Heterogeneity in Drug Delivery across the Blood-Brain Barrier Impacts Efficacy of Depatuxizumab Mafodotin (ABT-414) Therapy in Glioblastoma

AAPS Poster Number M141

Bianca-Maria Marin[1], Ann C. Mladek[1], Danielle M. Burgenske[1], Gaelle Muller-Greven[2], Mark A Schroeder[1], Lihong He[1], Zeng Hu[1], Katrina A. Bakken[1], Brett L Carlson[1], Paul Decker[3], Candece Gladson[2], William F. Elmquist[4], Jann N. Sarkaria[1]

Departments of [1]***Radiation Oncology, Mayo Clinic, Rochester, MN,*** [2]*Cancer Biology and Stem Cell Biology, Cleveland Clinic, Cleveland, OH*
[3]*Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN,* [4]*Brain Barriers Research Center, University of Minnesota, Minneapolis, MN*

Background

ABT-414 is a novel antibody-drug conjugate (ADC) of monomethyl auristatin F (MMAF), a microtubule destabilizing agent, and an anti-EGFR antibody (ABT-806).

The efficacy of ABT-414 was evaluated *in vitro* and *in vivo* across a panel of 13 GBM patient-derived xenografts (PDXs) with or without EGFR amplification.

When grown as flank tumors, 4 of 5 EGFR-amplified, vIII mutant lines tested were exquisitely sensitive to ABT-414 therapy. In contrast, response to ABT-414 therapy in orthotopic tumors was more heterogeneous.

We hypothesized that the difference in efficacy results could potentially be related to differences in blood-brain barrier (BBB) disruption and associated drug distribution between the PDXs.

Profound heterotopic efficacy

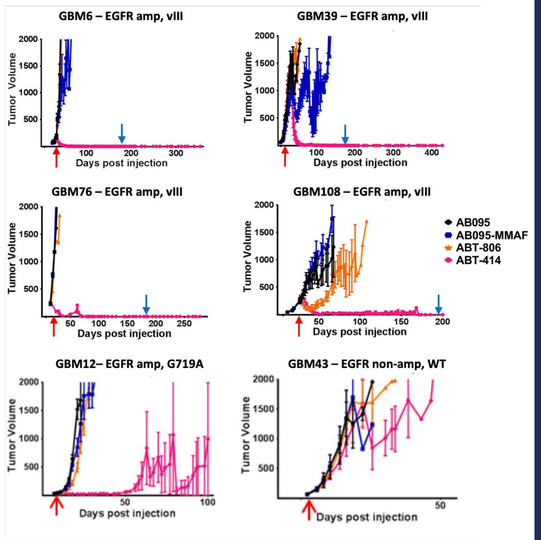


Figure 1. ABT-414 therapy provides profound and durable suppression of tumor growth in EGFR-amplified heterotopic PDXs. Mice with established flank tumors were treated with either AB095 (non-specific IgG; 10 mg/kg), AB095-MMAF (non-specific ADC; 5 mg/kg), ABT-806 (naked Ab; 10 mg/kg) or ABT-414 (ADC; 5 mg/kg) starting 14-20 days post injection. Efficacy was evaluated using serial tumor volume measurements.

Limited orthotopic efficacy

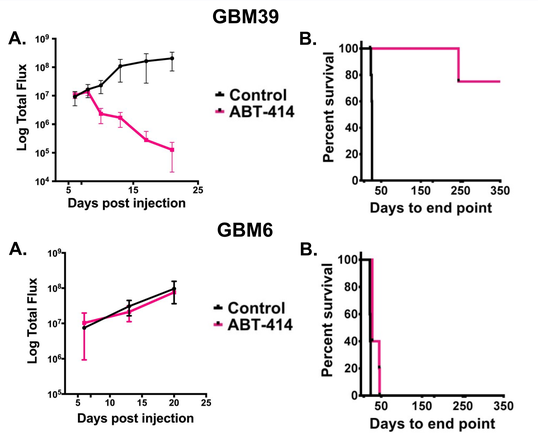


Figure 2. ABT-414 therapy provides variable tumor growth suppression and survival prolongation in orthotopic tumors. Mice with established GBM39 or GBM6 orthotopic tumors were treated with either AB095 or ABT-414 starting 7 days post injection. Efficacy was evaluated using bioluminescent imaging (**A**) and time to reach a moribund state (**B**).

