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 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 form 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 plasma, with no anti-drug antibodies detected in 27 patients treated with AEB1102 (Fig 2).

AEB1102 improved properties

Although we and others have successfully utilized an arginine depletion approach to impart a direct tumor growth inhibitory effect through L-Arg starvation (e.g. AEB1102 single-agent efficacy in melanoma, small cell lung cancer (SCLC), large cell non-small cell lung cancer (NSCLC) and Merkel cell Pdx mouse models (Fig 3)), the role of arginase I in regulating the immune system is not clear.

Methods

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 syngeneic mouse models were dosed with AEB1102 alone and in combination with anti-PTL-1 (10F.9G2) 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. In one case (Fig 4B), AEB1102 dosing started prior to tumor implantation. The increased life span (ILS) was calculated to indicate the median survival time.

In a non-staged CT26 colon carcinoma model combination therapy of AEB1102 with either anti-CTLA4 or anti-PD-L1 resulted in a higher ILS (68% and 55% respectively) when compared to monotherapies with anti-CTLA4, anti-PD-L1 (ILS 11%), anti-PTL-1 (ILS 18%) and AEB1102 (ILS 29%) (Fig 6).

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 immune checkpoint inhibitors (Table 1). Interestingly, while AEB1102 was compatible with anti-PD-L1 in both staged and non-staged models, combination therapy of AEB1102 with anti-CTLA4 resulted in opposite outcomes in a non-staged model compared to a staged model. We hypothesize that (i) if the tumor is not established, L-Arg depletion negatively impacts the T-cell priming in the lymph node and spleen where anti-CTLA4 is known to act (Fig 7); (ii) if the tumor is established and T-cell priming has already occurred, AEB1102 synergizes with anti-CTLA4. Anti-PD-L1/PD-L1 inhibitors on the other hand impair their effector function directly at the tumor site (Fig 7). Our data show that, when tumors are established, L-Arg depletion is not detrimental to immune checkpoint inhibitors, rather it enhances efficacy. 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 I (monotherapy) clinical trials. These data open the possibility of further improving outcomes in L-Arg-dependent cancers through combination of AEB1102 with immune checkpoint inhibitors.

References


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Disclosures

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