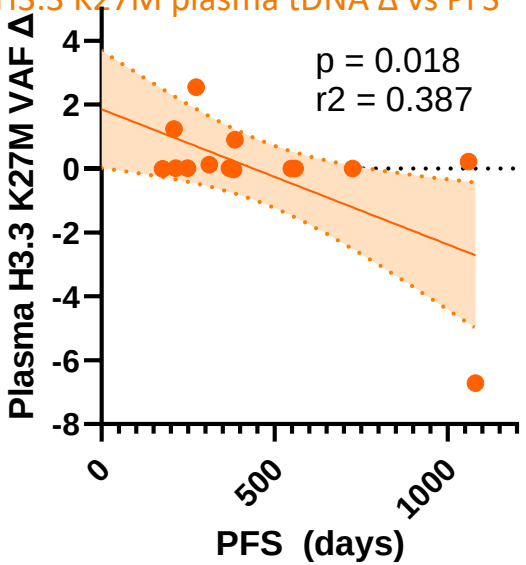
H3.3 K27M CSF tDNA Δ vs PFS



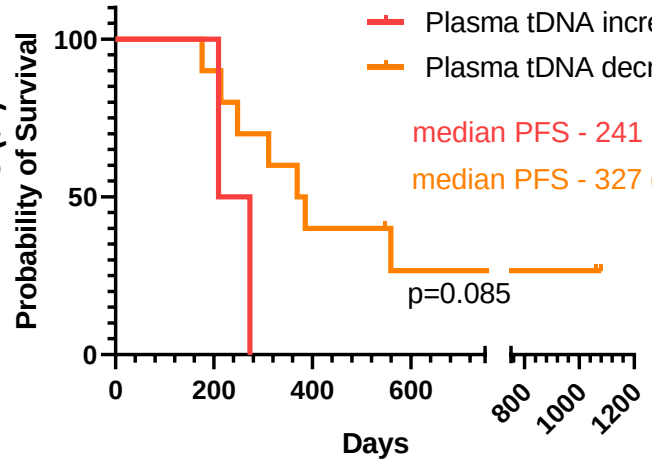
PFS by H3.3 K27M CSF tDNA Δ



H3.3 K27M plasma tDNA Δ vs PFS



PFS by H3.3 K27M plasma tDNA Δ



