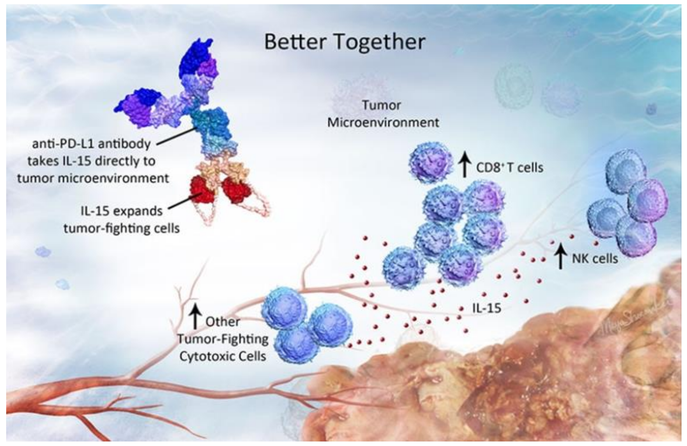
A Phase 1 Multiple Ascending Dose Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Preliminary Efficacy of KD033 in Subjects With Metastatic or Locally Advanced Solid Tumors

Jason J. Luke[1], Anthony J. Olszanski[2], Igor Puzanov[3], Dan Lu[4], Adrian Hackett[4], Stella Martomo[4], Olivier Schueller[4], Alessandro Mora[4], Miranda Schlitt[4], Jeegar Patel[4]

[1]University of Pittsburgh Medical Center, Pittsburgh, PA; [2]Fox Chase Cancer Center, Philadelphia PA; [3]Roswell Park Cancer Center, Buffalo, NY; [4]Kadmon Corporation, New York, NY

Mechanism of Action

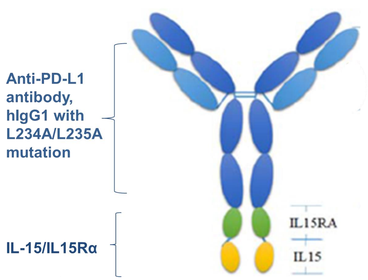
KD033 is an anti-PD-L1/IL-15 fusion protein and is the lead molecule from Kadmon's IL-15 fusion protein platform.



IL-15 is an immunostimulatory cytokine that expands key tumor-fighting immune cell types, including natural killer (NK), natural killer T (NKT) and memory T cells without expanding immunosuppressive Treg cells, allowing for robust and durable anti-tumor responses

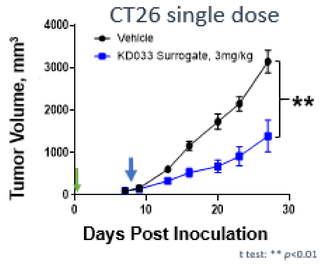
Background

KD033 is a fusion antibody molecule generated by combining a fully human, high affinity anti-human Programmed Death Ligand 1 (PD-L1) IgG1 antibody with the human IL-15 receptor alpha (IL15Rα) sushi domain and human IL-15 (IL-15). The fusion of anti-PD-L1 antibody to IL-15 significantly increases the maximal-tolerated dose (MTD) and increased efficacy in mice compared to free-IL-15. The increased safety and efficacy of PD-L1-targeted IL-15 observed in pre-clinical studies warranted evaluation of KD033 in humans.

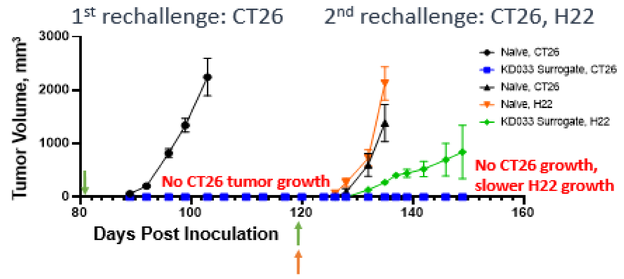


KD033 Surrogate Generated Memory Responses in Mice

KD033 Surrogate treatment resulted in robust anti-tumor response in syngeneic mouse model of colon carcinoma



KD033 Surrogate-treated tumor-free animals rejected the same and unrelated tumor growth without further treatment

