Synergistic efficacy of anti-PD-L1/IL-15 fusion protein in combination with anti-CTLA-4 antibody in a murine orthotopic 4T1 breast carcinoma model

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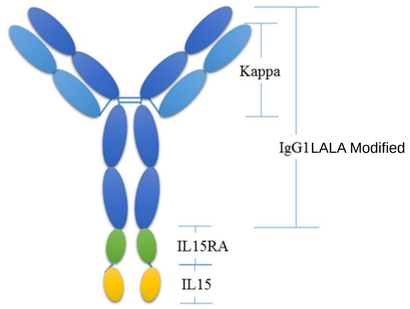
SITC 2019
Abstract # P485

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



- Anti-PD-L1/IL-15 was better tolerated than the non-targeting IL-15
- Single dose KD033 surrogate was efficacious in multiple syngeneic tumor models
- Single dose KD033 surrogate treatment in mice increased effector cells and generated memory responses
- KD033 treatment generated robust and dose-dependent effector cell increases in cynomolgus monkeys

(SITC 2018 P#414)

- KD033 surrogate-treated tumor-free animals rejected the same and unrelated tumor growth without further treatment, suggesting epitope spreading
- KD033 surrogate broadly induced innate and adaptive immune gene signatures
- KD033 surrogate treatment was associated with increased cytotoxic lymphocyte infiltrations in tumors and the microenvironment
- KD033 surrogate activity is predominantly dependent on CD8+ T cell cytotoxicity

(ESMO 2019 1221P)

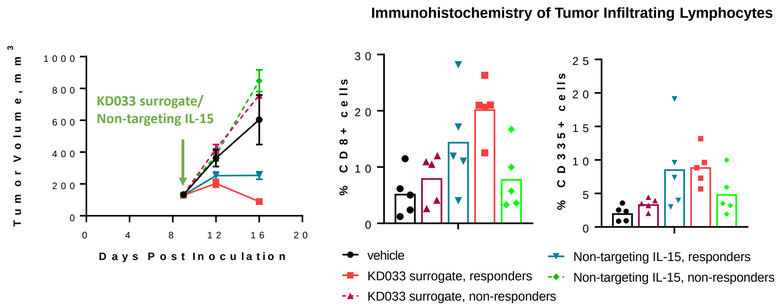
METHODS

- Gene transcriptions from KD033 surrogate treated responders versus non-responders in CT26 colon carcinoma model were analyzed for changes in gene signatures (Nanostring IO 360)
- CTLA-4 in combination with KD033 surrogate treatment was evaluated in mouse 4T1 breast cancer cells inoculated orthotopically in Balb/c mice

Analysis of Tumors from Mice Treated with KD033 surrogate

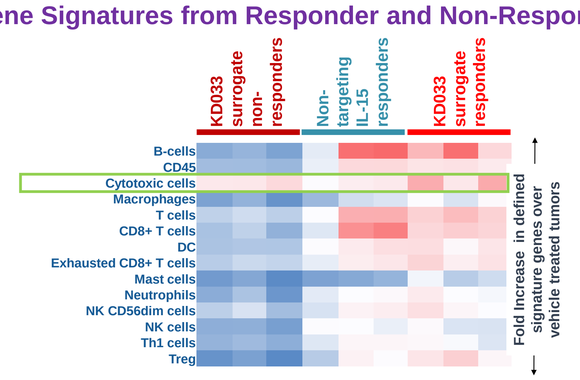
CT26 Colon Carcinoma Responders and Non-Responders

- 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

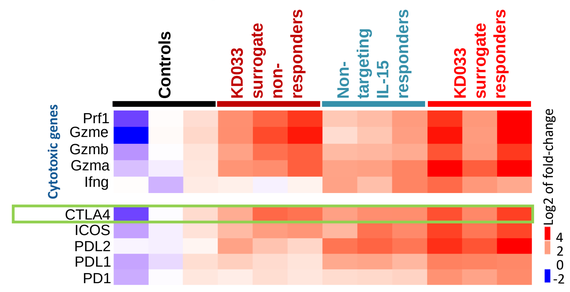


- Increased CD8+ lymphocyte infiltration in tumors from KD033 surrogate responders compared to the non-targeting IL-15 responders

Gene Signatures from Responder and Non-Responder Tumors



- Cytotoxic gene signature was increased in KD033 surrogate responders and non-responders tumors

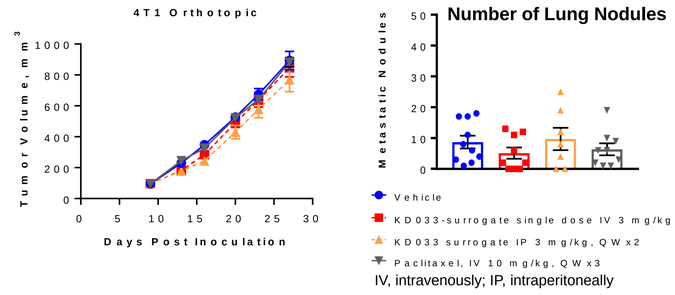


- Cytotoxic genes were increased in KD033 surrogate responder and non-responder more than in the non-targeting IL-15 responder tumors
- CTLA-4 was increased in KD033 surrogate responder and non-responder more than in the non-targeting IL-15 responder tumors; opportunity for combination therapy

KD033 surrogate in 4T1 Triple Negative Breast Cancer Model

- 4T1 is a murine breast cancer model with spontaneous metastases to distant organs such as the lung
- 4T1 mimics the late-stage aggressive triple negative breast cancer

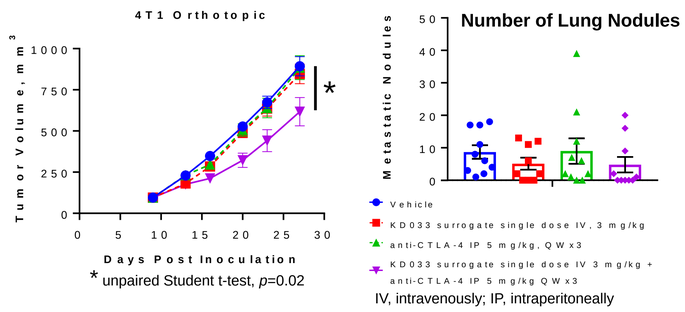
Monotherapy Treatments in 4T1



IV, intravenously; IP, intraperitoneally

- Monotherapy treatments with KD033 surrogate and Paclitaxel (standard of care) did not result in tumor growth inhibition
- Single dose KD033 surrogate IV monotherapy reduced the number of lung nodules

Combination Therapy Treatments in 4T1



* unpaired Student t-test, p=0.02

IV, intravenously; IP, intraperitoneally

- Anti-CTLA-4 monotherapy did not result in tumor growth inhibition; no change in the number of metastasis nodules
- KD033 surrogate in combination with anti-CTLA-4 resulted in significant reduction in tumor growth inhibition and reduction in the number of metastasis nodules

CONCLUSIONS

- Single dose intravenously administered KD033 surrogate reduced the number of distant metastasis nodules in the 4T1 breast cancer model
- Use of gene transcription analysis for combination strategy: CTLA-4 was upregulated in KD033 surrogate-treated tumors; KD033 surrogate in combination with anti-CTLA-4 treatment resulted in significant tumor growth inhibition and reduction in metastases in 4T1 triple negative breast cancer model
- A Phase 1 trial of KD033 is planned in 1H 2020

Disclosure: All authors are employed by Kadmon Corporation, LLC
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