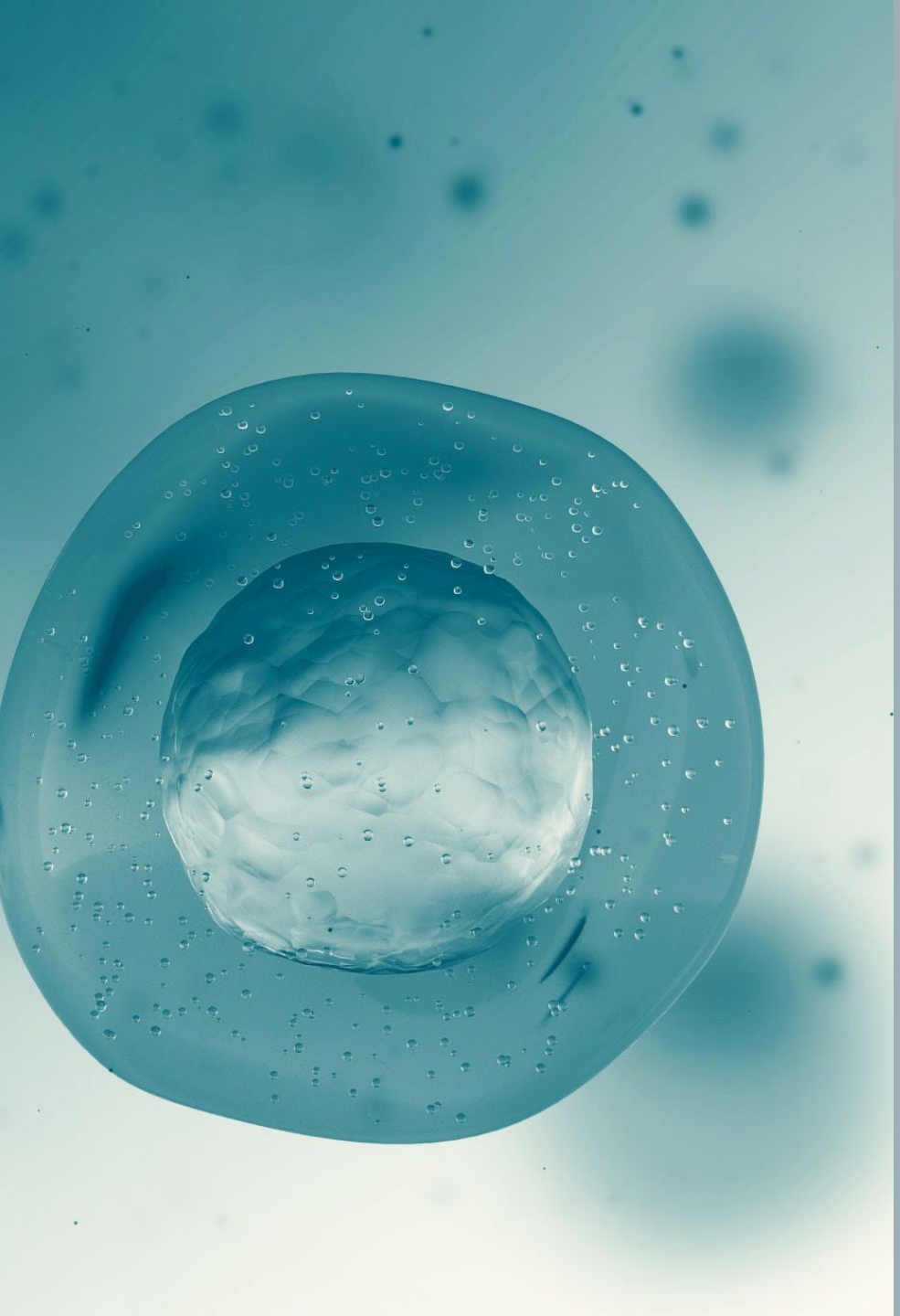

ADVANCES IN NEURO-ONCOLOGY: TARGETABLE MUTATIONS AND THERAPIES IN GLIOMAS

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Ochsner Regional Neurosciences Symposium

May 11, 2023

DISCLOSURES

I have no financial relationships to disclose

I will be discussing non-FDA-approved medications and/or off-label indications for FDA-approved medications