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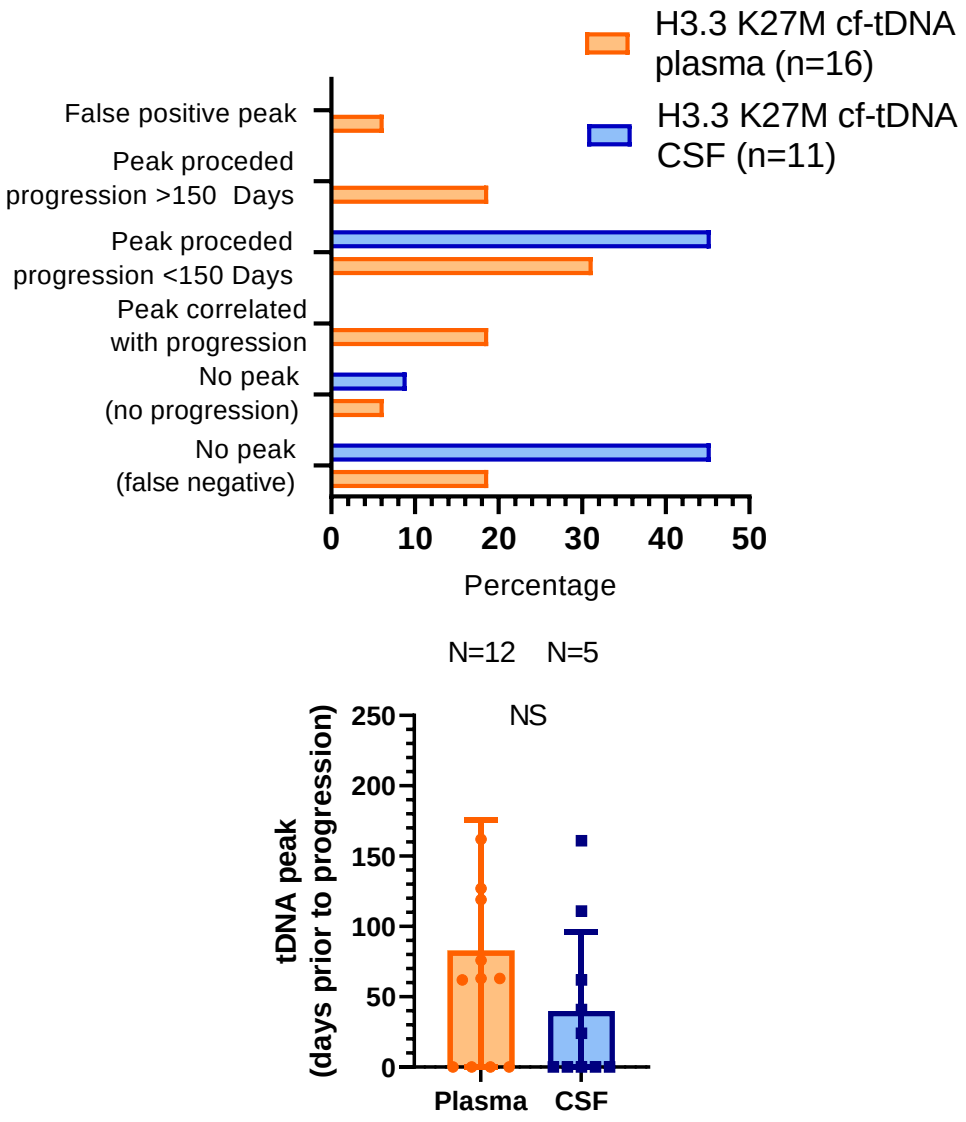
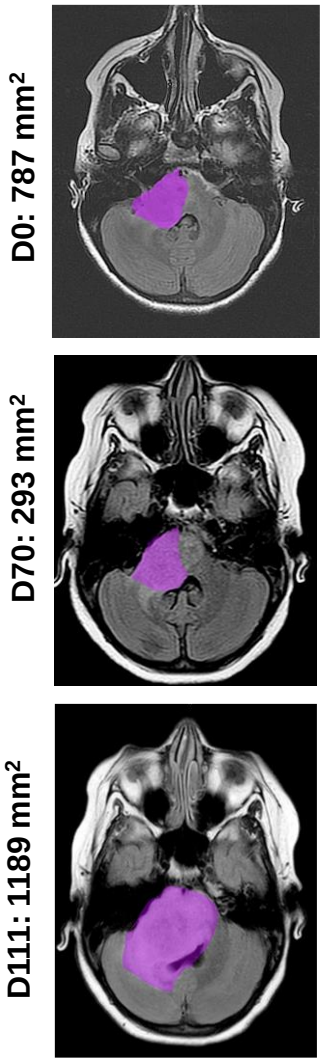
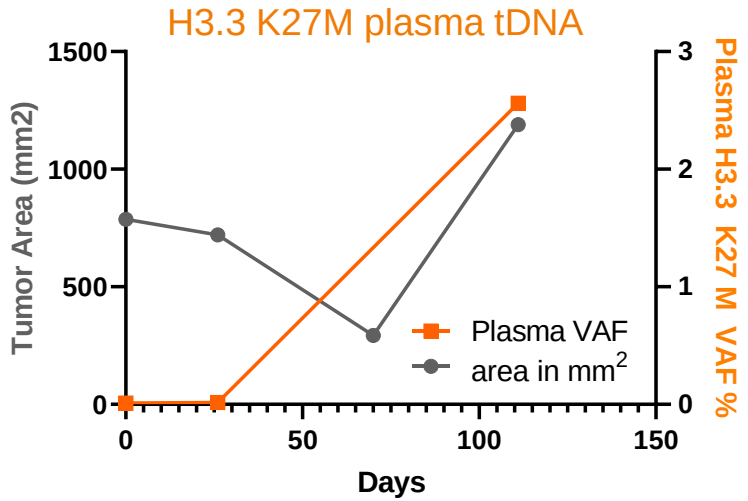
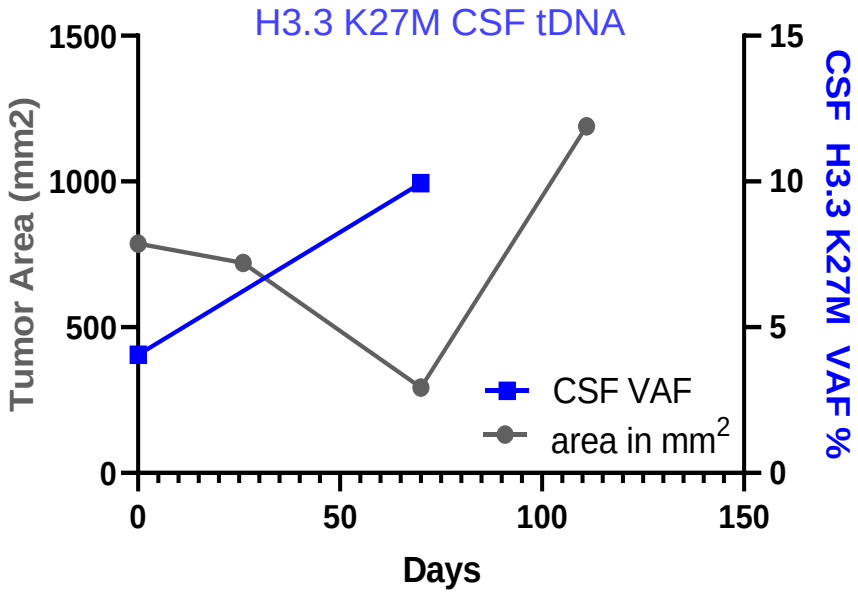
H3.3K27M cf-tDNA “spikes” can precede tumor progression





