Anti-PDL1/IL-15 fusion protein increases efficacy-associated rare effector cells in cynomolgus monkey and mouse peripheral blood

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**Background**

- Therapeutic antibodies targeting immune checkpoint inhibitors (IC) such as PD-1/PD-L1 effectively expand and reactive T cells in patients, leading to long-lasting response in multiple tumor types
- Only a fraction of patients responded to approved ICs; Majority are either resistant or quickly become refractory
- Other immunotherapy modalities: Immunosuppressive cytokines IL-2, IL-12 and IL-15 demonstrated clinical benefits as monotherapy or in combination with ICs
- Clinical trials combining PD-1/PD-L1 inhibitor with other therapies raised concerns for dosing and safety
- Kadmon’s approach: an anti-PD-L1/IL-15 fusion antibody (KD033/KD033 surrogate) by combining a proprietary, fully human, high affinity anti-human/mouse PD-L1 antibody with human IL-15 cytokine

**KD033: Anti-PD-L1/IL-15**

- Binds with high affinity to human/NHP PD-L1 and blocks PD-1 and CD80 interactions; we generated a mouse surrogate KD033 (srKD033) for all preclinical pharmacology studies
- Better tolerated systemically than the non-targeting antibody IL-15 fusion protein
- Efficacious in multiple syngeneic tumor models
- Increased effector cells in tumors and the microenvironment
- Induced innate and adaptive immune gene signatures
- Generated memory responses in mice
- Generated robust and dose-dependent effector cell increases in cynomolgus monkeys

**Analysis of Mice Treated with KD033 surrogate (srKD033)**

srKD033 treated CT26 Colon Carcinoma: Responders and Non-Responders

Single dose monotherapy of srKD033 showed better efficacy in the colon carcinoma CT26 model compared to higher and repeat dose of the anti-PD-L1 checkpoint antibody. About 20% of animal treated with srKD033 consistently became tumor free.

In this study, responders and non-responders from srKD033 treated CT26 mice were compared:

- **Responders:** Mice with no change or with decreasing tumor volumes at seven days post dose
- **Non-responders:** Mice with increasing tumor volumes at seven days post inoculation

**Possible In-Treatment Biomarker**

In contrast to Immunohistochemistry and gene transcription analysis, flow cytometry of peripheral blood showed limited significant difference between responder and non-respondent mice

**CONCLUSIONS**

- Tumors that responded to srKD033 exhibited increased TILs, enhanced adaptive and innate immune gene signatures that correlated with srKD033 retention in tumors
- No significant differences in CDB+ T and NK cell populations in the peripheral blood between srKD033 responders and non-responders
- CDB+ T/Tregs did not correlate with efficacy
- We demonstrated that increases in rare effector cells (γδ or NKT-like cells) significantly correlated with tumor response and represented a potential biomarker for clinical evaluation

**Disclosure:** All authors are employed by Kadmon Corporation, LLC

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