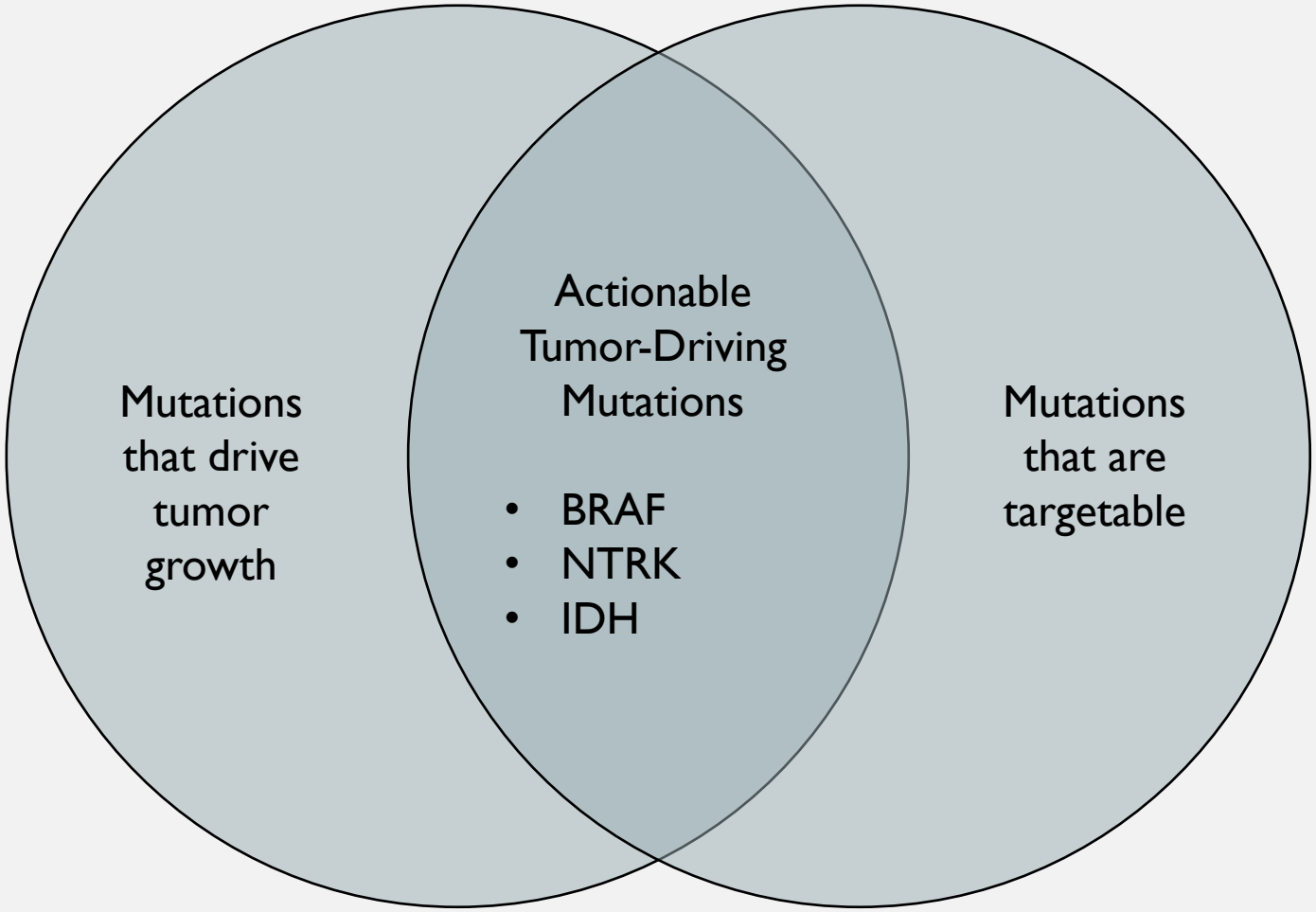
OVERVIEW

- Background
- Current promising targetable mutations
  - v-raf murine viral oncogene homolog B1 (BRAF) mutations
  - Neurotrophic receptor tyrosine kinase (NTRK) mutations
  - Isocitrate dehydrogenase (IDH) mutations
- Limitations
- Next steps

BACKGROUND

- Gliomas are primary brain tumors that arise from glial cells
- Gliomas are graded on a scale of 1 (least aggressive) to 4 (most aggressive) based on histologic and molecular assessment
- Tumors are thought to be diffuse at diagnosis, and so they are non-curable
- Standard treatment currently includes a combination of surgery, radiation therapy, and/or systemic chemotherapy
- Advances in genetic sequencing technology allow for identification of genetic mutations within tumor tissue

BACKGROUND


Mutations that drive tumor growth
Actionable Tumor-Driving Mutations
• BRAF
• NTRK
• IDH
Mutations that are targetable

BRAF MUTATIONS

BRAF mutations occur in about 10% of all gliomas and are more common in pleomorphic xanthoastrocytoma (PXA) and ganglioglioma

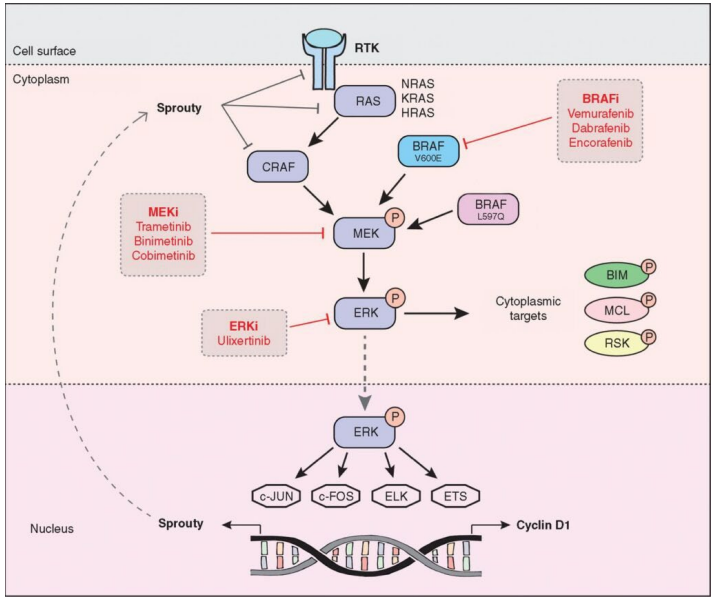
Known tumor driver in pediatric/low grade gliomas

