Efficacy and pharmacokinetics of EGFR-targeted antibody-drug conjugates following convection-enhanced delivery in mice with glioblastoma xenografts

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ABSTRACT

Purpose: Antibody-drug conjugates (ADCs) provide specific delivery of potent toxins to cancers. Unfortunately, the clinical benefits of these powerful therapeutics have not been realized in glioblastoma (GBM). The blood brain barrier (BBB) in GBM can limit distribution of ADCs into tumor tissue. To bypass the BBB, we tested convection enhanced delivery (CED) infusion of ADCs into orthotopic GBM patient derived xenografts.

Methods: Two EGFR-targeted ADCs with a similar antibody backbone but different toxins were compared: depatuxizumab mafodotin (Depatux-M) has a monomethyl auristatin F (MMAF) toxin, which is not cell permeant once released, and Losatuxizumab vedotin (ABBV-221) has a cell permeant monomethyl auristatin E (MMAE) toxin. Efficacy was evaluated in three GBM PDX models with amplified/mutant EGFRviii. Bioluminescence imaging and survival were used to evaluate efficacy. MMAE levels were quantified using LC-MS/MS, and NeuN immunostaining was used to evaluate neuronal cell loss.

Results: Efficacy was compared across models following treatment with Depatux-M and ABBV-221 delivered in three serial CED infusions (21 days apart) or seven intraperitoneal (IP) injections (7 days apart). The median survivals by treatment group are shown in the table. For the two more mature studies, the data demonstrate a consistent enhancement in survival with CED infusion of Depatux-M (60 mg) or ABBV-221 (66 mg) as compared to IP injection (5 mg /kg). CED infusion of C57BL6 non-tumor bearing mice at the therapeutic dose levels of Depatux-M and ABBV-221 were well tolerated and had no impact on NeuN+ neuronal density. At much higher concentrations, CED of 740 mg Depatux-M also had no effect on Neu+ cell density, while CED with 274 mg ABBV-221 resulted in marked loss of NeuN+ cell density and lethal toxicity by 5 days. Following CED infusion of 570 ng of free MMAE, toxin levels were relatively stable over a four-hour sampling period with an AUC of 3860±311 h*ng/g in the infused right hemisphere compared to 2.4±0.6 h*ng/mL in plasma. A similar brain exposure profile was observed following CED of 60 mg ABBV-221 with AUC for total MMAE of 3073±635 h*ng/g and free MMAE of 311±131 h*ng/g. Surprisingly, relatively high plasma exposure was observed following CED with total MMAE of 2924±449 h*ng/mL, while free MMAE was below the limit of quantitation.

Conclusions: CED of either Depatux-M or ABBV-221 can extend survival in EGFR amplified GBM PDXs. However, high concentrations of ABBV-221 are associated with increased neuronal cell loss and toxicity as compared to Depatux-M, suggesting a broader therapeutic window for the latter ADC.

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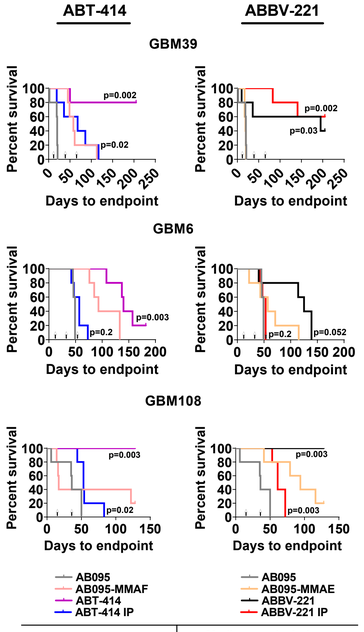


Treatment	Median survival, days		
	GBM6	GBM39	GBM108
AB095 – CED	49	20	36
AB095-MMAF – CED	93	58	17
Depatux-M – IP	57	68	53
Depatux-M – CED	140	>200	>130
AB095-MMAE – CED	57	19	94
ABBV-221 – IP	53	>200	61
ABBV-221 – CED	125	195	>130

Figure 1. Kaplan-Meier survival analysis of mice with GBM39-eGFP/fLuc2 and GBM6-eGFP/fLuc2 orthotopic tumors treated with CED infusions (shown by arrows). ABT-414 and ABBV-221 were also given intraperitoneally, 7 weekly injections. p values for endpoint comparison of respective groups to AB095 group are shown using Log-Rank test.

