Pegzilarginase in combination with agonist anti-OX40 therapy enhances T cell priming and effector function leading to improved tumor regression and survival

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Pegzilarginase in combination with agonist anti-OX40 therapy enhances effector function leading to improved tumor regression and survival

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INTRODUCTION

- Tumors defective in arginine biosynthesis are dependent on extracellular arginine.
- Pegzilarginase (AEB1102; Aeglea Biotherapeutics) is a bioengineered pegylated arginase 1 currently in clinical trials.
- In syngeneic tumor models, arginine depletion through pegzilarginase treatment has been shown (poster p#345) to:
  - Induce tumor autophagy
  - Increase MHCII expression
  - Activate T cells

Given that T cell activation can induce OX40 expression, we hypothesized that the combination of pegzilarginase with an OX40 agonist (aOX40) could synergize to enhance T cell priming and effector function, resulting in improved anti-tumor activity.

METHODS

Tumor implant + pegzilarginase (3 mg/kg; 1x/wk for 4 weeks) 

Day 8  Day 12  +aOX40 (250 ug) 

Tumor implant + pegzilarginase (3 mg/kg; 1x/wk for 4 weeks) 

Day 8  Day 12  +aOX40 (250 ug) 

16T CT26 (BALB/c) or 7.56S MCA-205 (C57BL/6) cells were implanted on day 0. For survival studies, mice were dosed with pegzilarginase+/−aOX40 on day 8, with a second dose of aOX40 on day 12. Subsequent doses of pegzilarginase were given weekly for 4 weeks. Graphs represent combined data from two replicate experiments.

Flow analysis experiments, treatment also began on day 8, followed by tissue harvest 1 week later. Statistics were analyzed by one-way ANOVA. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

TUMOR GROWTH AND SURVIVAL

CONCLUSIONS & FUTURE DIRECTIONS

- Arginine depletion through pegzilarginase synergizes with aOX40 to impair tumor progression.
- Combined pegzilarginase/aOX40 demonstrated superior anti-tumor activity relative to monotherapy.
- Enhanced efficacy is associated with increased effector T cell function.
- These data support exploration of this novel combination in future clinical trials.

MYELOID RESPONSE

- Aeglea BioTherapeutics
- EACRI Flow Cytometry Core
- EACRI Cancer Research Animal Division
- Providence Portland Medical Foundation
- Cancer Prevention and Research Institute of Texas Grant #DP140031 (Aeglea)

Figure 1. CT26 or MCA-205 tumors were implanted on day 0. On day 8, animals were treated with pegzilarginase+/−aOX40 (ip). Pegzilarginase was administered 1x/week for 4 weeks. Tumors were measured 2x/wk or until tumor burden was >175 mm².

Figure 2. CT26 tumor cells were inoculated on d0. Eight days later, mice were treated with pegzilarginase+/−aOX40 (ip). Three days later, TIL and LN were harvested for flow analysis. **P < 0.01.

- Combination therapy associated with increased T-cell activation (IFN-g, gzmA)

Figure 3. Myeloid compartment of CT26 TIL was analyzed for frequency of total macrophages, monocytes and neutrophils on d3 and d7 post-treatment. Arg1: arginase; MFI: Mean fluorescence intensity

- Combination therapy led to decreased arginase in myeloid cells

Figure 4. Graphs depict cell frequency (top) or mean fluorescence intensity (MFI) (bottom) compared to tumor burden using a Spearman correlation. Correlation plots (top), depict results from individual mice. Two cell types (Ki-67+CD8+; macrophage iNOS MFI) were selected to demonstrate negative correlations with tumor size, indicating that greater % or increased MFI of these phenotypes correlates with a smaller tumor size. Spearman correlations and their significance for all cell phenotypes are represented by a heat map (bottom). *P < 0.05, **P < 0.01, ***P < 0.001.

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DISCLOSURES

-Aeglea BioTherapeutics
-EACRI Flow Cytometry Core
-EACRI Cancer Research Animal Division
-Providence Portland Medical Foundation
-Cancer Prevention and Research Institute of Texas Grant #DP140031 (Aeglea)

-Aeglea employees have an equity interest in Aeglea BioTherapeutics, Inc.