BRAF V600E is the most common BRAF mutation

- Currently targetable by FDA-approved small molecule inhibitors

Other mutations include BRAF alterations, BRAF rearrangements/fusions, BRAF gains/amplifications

- Not currently targetable



https://cancercommons.org/latest-insights/mapk-pathway-in-cancer-new-treatments/

COMMON TARGETED THERAPIES IN BRAF V600E MUTATED GLIOMAS

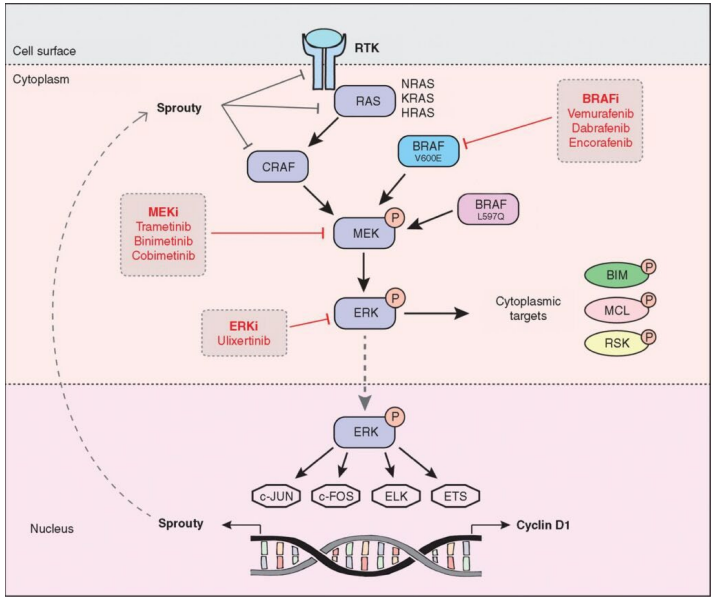
Initially developed for melanoma treatment

BRAF inhibitors

- Vemurafenib
- Dabrafenib

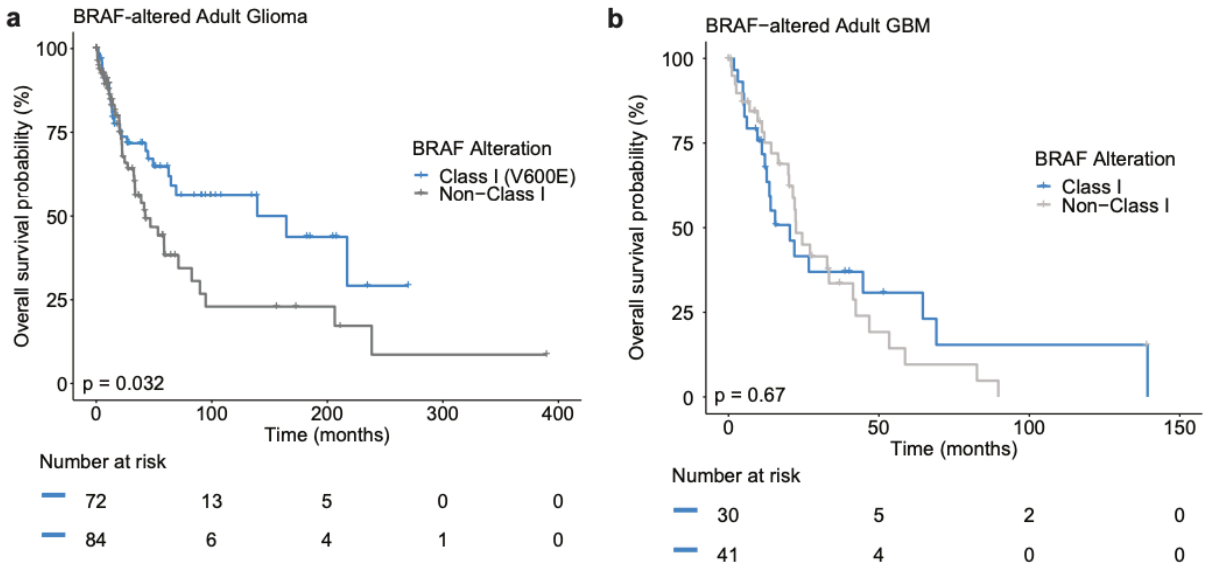
MEK inhibitors

- Trametinib
- Cobimetinib



BRAF MUTATIONS

In adult glioma, BRAF mutation type has prognostic value (excluding adult glioblastoma)