UMICH-PED20: 10 yo DMG-H3.3K27M

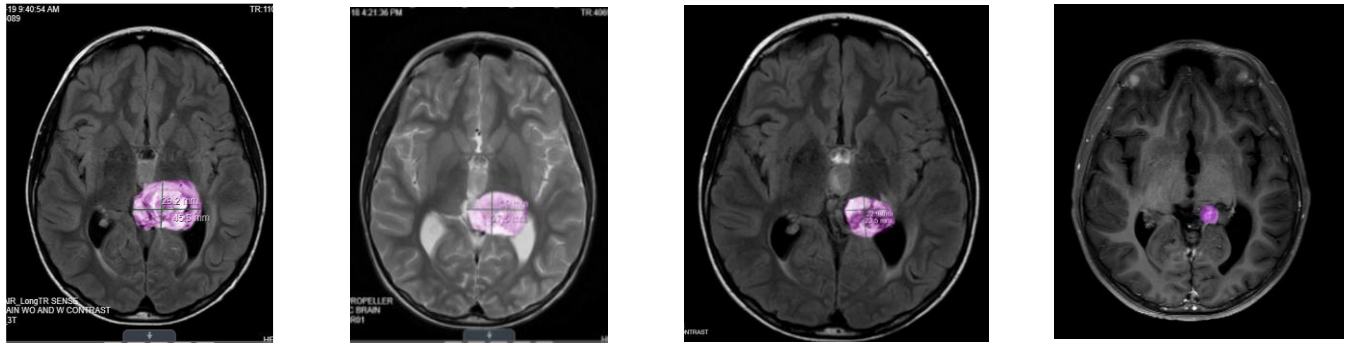


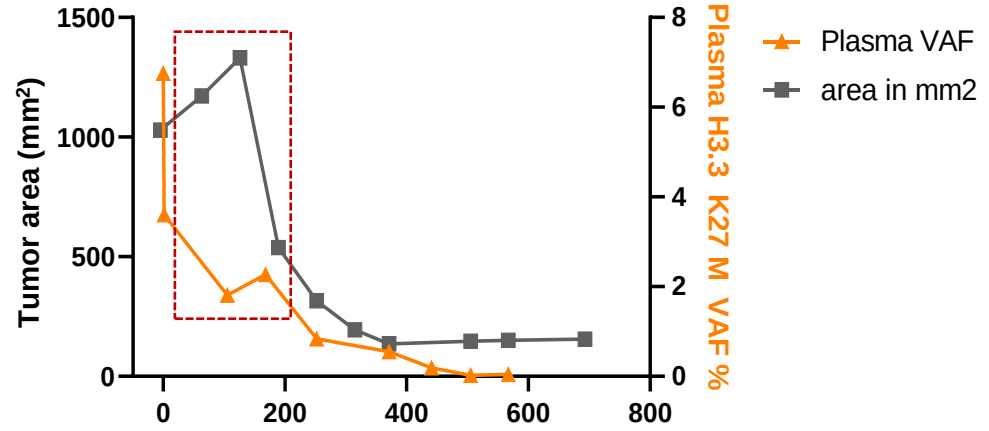


H3.3K27M cf-tDNA can help differentiate pseudo-progression and pseudo-response (bevacizumab)

UMICH-PED05:
6 yo DMG-H3.3K27M

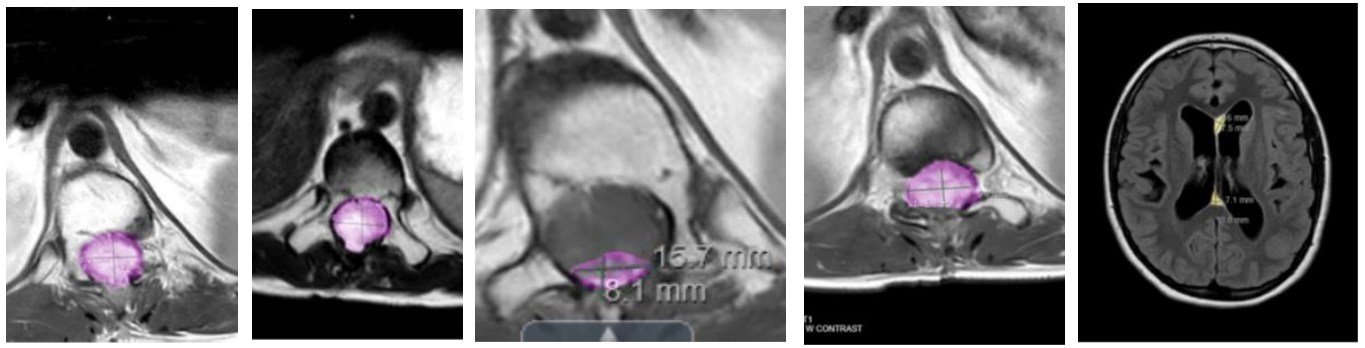
