

HOME > SCIENCE TRANSLATIONAL MEDICINE > VOL. 17, NO. 786 > A WINDOW-OF-OPPORTUNITY TRIAL REVEALS MECHANISMS OF RESPONSE AND RESISTANCE TO NAVTEMADLIN IN...

RESEARCH ARTICLE CANCER



A window-of-opportunity trial reveals mechanisms of response and resistance to navtemadlin in patients with recurrent glioblastoma

VERONICA RENDO , EUDOCIA Q. LEE , [..], AND RAMEEN BEROUKHIM +40 authors [Authors Info & Affiliations](#)

SCIENCE TRANSLATIONAL MEDICINE 19 Feb 2025 Vol 17, Issue 786

477



Editor's summary

Many glioblastomas express wild-type *TP53*, which may make them susceptible to pharmacological inhibition of MDM2 (murine double minute homolog 2), leading to reactivation of p53 signaling and tumor cell death. Here, Rendo and colleagues report the results of a surgical window-of-opportunity trial (NCT03107780) in 21 patients with recurrent glioblastoma, where patients received two doses of the MDM2 inhibitor navtemadlin before resection of their tumors, then continued the drug after resection. Despite the drug showing a pharmacodynamic impact on tumors, progression-free and overall survival were not improved. The authors then used DNA sequencing, transcriptomic and spatial analyses, and glioblastoma neurospheres to explore mechanisms of resistance and suggest that combination with temozolomide may improve results going forward. —Melissa L. Norton

Abstract

Inhibitors of murine double minute homolog 2 (MDM2) represent a promising therapeutic approach for the treatment of *TP53* wild-type glioblastomas (GBMs), reactivating p53 signaling to induce cancer cell death. We conducted a surgical window-of-opportunity trial (NCT03107780) of the MDM2 inhibitor navtemadlin (KRT-232) in 21 patients with *TP53* wild-type recurrent GBM to determine achievable drug concentrations within tumor tissues and biological mechanisms of response and resistance. Participants received navtemadlin at 120 mg ($n = 10$) or 240 mg ($n = 11$) for 2 days before surgical resection and after surgery until progression or unacceptable toxicity. Both 120 and 240 mg daily dosing achieved a pharmacodynamic impact, but median progression-free survival was 3.1 months. DNA sequencing of three recurrent tumors revealed an absence of *TP53*-inactivating mutations, indicating alternative mechanisms of resistance. To understand the mechanisms of response and resistance associated with navtemadlin, we conducted functional and spatial analyses of human tissue and patient-derived GBM neurosphere models. Navtemadlin induced partial tumor cell death as monotherapy, and combination with temozolomide enhanced apoptosis in GBM neurospheres while sparing normal bone marrow cells in vitro. We also observed up-regulation of oligodendrocyte differentiation genes with navtemadlin treatment and enrichment of oligodendrocyte transcription factor 2 (OLIG2)-positive cells at relapse, suggesting an unexplored mechanism of navtemadlin tolerance in GBM. Overall, these results indicated that clinically achievable doses of navtemadlin exert pharmacodynamic effects on GBM and suggest that combined treatment with temozolomide may be a route to more durable survival benefits.

Access the full article

View all access options to continue reading this article.



ALREADY A SUBSCRIBER OR AAAS MEMBER? SIGN IN AS AN [INDIVIDUAL](#) OR VIA YOUR [INSTITUTION](#)

Supplementary Materials

The PDF file includes:

Figs. S1 to S7

Table S1

DOWNLOAD

1.41 MB

Other Supplementary Material for this manuscript includes the following:

Data file S1

DOWNLOAD

14.31 KB

MDAR Reproducibility Checklist

DOWNLOAD

688.28 KB

REFERENCES AND NOTES

- 1 Y. Zhang, C. Dube, M. Gibert Jr., N. Cruickshanks, B. Wang, M. Coughlan, Y. Yang, I. Setiady, C. Deveau, K. Saoud, C. Grello, M. Oxford, F. Yuan, R. Abounader, The p53 pathway in glioblastoma. *Cancer* **10**, 297 (2018).

[CROSSREF](#) • [GOOGLE SCHOLAR](#)

- 2 M. Fischer, Census and evaluation of p53 target genes. *Oncogene* **36**, 3945–3956 (2017).

[CROSSREF](#) • [PUBMED](#) • [WEB OF SCIENCE](#) • [GOOGLE SCHOLAR](#)

SHOW ALL REFERENCES

eLetters (0)

eLetters is a forum for ongoing peer review. eLetters are not edited, proofread, or indexed, but they are screened. eLetters should provide substantive and scholarly commentary on the article. Neither embedded figures nor equations with special characters can be submitted, and we discourage the use of figures and equations within eLetters in general. If a figure or equation is essential, please include within the text of the eLetter a link to the figure, equation, or full text with special characters at a public repository with versioning, such as Zenodo. Please read our [Terms of Service](#) before submitting an eLetter.

LOG IN TO SUBMIT A RESPONSE

No eLetters have been published for this article yet.

Recommended articles from TrendMD

A single dose of peripherally infused EGFRVIII-directed CAR T cells mediates antigen loss and induces adaptive resistance in patients with recurrent glioblastom...

Donald M. O'Rourke, *Sci Transl Med*, 2017

Study reveals mechanisms of increased infectivity and antibody resistance of SARS-CoV-2 variants

Sophie M.-C. Gobeil, *Science*, 2021

Response: Biopesticides and Resistance

Ann Gibbons, *Science*, 1992

A first-in-human phase 0 clinical study of RNA interference–based spherical nucleic acids in patients with recurrent glioblastoma

Priya Kumthekar, *Sci Transl Med*, 2021

Response: Unusual Mutational Mechanisms and Evolution

Richard E. Lenski, *Science*, 1993

The Impact of Resistance Exercise on Muscle Mass in Glioblastoma in Survivors (RESIST): Protocol for a Randomized Controlled Trial

Melanie R Keats, *JMIR Preprints*, 2022

The Impact of Resistance Exercise on Muscle Mass in Glioblastoma in Survivors (RESIST): Protocol for a Randomized Controlled Trial

Melanie R Keats, *JMIR Res Protoc*, 2022

BABA-induced pathogen resistance: a multi-omics analysis of the tomato response reveals a hyper-receptive status involving ethylene

Martina Zapletalová, *Horticulture Research*

Healthcare Cost Analysis of Older Patients Using a Personal Emergency Response Service Uncovers Costs Savings Opportunity

Mariana Simons, *Iproceedings*, 2017

VEROnA Protocol: A Pilot, Open-Label, Single-Arm, Phase 0, Window-of-Opportunity Study of Vandetanib-Eluting Radiopaque Embolic Beads (BTG-002814) in Patients W...

Laura Beaton, *JMIR Res Protoc*, 2019

Powered by