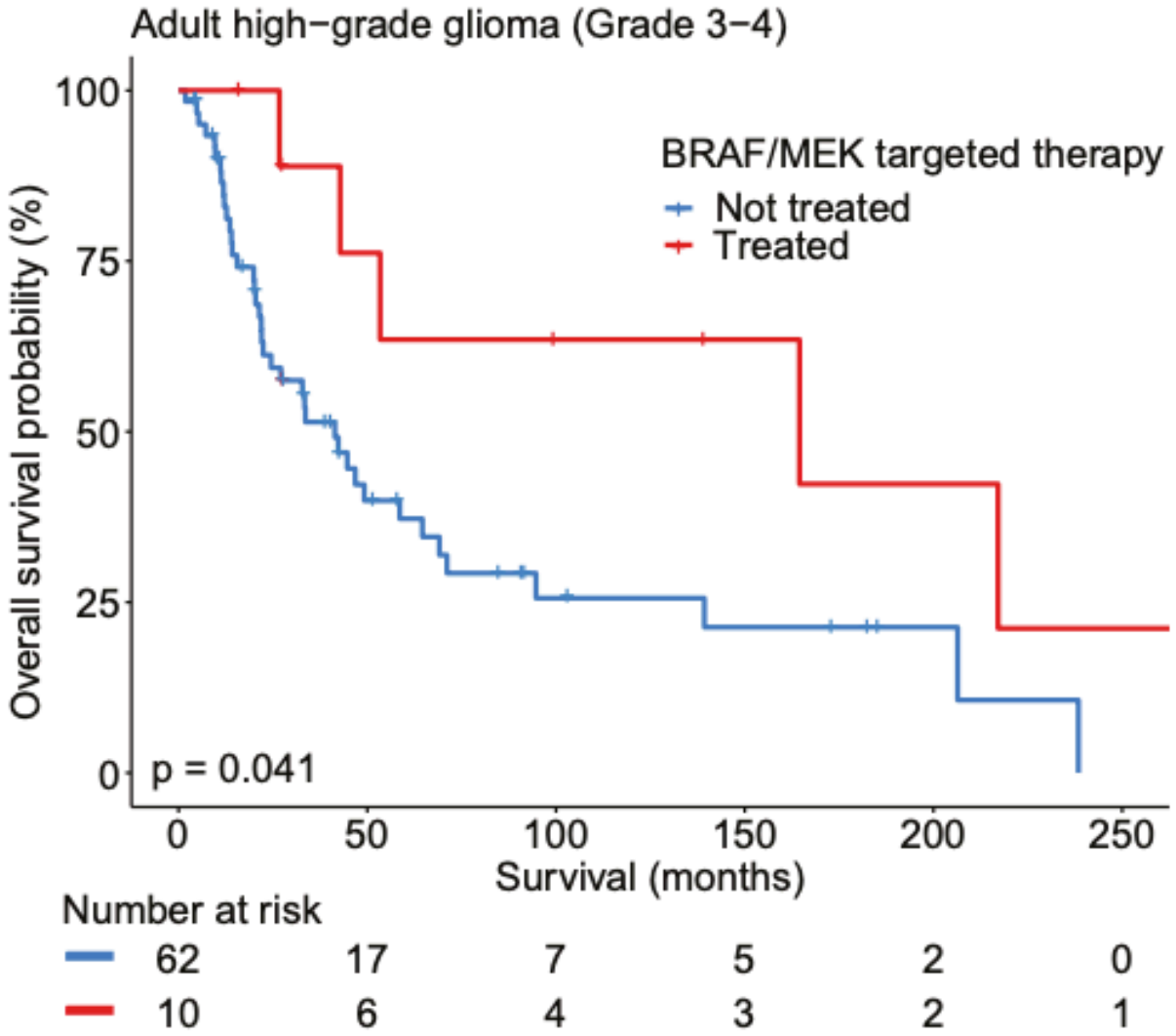
Schreck KC, Langat P, Bhave VM, Li T, Woodward E, Pratilas CA, Eberhart CG, Bi WL. Integrated molecular and clinical analysis of BRAF-mutant glioma in adults. NPJ Precis Oncol. 2023 Feb 28;7(1):23.

BRAF MUTATIONS

Targeted therapies include:

- BRAF inhibition with vemurafenib or dabrafenib
- MEK inhibition with trametinib
- BRAF/MEK inhibition with dabrafenib + trametinib

This analysis did not control for specific type of targeted treatment



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TOLERABILITY OF BRAF TARGETED THERAPIES

Common side effects	Monitoring considerations
• Diarrhea/colitis • Skin issues: sun sensitivity, rashes • Neutropenia • Liver abnormalities • Prolonged QTc • Peripheral edema • Hypertension	• CBC • CMP • EKG • TTE

NTRK FUSIONS

- NTRK fusions are rare in gliomas, present in <1% of cases
- Most common mutations include NTRK1 or NTRK3 rearrangements, and the most frequent gene fusion is ETV6-NTRK3
- Although they are rare, they can drive tumor growth, and therefore can be a good target for therapy

TARGETED TREATMENT FOR NTRK MUTATED GLIOMA: TRK INHIBITORS

Great responses have been seen in non-CNS cancers with NTRK fusions

Two FDA-approved medications for solid tumors with NTRK fusions:

- Larotrectinib: see image
- Entrectinib
  - Available case reports in a few pediatric glioma patients

Doz et al. Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. Neuro Oncol. 2022 Jun 1;24(6):997-1007.