D5: 1029 mm² **D168: 1331 mm²** **D189: 538 mm²** **D881: 560 mm²**

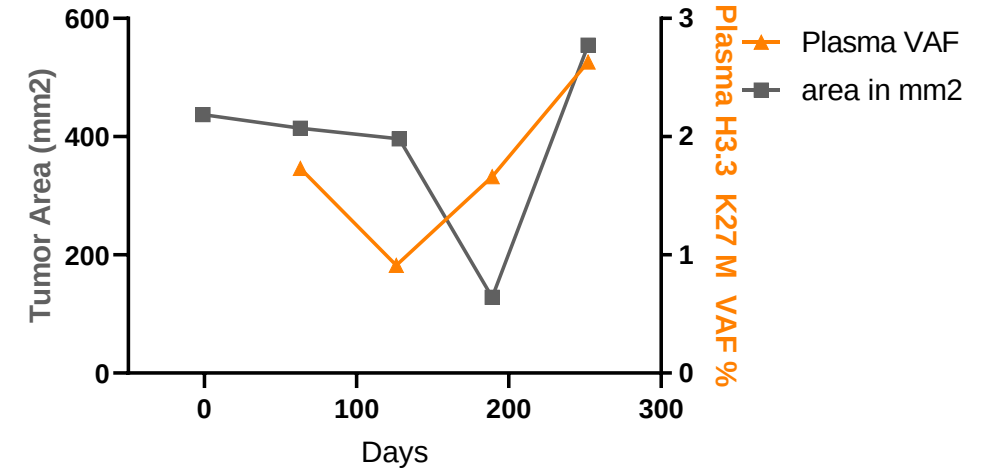




UMICH-PED07:
13 yo SPINAL GLIOMA-H3.3K27M

D1: 437 mm² **D5: 414 mm²** **D5: 128 mm²** **D5: 358 mm² + 196.6 mm² = 554.68 mm²**





