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

S Martomo*, D Lu, Z Polonskaya, X Luna, F Miyara, J Patel

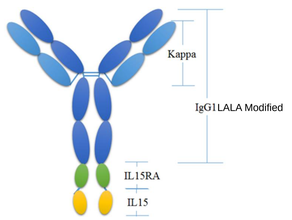
Kadmon Corporation, LLC, New York, NY

ESMO Immuno-oncology 2019
Biomarker
#14P

Background

- Therapeutic antibodies targeting immune checkpoint inhibitors (ICI) such as PD-1/PD-L1 effectively expand and reactivate T cells in patients, leading to long-lasting response in multiple tumor types
- Only a fraction of patients responded to approved ICIs; Majority are either resistant or quickly become refractory
- Other immunotherapy modalities: immunostimulatory cytokines IL-2, IL-12 and IL-15 demonstrated clinical benefits as monotherapy or in combination with ICIs
- 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

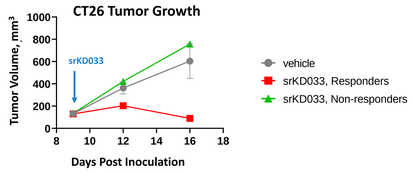
Analysis of Mice Treated with KD033 surrogate (srKD033)

srKD033 treated CT26 Colon Carcinoma: Responders and Non-Responders

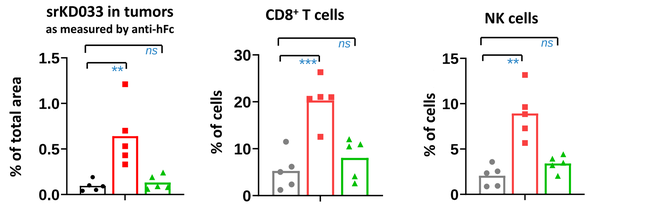
Single dose monotherapy of srKD033 showed better efficacy in the colon carcinoma CT26 model compared to higher and repeat dose of the anti-PD-L1 checkpoint antibody. About 20% of animal treated with srKD033 consistently became tumor free.

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



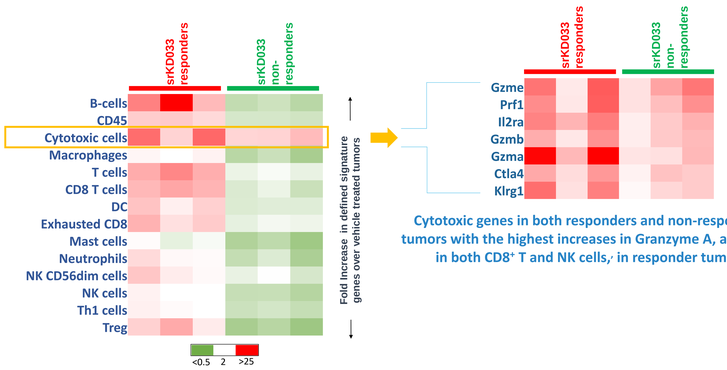
Immunohistochemistry analysis of tumors showed differences between responders and non-responders



Higher percentages of CD8+ T and NK cells and more srKD033 were retained in the tumors of responder mice (red) compared to non-responders at day 7 after treatment

Gene transcription analysis of tumors showed differences between responder and non-responders

Increases in innate and adaptive immune gene signatures were observed in responder tumors while only cytotoxic cells signature was increased in non-responder tumors

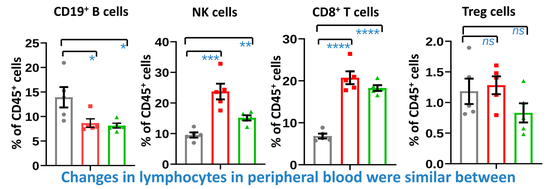


Cytotoxic genes in both responders and non-responders tumors with the highest increases in Granzyme A, abundant in both CD8⁺ T and NK cells, in responder tumors

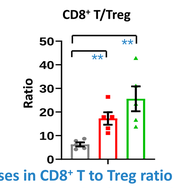
Increases in adaptive, including B cells, and innate immune cell gene signatures in responder tumors

Possible In-Treatment Biomarker

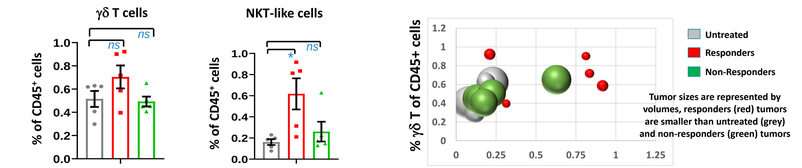
In contrast to immunohistochemistry and gene transcription analysis, flow cytometry of peripheral blood showed limited significant difference between responder and non-responder mice



Changes in lymphocytes in peripheral blood were similar between responders (red) and non-responders (green)

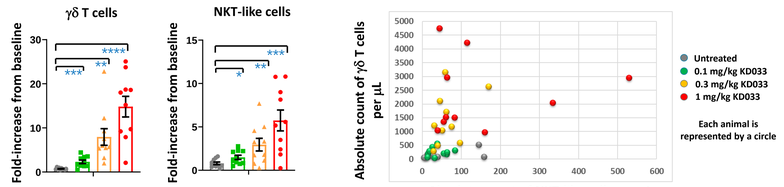


Increases in CD8⁺ T to Treg ratio did not correspond to increased tumor growth inhibition (TGI)



Increasing γδ T or NKT-like cells in peripheral blood corresponded to 80% of responders at day 7

KD033 treatment in cynomolgus monkeys showed significant increases in γδ and NKT-like cells in peripheral blood



Increased γδ T or NKT-like in peripheral blood can be observed in eighty and one hundred percent of the monkeys 7 days after treatment with 0.3 (orange) and 1 mg/kg (red) of KD033 respectively

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 CD8⁺ T and NK cell populations in the peripheral blood between srKD033 responders and non-responders
- CD8⁺ 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
* To whom correspondence should be addressed: Stella.Martomo@Kadmon.com