Table 2 Efficacy

Parameter	*n* = 33
Response	
Evaluable patients	*n* = 33
Objective response rate, % (95% CI)	30 (16–49)
Pediatric patients (<18 years; *n* = 26)	38 (20–59)
Pediatric high-grade glioma (*n* = 13)	38 (14–68)
Pediatric low-grade glioma (*n* = 7)	43 (10–82)
Best response, *n* (%)	
Complete response	3 (9)[a]
Partial response	7 (21)[b]
Stable disease ≥24 weeks	15 (45)
Stable disease <24 weeks	5 (15)
Progressive disease	3 (9)
Disease control rate ≥24 weeks, *n* (%; 95% CI)[c]	24 (73; 54–87)
Pediatric patients (aged <18 years)	20 (77; 56–91)
Adult patients (aged ≥18 years)	4 (57; 18–90)
Duration of response	
Median, months (95% CI)	Not reached (3.8–NE)[d]
Range, months	3.8 to 22.0+
Ongoing response rate at 12 months,[e] % (95% CI)	75 (45–100)
Progression-free survival	
Median, months (95% CI)	18.3 (6.7–NE)[f]
Progression-free survival rate at 12 months,[e] % (95% CI)	56 (38–74)
Progression-free survival rate at 24 months,[e] % (95% CI)	42 (18–65)
Overall survival	
Median, months (95% CI)	Not reached (16.9–NE)[f]
Overall survival rate at 12 months,[e] % (95% CI)	85 (71–99)
Overall survival rate at 24 months,[e] % (95% CI)	58 (28–88)

[a]All complete responses were seen in pediatric cases: 2 in pediatric high-grade gliomas and 1 in pediatric non-glioma.
[b]All partial responses were seen in pediatric cases: 3 in pediatric high-grade gliomas with 2 pending confirmation, 3 in pediatric low-grade gliomas, and 1 in pediatric non-glioma.
[c]Disease control rate is the proportion of patients with best overall response of confirmed complete response, partial response, or stable disease lasting 24 weeks or more following the initiation of larotrectinib. Stable disease is measured from the date of the first dose of larotrectinib. Disease control rate calculation included 1 patient with unconfirmed partial response.
[d]In patients with confirmed responses (*n* = 8), with a median follow-up of 12.0 months.
[e]Kaplan–Meier estimates.
[f]In 33 patients with a median follow-up of 16.5 months.
CI: confidence interval; NE: not estimable.

TOLERABILITY OF NTRK TARGETED THERAPIES

Common side effects

- Liver function abnormalities
- Anemia
- Weight gain
- Dizziness
- Ataxia
- Paresthesias

Monitoring considerations

- CBC
- CMP
- Weight

IDH MUTATIONS

- IDH-1 mutations are the most common IDH mutation in gliomas
- IDH-2 mutations also occur
- IDH mutations are found in about 80% of low-grade gliomas
- Lack of IDH mutation is required for a glioblastoma diagnosis per CNS WHO 2021

TARGETED THERAPIES IN IDH-MUTANT GLIOMAS

- Targeted therapies initially developed to treat acute myeloid leukemia
- IDH1 mutation
  - Ivosidenib
- IDH2 mutation
  - Enasidenib
- IDH1 or IDH2 mutation
  - Vorasidenib

