ABSTRACT

J Neurooncol. 2022 Dec 29. doi: 10.1007/s11060-022-04193-3. Online ahead of print.

ABTC-0904: targeting glioma stem cells in GBM: a phase 0/II study of hedgehog pathway inhibitor GDC-0449.

Sloan AE(1), Nock CJ(2), Ye X(3), Buerki R(4), Chang S(5), Lesser G(6), Norden A(7), Cloughesy T(8), Olson J(9), Kerstetter-Fogle A(10), Rich J(11), Fisher J(3), Desideri S(3), Takebe N(12), Timmer W(12), Grossman S(3), Prados M(5).

Author information:
(1)Chief of Neuroscience, Piedmont Healthcare, Atlanta, USA. Andrew.Sloan@Piedmont.org.
(2)Department of Medicine, UH-Seidman Cancer Center and Case Comprehensive Cancer Center, Cleveland, OH, USA.
(3)Adult Brain Tumor Consortium, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD, USA.
(4)Department of Neurology, UH-Seidman Cancer Center and Case Comprehensive Cancer Center, Cleveland, OH, USA.
(5)Department of Neurosurgery, University of California, San Francisco, San Francisco, CA, USA.
(6)Department of Radiation Oncology, Wake Forest University, Wake Forest, NC, USA.
(7)Department of Medicine, Dana Farber Cancer Institute, Boston, MA, USA.
(8)Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA.
(9)Department of Neurosurgery, Emory University, Atlanta, GA, USA.
(10)Chief of Neuroscience, Piedmont Healthcare, Atlanta, USA.
(11)Department of Neurology and Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA.
(12)National Cancer Institute, Clinical Investigations Branch, National Institutes of Health, Bethesda, MD, USA.

PURPOSE: Gliomagenesis and resistance of glioblastoma (GBM) are believed to be mediated by glioma stem cells (GSC). Evidence suggests that SHH signaling promotes GSC proliferation and self-renewal.

METHODS: ABTC-0904 was a two-arm, multicenter phase 0/II study of GDC-0449, an oral inhibitor of Smoothened (SMO) in patients undergoing resection for recurrent GBM. All patients (Arms I and II) had surgery and received drug post-operatively. Only patients in Arm I received drug prior to surgery. The primary objective was to determine 6-month progression free survival (PFS-6). Secondary endpoints include median PFS (mPFS) and overall survival (mOS), response rate, and toxicity. Correlative studies included bioanalysis of GDC-0449, and inhibition of SHH signaling, GSC proliferation and self-renewal.

RESULTS: Forty-one patients were enrolled. Pharmacokinetics of GDC-0449 in plasma demonstrated levels within expected therapeutic range in 75% of patients. The proportion of tumorcells producing CD133+ neurospheres, neurosphere proliferation, self-renewal, and expression of the SHh downstream signaling was significantly decreased in Arm I following GDC-0449 treatment ($p < 0.005$; $p < 0.001$ respectively) compared to Arm II (no drug pre-op). Treatment was well tolerated. There were no objective responders in either arm. Overall PFS-6 was 2.4% (95% CI 0.9-11.1%). Median PFS was 2.3 months (95% CI 1.9-2.6) and mOS was 7.8 months (95% CI 5.4-10.1).

CONCLUSIONS: GDC-0449 was well tolerated, reached tumor, and inhibited CD133+ neurosphere formation, but had little clinical efficacy as a single agent in rGBM. This suggests growth and maintenance of rGBM is not solely dependent on the SHH pathway thus targeting SMO may require combined approaches.

DOI: 10.1007/s11060-022-04193-3
PMID: 36581779