INTRACRANIAL TUMOR GROWTH

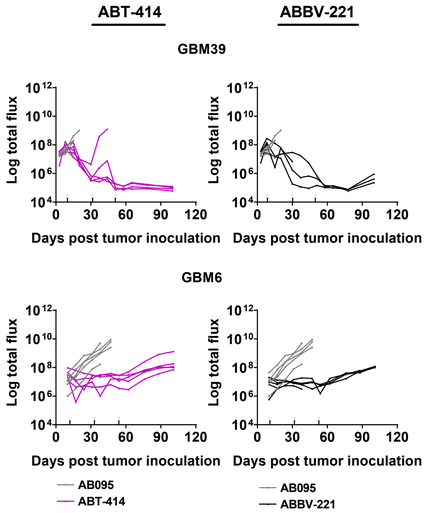


Figure 2. Intracranial tumor growth of GBM39-eGFP/fLuc2 and GBM6-eGFP/fLuc2 orthotopic tumors over a period as measured by bioluminescent imaging (BLI). Mice were treated with mentioned drugs infused thrice by CED (20 µL) at 21 days interval.

EFFECTS ON NEURONS

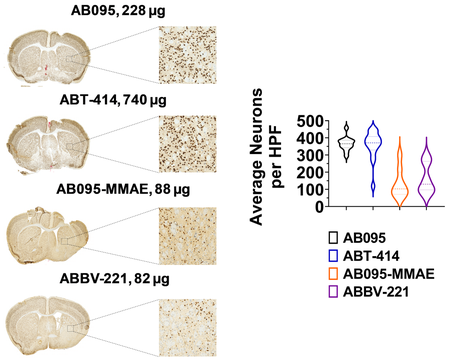
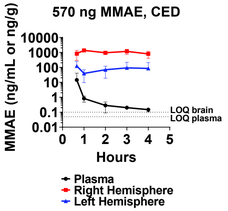
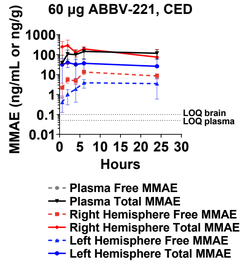


Figure 3. NeuN staining of brain sections (representative image from n=3 mice per group) from non-tumors bearing C57BL6 mice given a single CED infusion and euthanized 14 days later. Average number of neurons per high power field (HPF) is quantified across all mice treated and presented in a plot on right-side.

PHARMACOKINETICS OF MMAE



Tissue	AUC_{last} h*ng/mL or h*ng/g
Plasma	2.4 ± 0.6
Right Hemisphere	3860 ± 311
Left Hemisphere	293 ± 80



Tissue	AUC_{last} h*ng/mL or h*ng/g
Plasma Free MMAE	NC
Plasma Total MMAE	2924 ± 449
Right Hemisphere Free MMAE	311 ± 131
Right Hemisphere Total MMAE	3073 ± 635
Left Hemisphere Free MMAE	102 ± 44
Left Hemisphere Total MMAE	625 ± 177

Figure 4. Concentration-time profiles for MMAE in right and left hemispheres as well as plasma following CED administration of 570 ng MMAE or 60 µg ABBV-221, where only concentrations above LOQ are plotted. Overall AUCs and AUC_{last} for MMAE calculated from plasma, right hemisphere, and left hemisphere are shown in Tables.

REFERENCES

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SUMMARY AND CONCLUSIONS

- CED of either EGFR-targeting ADCs extends survival in EGFR amplified GBM PDXs.
- Therapeutic window for ABT-414 is broader compared to ABBV-221.
- Higher concentration of ABBV-221 resulted in neuronal cell loss and toxicity.
- Further investigation is warranted to develop novel EGFR-targeting ADCs with toxins which have higher efficacy and low toxicity.