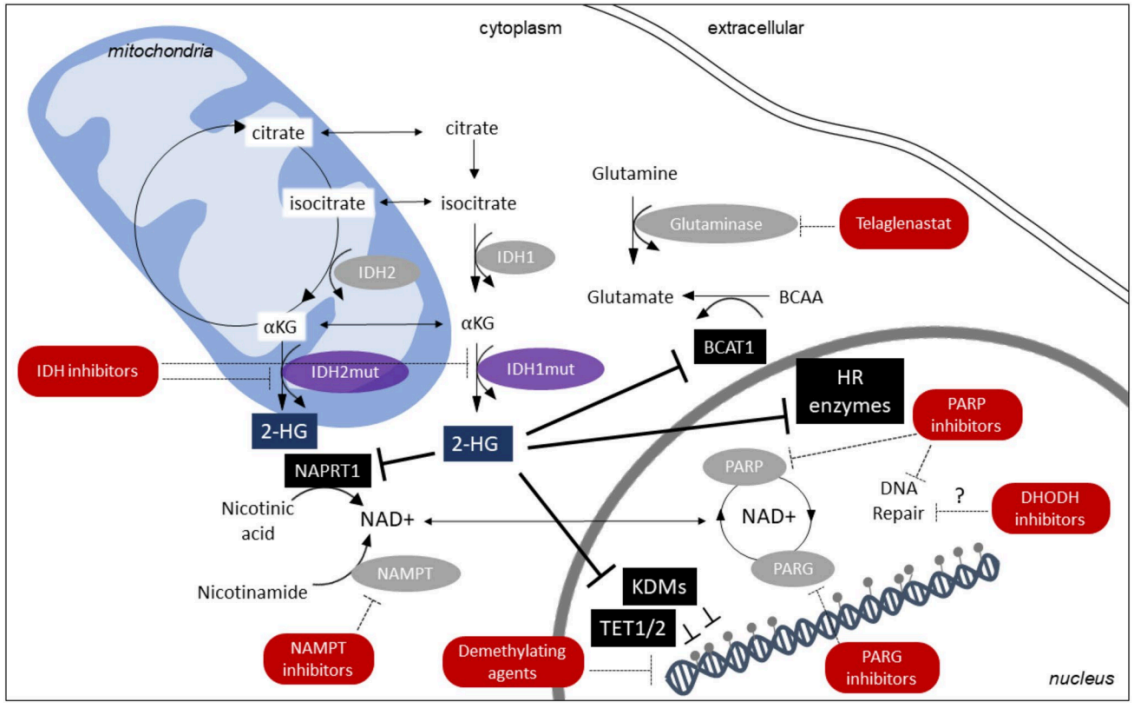


Fig. 1 IDH-mutant enzymes produce D-2-hydroxyglutarate (2-HG), which alters metabolic programs and promotes gliomagenesis. Direct targets of D-2-HG are shown in black. Drugs that target these various processes are shown in red. Abbreviations: IDH, isocitrate dehydrogenase; αKG, alpha ketoglutarate; NAD, nicotinamide adenine dinucleotide; NAPRT1, nicotinate phosphoribosyltransferase 1; NAMPT, nicotinamide phosphoribosyltransferase; BCAT1, branched chain amino acid transaminase 1; BCAA, branched chain amino acid; HR, homologous recombination; PARP, poly (ADP-ribose) polymerase; PARG, poly (ADP-ribose) glycohydrolase; DHODH, dihydroorotate dehydrogenase; KDMs, histone lysine demethylases; TET 1/2, ten-eleven translocation methylcytosine dioxygenase

Miller JJ. Targeting IDH-Mutant Glioma. Neurotherapeutics. 2022 Oct;19(6):1724-1732.

IVOSIDENIB – PHASE I TRIAL

- 66 adult patients with recurrent IDH1-mutated glioma were enrolled
- Partial response was observed in 1 patient
- Control of disease was observed in 44 patients
- Non-enhancing tumors responded more favorably than enhancing tumors
- Estimated tumor growth rate decreased following ivosidenib treatment