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Conclusions

- Serial CSF collection is feasible and useful in management of glioma
- ddPCR is highly sensitive and specific for H3K27M tDNA in CSF and plasma
- Change in tumor area / VAF over time don't correlate – but "patterns" of change demonstrate potential clinical utility
    - Sustained reduction in tDNA correlates with / predicts long term response
    - Increase in tDNA correlates with progression – may predict progression in 2-4 months
    - H3K27M tDNA patterns less affected by pseudo-progression and bevacizumab than MRI

cf-tDNA, cell-free tumor DNA; CSF, cerebrospinal fluid; ddPCR, droplet digital polymerase chain reaction; H3 K27M, Histone 3 lysine to methionine substitution at residue 27;

- Koschmann Lab
  - Clarissa Babilla
  - Josh Bradin
  - Evan Cantor, MD
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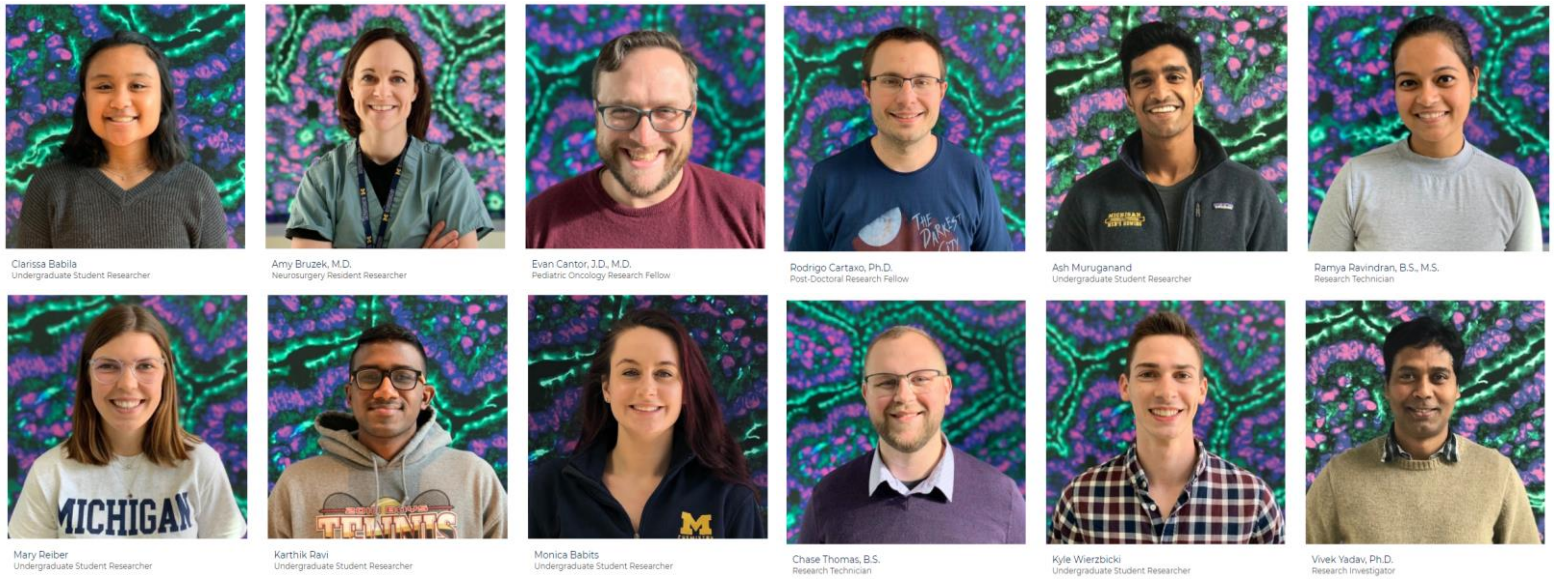
  - Vivek Yadav, PhD



- Collaborators (external)
  - Josh Allen, PhD, Rohinton Tarapore PhD (Chimerix)
  - Sharon Gardner MD (NYU)
  - Yazmin Odia, MD (Miami Cancer Institute)
  - Cassie Kline, MD (CHOP)
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NIH National Institute of Neurological Disorders and Stroke

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Pediatric Brain Tumor Foundation