INTRODUCTION

Normal cells make their own supply of arginine using the enzymes ornithine transcarbamylase (OTC), argininosuccinate synthase (ASS1), and argininosuccinate lyase (ASL). In many tumor cells, silencing one or more of these enzymes disables arginine synthesis, making tumor cells dependent on extracellular arginine uptake for survival (Fig 1 and 2). This makes tumors potentially vulnerable to arginine deprivation by AEB1102, an engineered form of human arginase 1. This optimized form of native human arginase 1, generated by substituting the manganese cofactor for cobalt results in a clinical candidate molecule with significantly improved catalytic activity and stability (Fig 3). The goal of Aeglea Biotherapeutics is to perform all non-clinical and chemistry, manufacturing & controls (CMC) activities and initiate clinical development in both solid tumors and hematologic malignancies.

METHODS

A product development CPRIT Grant (TX) provided insight into non-clinical animal pharmacology and manufacturing for AEB1102. Using AEB1102 from this prior grant, IND enabling in vitro and in vivo non-clinical oncology studies were performed with the A375 melanoma model. Additional in vivo studies were also performed using patient derived xenograft (PDx) models, with one of these models being derived from a patient with the B-RAF V600E mutation. A pilot dose range finding study with AEB1102 was performed in monkeys to identify doses to be utilized in subsequent GLP toxicology studies. Bioanalytical assays to determine PK and PD were developed and validated. AEB1102 CMC activities that were optimized in preclinical models confirm the sensitivity of this histology to arginine deprivation with AEB1102. The Phase 1 clinical trial is now enrolling solid tumor patients at START in San Antonio and the University of Colorado.

RESULTS

To confirm efficacy of AEB1102 as an anti-tumor therapeutic the enzyme was tested against a panel of 10 xenograft cell lines with the A375 melanoma cell line being the most sensitive to arginine deprivation. In vivo efficacy with AEB1102 administered once weekly significantly delayed A375 tumor growth in mice and yielded a survival benefit (Fig 5). These data were used to establish doses used in the GLP toxicology studies that identified an NOAEL in both species as well as providing data that suggests the PK properties of AEB1102 are compatible with once per week dosing in the clinic.

To confirm the literature data that proposes certain tumor types as being candidates for responsiveness to arginine deprivation we performed quantitative in vitro hybridization for OTC, ASS1 and ASL on clinical samples from melanoma (Fig 6A-C) and HCC (Fig 7A-C). These histologies have been reported as having 100% penetrance of arginine dependence (Fig 2). Immunohistochemistry of ASS1 was also performed to confirm the correlation of message and protein expression (Fig 6D and 7D). Our data confirms previous findings that melanoma is a cancer type that should be sensitive to arginine deprivation therapy owing to the loss of ASS1 expression in a significant percentage of patient samples. In contrast, ASS1 expression in HCC was not reduced to the same extent as that observed in melanoma and as such HCC was de-prioritized for further investigation.

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CONCLUSION

Aeglea Biotherapeutics has successfully executed on all non-clinical and CMC activities necessary to support the clinical development of AEB1102. Expression profiling of melanoma and HCC clinical samples indicates melanoma is a more arginine dependent histology owing to the greater loss of ASS1 expression and as such a candidate histology to pursue in future clinical studies. In support of this in vivo studies using melanoma pre-clinical models confirm the sensitivity of this histology to arginine deprivation with AEB1102. The Phase 1 open label dose escalation clinical study in solid tumors initiated patient dosing in October 2015. A second Phase 1 study in hematologic malignancies is planned for 2016.