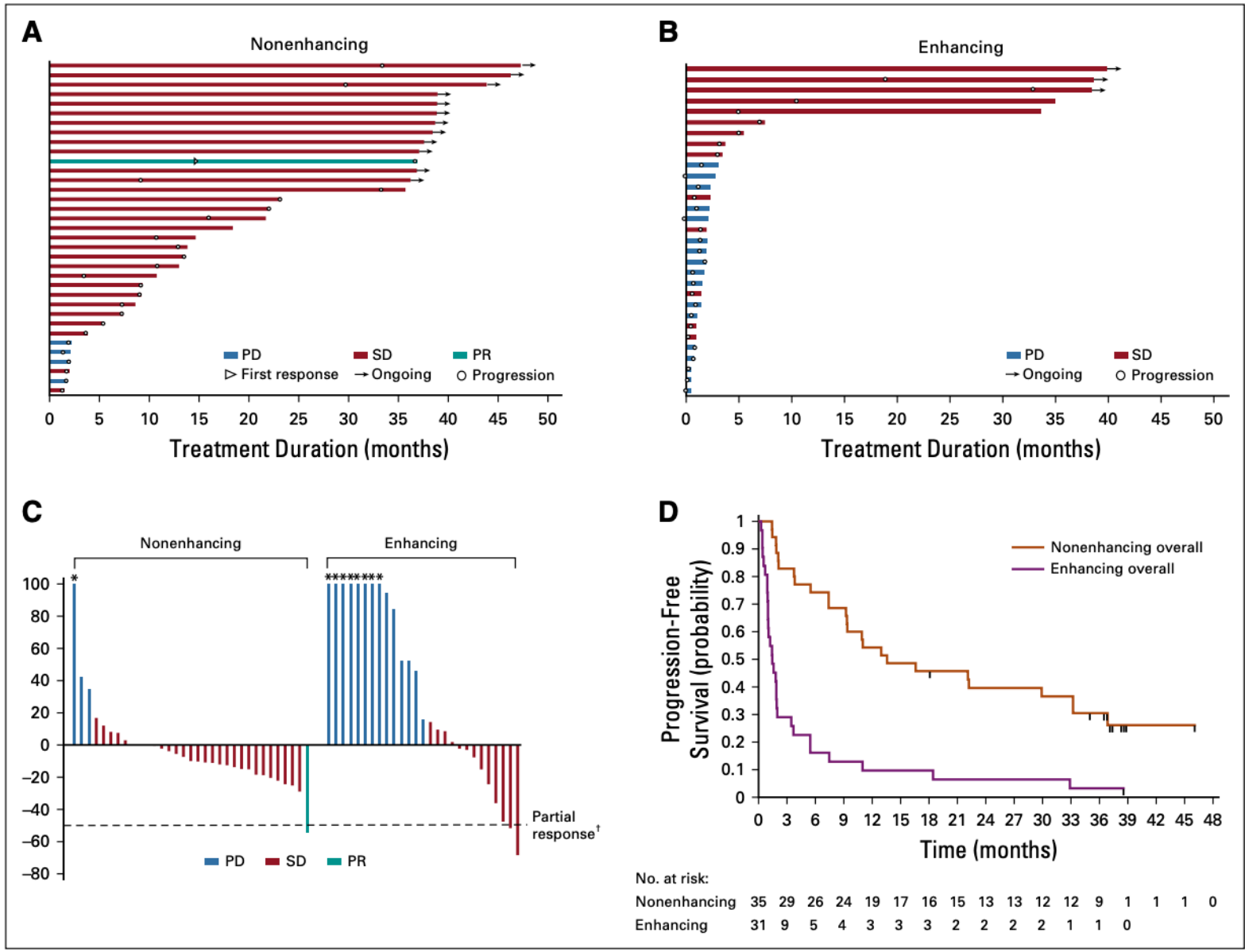


FIG 1. Clinical activity and efficacy of ivosidenib in patients with glioma. (A) Time receiving ivosidenib for the 35 patients with nonenhancing glioma. Twelve patients remain on treatment as of the data cutoff. (B) Time receiving ivosidenib for the 31 patients with enhancing glioma. Three patients remain on treatment as of the data cutoff. (C) Best response in evaluable patients with measurable disease (27 enhancing and 33 nonenhancing), expressed as the percent change in sum of products of the diameters from the target lesions at start of treatment. (D) Investigator-assessed progression-free survival according to glioma type for all evaluable patients with glioma (n = 66). Tick marks indicate censored data. PD, progressive disease; PR, partial response; SD, stable disease. (*) Lesion growth > 100%. (†) Two patients with enhancing disease had decreases of > 50% that were not confirmed and are indicated as SD.

Mellinghoff IK et al. Ivosidenib in Isocitrate Dehydrogenase 1-Mutated Advanced Glioma. J Clin Oncol. 2020 Oct 10;38(29):3398-3406.

