



**Targeted IL-15
Immunotherapy Platform**

May 2021



About Kadmon



Research



Clinical Pipeline



Commercial Operation

- **Late-stage biopharma company headquartered in New York, NY (Nasdaq: KDMN)**
- **Therapeutic focus areas:**
 - Immune and fibrotic diseases
 - Immuno-oncology (I-O)
- **Lead candidate: Belumosudil, a small molecule ROCK2 inhibitor for the treatment of chronic graft-versus-host disease (cGVHD)**

Executive Summary: Kadmon IL-15 Immuno-oncology (I-O) Platform

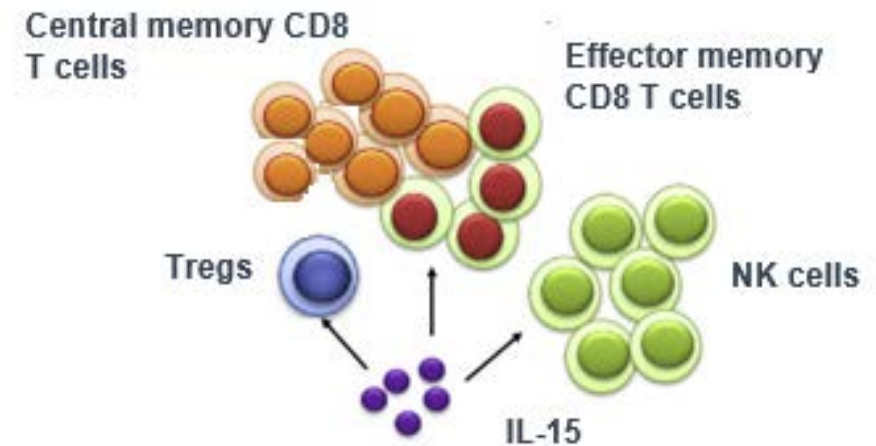
- Kadmon's I-O platform seeks to harness the immuno-stimulatory activity of IL-15 to treat cancer
- Lead candidate: KD033, a proprietary anti-PD-L1 monoclonal antibody fused to IL-15
 - Phase 1 clinical trial of KD033 ongoing in patients with metastatic or locally advanced solid tumors
 - Patent protection through 2035 (without extension)
- Additional IL-15 fusion proteins in development

IL-15 Stimulates Immune Response without Immunosuppression

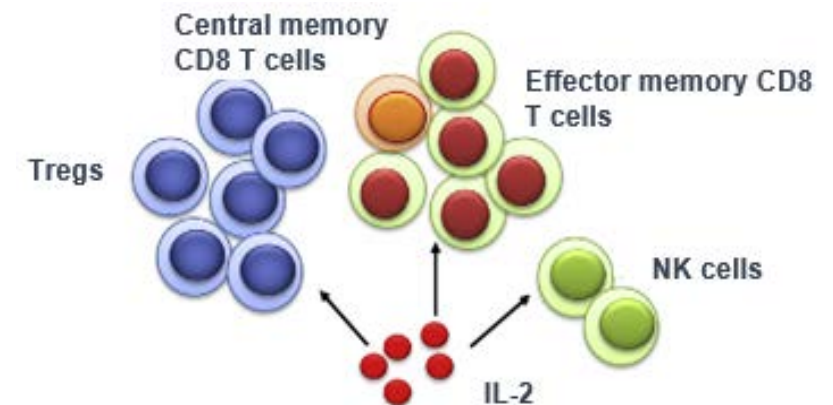
IL-15 May Offer Unique Advantages over IL-2

- **IL-15 is a selective immuno-stimulatory cytokine**
 - Promotes CD8 memory T, natural killer (NK), and NKT cells to induce long-lasting responses
 - Does not stimulate immunosuppressive Treg cells, promoting response durability
- **Engineered IL-2 is currently being studied in combination with I-O therapies**
 - Broadly stimulates immunosuppressive Treg cells, potentially reducing efficacy
 - Requires genetic engineering to skew activity toward immuno-stimulatory CD8 T cells

IL-15 promotes CD8 memory T cells without stimulating Tregs, promoting response durability



