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

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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 (PDGs) 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 PDGs.

Background

Figure 1. ABT-414 therapy provides profound and durable suppression of tumor growth in EGFR-amplified heterotopic PDGs. 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.

Profound heterotopic 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).

Limited orthotopic efficacy

Variable ABT-414 distribution and BBB disruption

Figure 3. ABT-414 therapy provides highly variable drug delivery across different PDGs. Mice with established GBM39 (A) or GBM6 (B) orthotopic tumors were given a single dose of either 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).

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.