AB036. Targeting glioblastoma *de-novo* purine metabolism to overcome chemoradiation resistance: an interim result of phase 0/1 clinical trial in newly diagnosed and recurrent glioblastoma

Yoshie Umemura[1,2], Nathan Clarke[2], Wajd Al-Holou[3], Ameer Elaimy[4], Andrew Scott[4], Denise Leung[2], Michelle Kim[4], Sean Ferris[5], Jennifer Thomas[4], Jason Heth[3], Matthew Schipper[5], Krithika Suresh[6], Theodore Lawrence[4], Daniel Wahl[4]

[1]Neuro-Oncology Division & Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, AZ, USA; [2]Department of Neurology, University of Michigan, Ann Arbor, MI, USA; [3]Department of Neurosurgery, University of Michigan, Ann Arbor, MI, USA; [4]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA; [5]Department of Pathology, University of Michigan, Ann Arbor, MI, USA; [6]Department of Biostatistics, University of Michigan, Ann Arbor, MI, USA

Correspondence to: Yoshie Umemura, MD. Neuro-Oncology Division & Ivy Brain Tumor Center, Barrow Neurological Institute, 2910 N 3rd Ave., Suite 420, Phoenix, AZ 85013, USA; Department of Neurology, University of Michigan, Ann Arbor, MI, USA. Email: Yoshie.Umemura@barrowneuro.org.

Background: Glioblastoma cells preferentially use *de-novo* purine synthesis pathway, whereas normal brain prefers salvage pathway. Mycophenolate mofetil (MMF), a commonly used oral immunosuppressant that inhibits inosine-5'-monophosphate dehydrogenase (IMPDH), a key enzyme in the *de-novo* purine pathway. Pre-clinical suggested MMF can improve radiation and temozolomide efficacy in glioblastoma which led to this phase 0/1 trial (NCT04477200) to assess MMF's tolerability with chemoradiation in glioblastoma, mycophenolic acid accumulation, and purine synthesis inhibition in tumor.

Methods: In the phase 0 study, eight recurrent glioblastoma patients received MMF at doses ranging 500–2,000 mg BID for 1-week before surgery. The tissues were analyzed using mass spectrometry for drug accumulation and purine synthesis inhibition. In the phase 1 study, adult patients were given MMF starting at 1,000 mg orally (PO) twice daily (BID), with the possible dose ranging 500–2,000 PO BID. Nineteen recurrent glioblastoma patients (target N=30) received MMF 1-week prior to and concurrently with re-irradiation (40.5 Gy). Thirty newly diagnosed glioblastoma patients received MMF 1-week prior to and concurrently with chemoradiation, followed by MMF 1-day before and during 5 days of each adjuvant temozolomide cycle.

Results: Both enhancing and non-enhancing tumors from phase 0 subjects yielded >1 μM active drug metabolite, and the guanosine triphosphate: inosine monophosphate ratio was decreased by 75% in enhancing tumors in MMF-treated patients compared to untreated controls (P=0.009), indicating effective target engagement and inhibition of purine synthesis. In the phase 1 study, no dose-limiting toxicities (DLTs) were observed at the interim analysis at MMF 1,000–1,500 mg BID combined with chemoradiation. At 2,000 mg BID, there was no DLT combined with temozolomide alone, however, there were four DLTs noted (hemiparesis, cognitive disturbance, fatigue, thrombocytopenia) when combined with radiotherapy and temozolomide together, though all were reversible. Interim median overall survival in recurrent phase 1 is 15.6 months, and not reached yet in newly diagnosed phase 1.

Conclusions: MMF with chemoradiation has been reasonably well tolerated and showed promising evidence of brain tumor target engagement and drug accumulation. This study led to a recommended phase 2 dose of MMF 1,500 mg BID and will provide a preliminary efficacy estimate for a randomized phase 2/3 trial through the Alliance for Clinical Trials in Oncology.

Keywords: Glioblastoma; purine metabolism; mycophenolate mofetil (MMF)

Acknowledgments

Funding: This study was supported by Gateway for Gancer Research (G-21-1000) and NIH/NCI (R37 CA258346-05: NIHDHHS-US).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-24-ab-036/coif). Y.U.

received research support from Servier, Chimerix, ONO Pharma, BTG Specialty Pharmaceuticals, and Gateway for Cancer Research, received honoraria from Neurodiem and Intellisphere, LLC for educational written content and speaking event, served on advisory boards for Servier and Oncoboard, and as a consultant for Servier. W.A.H. received payment for consulting for Servier. D.L. consulted for GLG, served on Advisory Board for Servier, and received honoraria for educational lectures at Spectrum Health Center (MI, USA). M.S. received payment for consulting for Innovative Analytics. D.W. provided consulting to Admare, which seeks develop metabolic inhibitors for brain tumors, and received grants or contracts from NCI, NINDS, Ivy Foundation, Damon Runyon Cancer Research Foundation, and V foundation. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by University of Michigan Institutional Review Board (IRB No. HUM00175785). Written informed consent was obtained from all patients in this clinical trial.

Cite this abstract as: Umemura Y, Clarke N, Al-Holou W, Elaimy A, Scott A, Leung D, Kim M, Ferris S, Thomas J, Heth J, Schipper M, Suresh K, Lawrence T, Wahl D. AB036. Targeting glioblastoma *de-novo* purine metabolism to overcome chemoradiation resistance: an interim result of phase 0/1 clinical trial in newly diagnosed and recurrent glioblastoma. Chin Clin Oncol 2024;13(Suppl 1):AB036. doi: 10.21037/cco-24-ab036