Neuro Oncol. 2025 Mar 22:noaf079. doi: 10.1093/neuonc/noaf079. Online ahead of print.

A multi-institutional phase 1 clinical trial exploring upfront multimodal standard of care and combined immunotherapies for newly diagnosed glioblastoma

Patrick Y Wen [1 2], Andrea Manzanera [3], Caroline Duault [4], Edgar Gonzalez-Kozlova [5], Lenika Lopez [3], Stuart A Grossman [2 6], Xiaobu Ye [2 6], Joy Fisher [2 6], Ian Lee [7], Tobias Walbert [7], James Snyder [7], Steven Brem [8], Arati Desai [8], Stephen J Bagley [8], Chandana Kakani [8], Roy Strowd [9], Stephen Tatter [9], Adrian Laxton [9], Glenn Lesser [9], Nduka Amankulor [8], Frank Lieberman [10], Jan Drappatz [10], Megan Mantica [10], Dan Triggs [1 11], Cara Haymaker [12], Ignacio I Wistuba [12], Gheath Al-Atrash [12], Julia Mendoza Perez [12], Andrew Futreal [12], Latasha D Little [12], M D Habibul Islam [12], Dzifa Duose [12], Peixin Jiang [12], Alexandre Reuben [12], Sean E Lawler [1 11 13], Mina Pichavant [4], Andrew Gentles [4], Sean Bendall [4], Alex Kong [4], Christine Camacho [4], Diane Del Valle [5], Seunghee Kim-Schulze [5], Sacha Gnjatic [5], Elad Sharon [14], M Oskar Nowicki [1 11], Pierpaolo Peruzzi [1 11], Doug Lane [3], Estuardo Aguilar-Cordova [3], Laura K Aguilar [3], Garrett Nichols [3], Jessica Dwyer [3], Paul Peter Tak [3], Holden Maecker [4], Francesca Barone [3], E Antonio Chiocca [1 11]

PMID: 40120123 DOI: 10.1093/neuonc/noaf079

Background: For newly diagnosed glioblastoma (GBM), combination of surgical upfront immunotherapy with aglatimagene besadenovec (CAN-2409), followed by chemoradiation and then adjuvant nivolumab has not been tested. The aim of this study was to test the safety of this regimen and determine metrics of immune activation that may correlate with clinical outcomes.

Methods: 41 patients with suspected newly diagnosed GBM by imaging were enrolled in this multi-institutional, open label, phase 1b clinical trial before surgical resection. Frozen section confirmation of high-grade glioma was required for administration of aglatimagene besadenovec. This was then followed with chemoradiation and adjuvant nivolumab. Tumor and blood were assayed for genetic and immune markers before and during treatment.

Results: The regimen was well tolerated and generated measurable immune activation. Factors linked to survival were identified, such as baseline mutated gene pairs (e.g. MED15/ HRC), tumor immune cell composition, and changes in systemic cytokine, immune cells, and T cell diversity. The most significant serial systemic immune changes were observed in a long-term survivor subset of patients with gross total resection (GTR)/ methylated methylguanine methyltransferase (MGMT) promoter tumors. Median overall survival (mOS) in these patients was 30.6 months, while it was less for patients with unmethylated or subtotal resections.

Conclusions: These findings suggest the opportunity for patient stratification and the potential for more durable antitumor immune responses in future clinical trials of this multimodal standard of care and combined immunotherapy regimen. ClinicalTrials.gov identifier: NCT03576612.

Keywords: Clinical trial; brain tumor; gene therapy; glioma; immunotherapy.