Variable ABT-414 distribution and BBB disruption

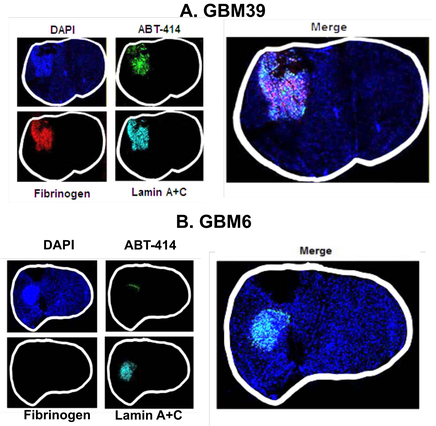


Figure 3. ABT-414 therapy provides highly variable drug delivery across different PDXs. Mice with established GBM39 (**A**) or GBM6 (**B**) orthotopic tumors were given a single dose of either AB095 or ABT-414 and euthanized four days later. Immunofluorescence (IF) was used to detect human IgG (ABT-414) and murine fibrinogen.

Artificial BBB disruption increases ABT-414 efficacy

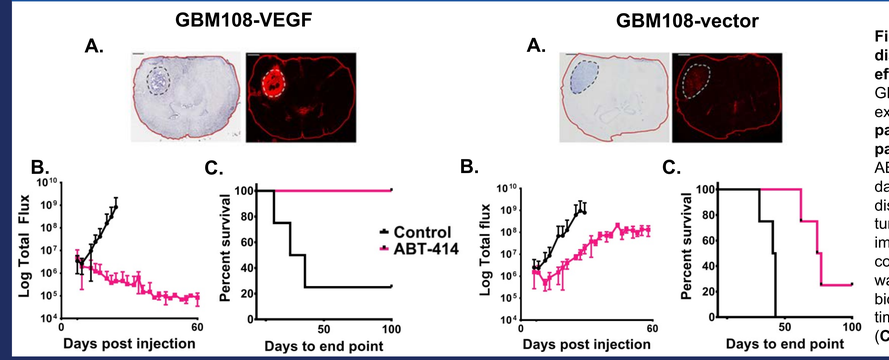


Figure 4. Artificial BBB disruption increases ABT-414 efficacy. Mice with established GBM108 orthotopic tumors expressing either VEGF (**left panel**) or empty vector (**right panel**) were treated with either AB095 or ABT-414 starting 7 days post injection. BBB disruption was assessed by tumor accumulation of an impenetrant TexasRed-dextran conjugate (**A**). Tumor response was monitored by bioluminescent imaging (**B**) and time to reach a moribund state (**C**).

Direct injection improves ABT-414 efficacy and delivery in GBM6

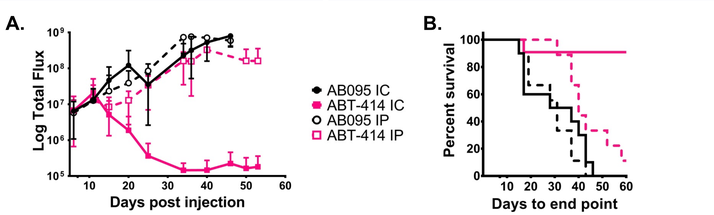
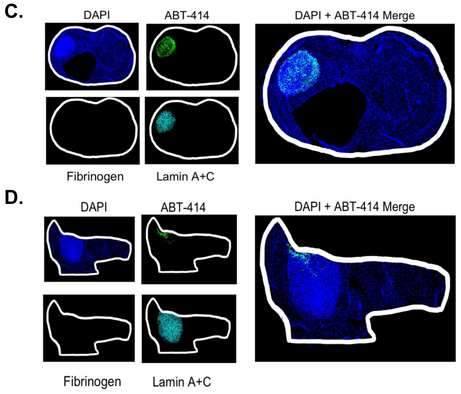


Figure 5. Intratumoral administration of ABT-414 increases delivery and efficacy. Mice with established GBM6 orthotopic tumors were treated with four weekly doses of AB095 or ABT-414, delivered either intratumorally or intraperitoneally. Efficacy was evaluated using serial bioluminescent imaging (**A**) and measuring time to reach a moribund state (**B**).



Mice with established GBM6 orthotopic tumors were given a single dose of ABT-414 either intratumorally (**C**) or intraperitoneally (**D**) and euthanized four days later. Immunofluorescence was used to detect human IgG (ABT-414) and murine fibrinogen.

Conclusions

ABT-414 is a highly effective EGFR-targeted therapeutic for EGFR-amplified, vIII mutant models.

However, treatment efficacy may be limited by inadequate drug-delivery across an intact BBB.

Collectively, these data support the concept of using novel strategies to enhance delivery of ADC therapeutics across the BBB for effective treatment of GBM.