Introduction

Tumor dependence on specific amino acids for survival and proliferation is well recognized and has been exploited effectively with the use of asparaginases for the treatment of acute lymphoblastic leukemia. Sensitivity of tumors to L-Arginine (L-Arg) deprivation results from a sub-optimal ability to make L-Arg as a result of 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).

AEB1102 mechanism of action

Native human arginase I displays low activity and low stability in serum meaning this of the enzyme is not a viable drug candidate. Aeglea BioTherapeutics Inc has developed an alternative approach using a bioengineered human PEGylated arginase I (AEB1102) with enhanced pharmacological properties. Replacement of manganese, the natural metal co-factor in native human arginase I, with cobalt confers improved catalytic activity, serum stability and L-Arg depletion in serum (Fig 2).

AEB1102 improved properties

AEB1102 was administered at a dose of 3mg/kg which results in depletion of L-Arg in serum to levels below 1 μM for ~3 days (data not shown). All xenograft models were dosed with AEB1102 alone and in combination with anti-PD-L1 (10F.9G2), anti-PD-1 (RMP1-14) or anti-CTLA4 (9D9) monoclonal antibodies (mAbs). Dosing of test compounds occurred in either freshly seeded models, referred to as non-staged (3 days post seeding) or in established palpable tumors referred to as staged models. The tumor growth inhibition (TGI) and the increased life span (ILS) were calculated to indicate the antitumor effectiveness and the median survival time.

Methods

In the CT26 colon carcinoma model combination therapy of AEB1102 with anti-PD-L1 (Fig 4) resulted in a higher anti-tumor effect (TGI 86%) compared to AEB1102 alone (TGI 72%) and anti-PD-L1 alone (TGI 60%). Anti-PD-1 in combination with AEB1102 also resulted in an improved response (TGI 75%) compared to AEB1102 alone (TGI 67%) and anti-PD-1 alone (TGI 12%) (Fig 5).

CT26: AEB1102 + anti-PD-1

Similarly, in the Lewis Lung model, combination of AEB1102 with anti-PD-1 resulted in a higher anti-tumor effect (TGI 60%) than monotherapy with AEB1102 (TGI 52%) or anti-PD-1 (TGI 31%) (Fig 6).

CT26: AEB1102 + anti-CTLA4

In contrast, combination of AEB1102 with anti-CTLA4 showed less anti-tumor effect (TGI 80%) than anti-CTLA4 alone (TGI 96%) (Fig 7).

Results

Fig. 4. Tumor volumes and survival curves in a non-staged CT26 model

Although we and others have successfully utilized arginase I to impair a direct tumor cell killing effect through L-Arg starvation (e.g. AEB1102 single agent efficacy in melanoma and small cell lung cancer (SCLC) PDx models (Fig 3)), the role of arginase I in regulating the immune system is not clear.

Fig. 3. AEB1102 efficacy in a melanoma and a small cell lung cancer (SCLC) patient-derived xenograft (PDx) model

Similarly, in the Lewis Lung model, combination of AEB1102 with anti-PD-1 resulted in a higher anti-tumor effect (TGI 60%) than monotherapy with AEB1102 (TGI 52%) or anti-PD-1 (TGI 31%) (Fig 6).

CT26: AEB1102 + anti-PD-1

In contrast, combination of AEB1102 with anti-CTLA4 showed less anti-tumor effect (TGI 80%) than anti-CTLA4 alone (TGI 96%) (Fig 7).

Fig. 5. Tumor volumes and survival curves in a staged CT26 model

CT26: AEB1102 + anti-CTLA4

In contrast, combination of AEB1102 with anti-CTLA4 showed less anti-tumor effect (TGI 80%) than anti-CTLA4 alone (TGI 96%) (Fig 7).

Conclusion

Collectively these results demonstrate that disrupting the L-Arg physiological balance in the tumor microenvironment inhibits tumor growth and further sensitizes the tumor to immunotherapy with anti-PD1 and anti-PD-L1. However, the same effect was not observed with anti-CTLA4 therapy when combined with AEB1102 (in a non-staged model). This contrasting effect between the PD1 and CTLA4 pathway inhibitors may be due to their different mechanism of action (Fig 8) or experimental design. We hypothesize that L-Arg depletion negatively impacts the T-cell priming in lymph node and spleen where anti-CTLA4 is known to act. Anti-PD-1/PD-L1 inhibitors on the other hand impart their effector function directly at the tumor site. Our data shows that L-Arg depletion is not detrimental to anti-PD-1/PD-L1 inhibitors, rather it enhances efficacy (in both staged and non-staged models). Precedent for maintenance of T-cell function in absence of L-Arg has been reported while arginase I activity has been shown to support metabolic and effector activity of group 2 innate lymphoid cells. AEB1102 is currently in Phase 1 (monotherapy) clinical trials. These data open the possibility of further improving outcomes in L-Arg dependent histologies such as melanoma and SCLC through combination of AEB1102 with anti-PD-1 and anti-PD-L1 mAbs.

References


Support

This study was funded by Aeglea BioTherapeutics Inc. and the Cancer Prevention and Research Institute of Texas (Grant # DP140031). AEGLEA BIO THERAPEUTICS INC.

Disclosures

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