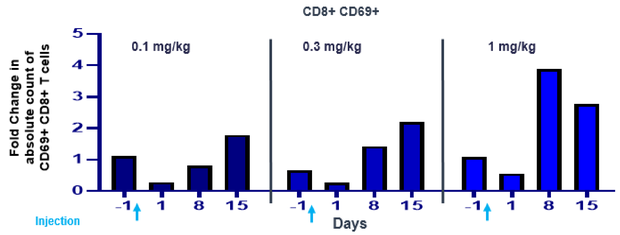


CT26 colon carcinoma, single dose KD033 Surrogate on day 9 post inoculation, no further treatments

KD033 Surrogate injection | **CT26 inoculation** | **H22 inoculation**

KD033 Surrogate is the murine cross-reactive KD033 used in mouse studies

In Cynomolgus Monkey, KD033 Activates Lymphocytes and Induces Proliferation of CD8+ T and NK Cells in PBMCs



Fold increases in lymphocyte cell numbers 7 days after KD033 infusion (Day 8)

	Total T	CD8+T	NK	NKT-Like
0.1 mg/kg	1	1	1.3	1.5
0.3 mg/kg	2.3	2.8	2.5	3
1 mg/kg	6.1	8.1	5.1	5.8

- **Sustained CD8+ T and NK cell activation and proliferation in cynomolgous monkeys after a single dose of KD033**
- **Increase in activated CD8+ T cell was observed after KD033 infusion**
- **Increase In cell numbers were observed 7 days after KD033 infusion (Day 8)**

Phase 1 Trial Design

Phase 1a:Single Agent Dose Escalation
'3 + 3' Design – 3 Patients Per Cohort

Cohort 1 – Single Dose Escalation 3, 6 & 12.5 ug/kg → Cohort 2 25 ug/kg → Cohort 3 50 ug/kg → Cohort 4 100 ug/kg → Cohort 5 200 ug/kg → Cohort 6 400 ug/kg → Cohort 7 600 ug/kg

SRC recommendation of RP2D of KD033 based on MTD, drug exposure and biological effect

Phase 1b:Single Agent Expansion at RP2D

PD-1/PD-L1 Relapsed / Refractory ~15 Patients

Objectives

The primary objective is to determine the safety and tolerability and the MTD/RP2D of KD033. KD033 is administered as an IV infusion over 30 minutes every 14 days (i.e., a cycle equals 2 weeks).

Secondary objectives include characterization of PK and immunogenicity, evaluation of immune correlates that will potentially differentiate the impact of KD033 versus monotherapy as well as investigate IL-15 biology and determine best overall response and duration of response.

Methodology

- **The starting dose of KD033 is 3 µg/kg, with step-up dosing to 12.5 µg/kg in the first cohort of 3 subjects.**
- **After the first cohort, the dose escalation will use a standard 3+3 design with planned doses from 25 µg/kg to 600 µg/kg.**
- **The dose escalation phase will be followed by one expansion cohort, which will enroll patients with solid tumors who received PD-1/PD-L1 inhibitor but have either progressed or are refractory to therapy.**

Key Inclusion Criteria

- **Male or female subjects aged ≥ 18 years at the time of Screening**
- **Histologically or cytologically confirmed/documented advanced and/or metastatic solid tumor, with at least one tumor lesion of location accessible to biopsy**
- **Patients must be willing to provide a tumor biopsy at the following time points: Pre treatment and at Cycle 4, Day 1 (Biopsy is optional for patients enrolled in first 3 dose escalation cohorts)**
- **Radiologically measurable disease at baseline - More than 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes which must have a short axis of ≥15 mm**
- **Life expectancy of at least 3 months**
- **Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≤ 1**

Key Exclusion Criteria

- **Use of immunotherapy, biological therapy, cytokine therapy or immunomodulating agents < 21 days prior to first dose of study drug**
- **Use of chemotherapy/TKI therapy <14 days to first dose of study drug**
- **Anti PD-L1/anti PD-1 therapy < 6 weeks prior to first dose of study drug**
- **Radiotherapy or systemic therapy with immunosuppressive agents including corticosteroids within 14 days before the start of study drug administration**
- **Ongoing or recent (within 2 years) evidence of significant autoimmune disease that required systemic immunosuppressive treatments**
- **History or clinical evidence of central nervous system primary tumors or metastases including leptomeningeal metastases**
- **Known severe hypersensitivity reactions to monoclonal antibodies, any history of or recent (within 6 months) of anaphylaxis**

Study Status

Cohort 3 enrollment is ongoing.

AACR 2021
Abstract Number: CT227
NCT04242147