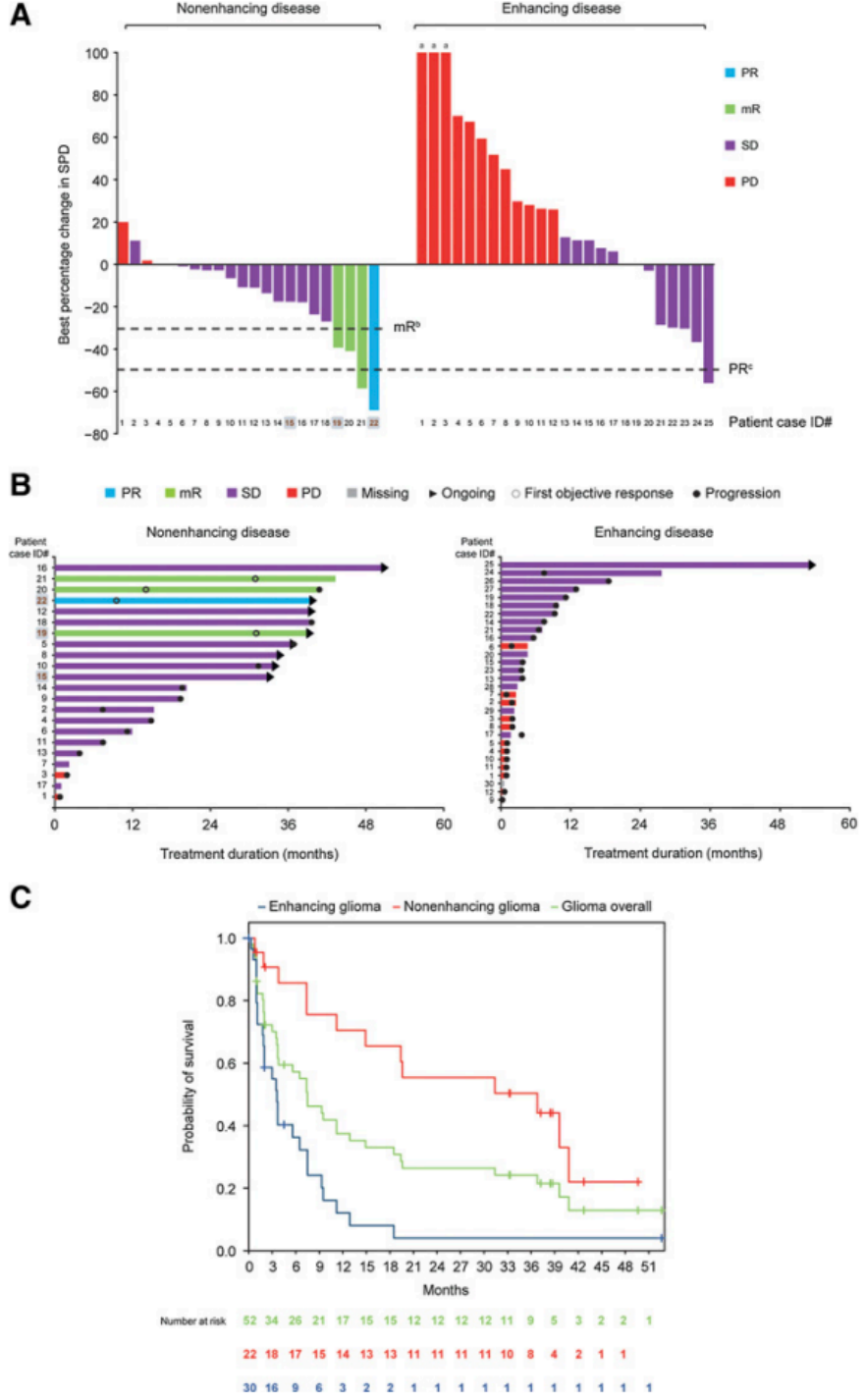
VORASIDENIB – PHASE I TRIAL

- 52 adult patients with recurrent IDH-1 or IDH-2 mutated glioma were enrolled
- Partial response was seen in 1 patient; minor response was seen in 3 patients; and disease control was seen in 17 patients
- Median PFS was 36.8 months for non-enhancing tumors and 3.6 months for enhancing tumors

Mellinghoff IK et al. Vorasidenib, a Dual Inhibitor of Mutant IDH1/2, in Recurrent or Progressive Glioma; Results of a First-in-Human Phase I Trial. Clin Cancer Res. 2021 Aug 15;27(16):4491-4499.

Figure 1.

Clinical activity and efficacy of vorasidenib in patients with glioma. **A,** Best response in evaluable patients with measurable disease (25 enhancing and 22 nonenhancing) expressed as the percentage change in SPD of target lesions from the start of treatment. Among the 52 patients, 4 patients with enhancing disease had evaluable but nonmeasurable disease, and 1 withdrew from the study before tumor response evaluations. **B,** left, Treatment duration and best response for patients with nonenhancing glioma; 8 patients remained on treatment. **B,** right, Treatment duration and best response for patients with enhancing glioma; 1 patient remained on treatment. In **A** and **B**, shaded patient case ID numbers (#) written in bold brown font indicate patients with nonenhancing glioma for whom brain MRI images and volumetric growth curves are shown in **Fig. 2**. **C,** One patient with nonenhancing disease had a >50% reduction from baseline that was not confirmed with subsequent scan and is therefore categorized as mR. [a]Lesion growth >100%. [b]An mR is defined as a ≥25% but ≤50% decrease in tumor measurements relative to baseline. [c]A >50% decrease in tumor measurements relative to baseline corresponds to a PR. A >50% reduction from baseline was not confirmed with subsequent scan in 1 patient with nonenhancing disease and was therefore categorized as mR. One patient with enhancing disease had a >50% reduction that was not confirmed and was categorized as SD. PD, progressive disease; SD, stable disease; SPD, sum of products of the diameters.



TOLERABILITY OF IDH-INHIBITORS

Common side effects	Monitoring considerations
• Headache • Fatigue • Nausea • Diarrhea • Liver enzyme abnormalities • Hypophosphatemia • Neutropenia	• CBC • CMP • Phosphate

LIMITATIONS

- Targeted genetic therapies have shown promise in treating gliomas by inhibiting specific molecular pathways that are dysregulated in these tumors.
- Targeted therapies can be limited by the heterogeneity and complexity of gliomas, which can make it difficult to identify effective therapies for all patients.
- One limitation of targeted genetic therapies is the development of resistance over time, which can lead to tumor progression and decreased effectiveness of the therapy.
- Targeted therapies may be expensive or difficult to administer, limiting their accessibility to patients.
- The optimal sequencing and combination of targeted therapies with other treatments such as surgery, radiation therapy, and chemotherapy is still being investigated and may vary based on the specific tumor characteristics and patient factors.

NEXT STEPS

- Identifying additional genetic mutations that can be targeted by therapies, or developing combination therapies that target multiple pathways simultaneously
- Increasing access to targeted therapies for glioma patients is also a priority, as these therapies may currently be limited in their availability or affordability for some patients
- Developing strategies to overcome drug resistance and prevent disease progression in patients receiving targeted therapies
- Continued research into the biology of gliomas and the mechanisms of targeted therapy action to develop novel therapies