Reducing systemic arginine with arginase (AEB1102) therapy does not suppress the immune response induced by anti-PD-1 and anti-PD-L1, and even has additive anti-tumor and synergistic survival benefit

G. Agnello, S. E. Alters, D. G. Lowe and S. W. Rowlinson - Aeglea BioTherapeutics, Inc., 901 S Mo Pac Expy Ste 250, Barton Oaks Plaza One, Austin TX 78746

Poster #3964

Introduction
Tumor dependence on specific amino acids for survival and proliferation is well recognized and has been exploited effectively with the use of asparaginase for the treatment of acute lymphoblastic leukemia. Sensitivity of tumors to l-Arginine (l-Arg) deprivation results from an impaired ability to make l-Arg due to decreased functional expression of one or more of the three enzymes of the l-Arg biosynthetic pathway ornithine transcarbamylase (OTC), argininosuccinate synthase (ASS1) and argininosuccinate lyase (ASL) (Fig. 1).

AEBl02 mechanism of action
We have successfully utilized an l-Arg depletion approach to impact a direct tumor growth inhibitory effect. ASS1 is expressed in most tissues, however certain cancers fail to express ASS1. Our single-agent pre-clinical efficacy data show that tumors with no or low expression of ASS1 are the most sensitive to AEBl02, providing the opportunity to target tumor metabolism with a precision medicine approach. Interestingly, tumors derived from the neural crest (e.g. melanoma, small cell lung cancer (SCLC), large cell non-small cell lung cancer (NSCLC), melanoma cells) with no or low expression of ASS1 were found to show high sensitivity to AEBl02 (Fig. 3). In contrast to ASS1, OTC expression is restricted to the small bowel and liver. Our data suggest that, among the models tested, hepatocellular carcinomas (HCC) with high expression of ASS1 but low expression of OTC are sensitive to AEBl02 (Fig. 4).

AEBl02 single-agent pre-clinical efficacy

AEBl02 efficacy in inhibitors

In a non-small cell CT26 colon cancer model, combination therapy of AEBl02 with anti-PD-L1 (Fig 5A) resulted in an improved survival (83% 5% 13% complete responders compared to AEBl02 alone (53% 13%) and anti-PD-L1 alone (53% 33%). When AEBl02 was pre-dosed prior to tumor inoculation, an HIL of 129% with 37% complete responders was observed in the group treated with AEBl02 in combination with anti-PD-L1, while monotherapy with AEBl02 and anti-PD-L1 resulted in 29% and 7% HIL respectively and no complete responders (Fig 5B). When the complete responders were re-challenged with fresh CT26 cells, the tumor failed to establish, suggesting the development of an immune memory response as a result of the previously measured combined therapy of AEBl02 and anti-PD-L1.

CT26: AEBl02 + anti-PD-L1 (Non-staged)

AEBl02 + Immune Checkpoint Inhibitors

In contrast, combination of AEBl02 with anti-CTLA4 in a non-staged CT26 model resulted in a shorter median survival time (LS 67% 17% anti-CTLA4 alone 4% 3% AEBl02 4% 9% anti-CTLA4 + AEBl02) (Fig 6A). In a staged MC38 colon carcinoma model combination therapy of AEBl02 with either anti-CTLA4 or anti-PD-L1 resulted in a higher ILS (68% and 55% respectively) when compared to monotherapies with anti-CTLA4 (11% ILS), anti-PD-L1 (18% ILS) and AEBl02 (29% ILS) (Fig 7).

Conclusion
- Disrupting the l-Arg physiological balance in the tumor microenvironment inhibits tumor growth and further synergizes with immune checkpoint inhibitors (ICI)
- When tumors are established l-Arg depletion via AEBl02 administration is not detrimental to immune CPI, rather it enhances efficacy
- AEBl02 creates a favorable balance with immune CPI
- AEBl02 robustly depletes l-Arg in plasma, with no anti-drug antibodies detected in 27 patients treated with AEBl02
- These data open the possible of further improving outcomes in l-Arg dependent cancers through combination of AEBl02 with immune CPI

Support: This study was Funded by Aeglea BioTherapeutics, Inc. and the Cancer Prevention and Research Institute of Texas (CPRIT RP180376-01).

Exclusions: All authors are employees of, and have an equity interest in Aeglea BioTherapeutics, Inc..