IL-2 induces Treg proliferation, resulting in immunosuppression

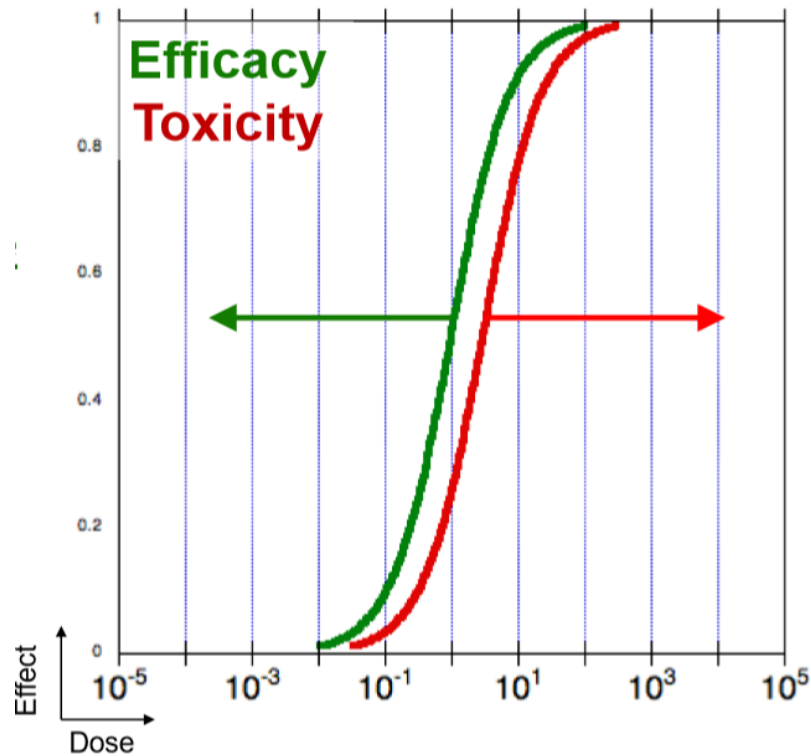


Sim GC et al. *Cytokine & growth factor reviews*. 2014

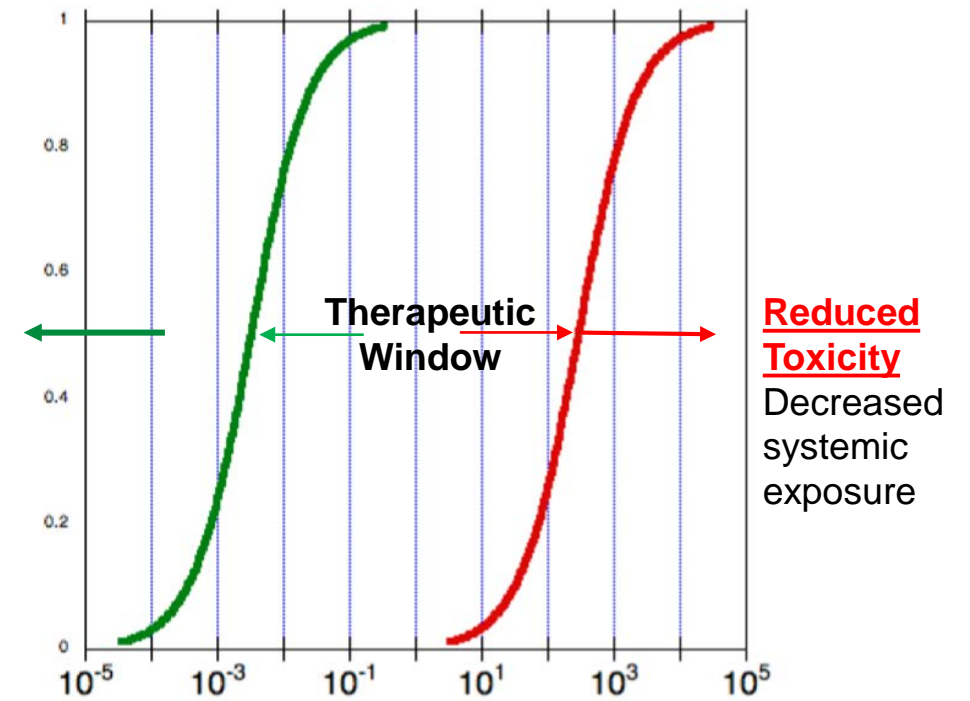
Challenge: Recombinant IL-15 Therapy has a Limited Therapeutic Window

Opportunity: Targeting IL-15 to tumor microenvironment with a monoclonal antibody enhances efficacy and reduces toxicity, improving therapeutic index

Non-targeted IL-15



Targeted IL-15



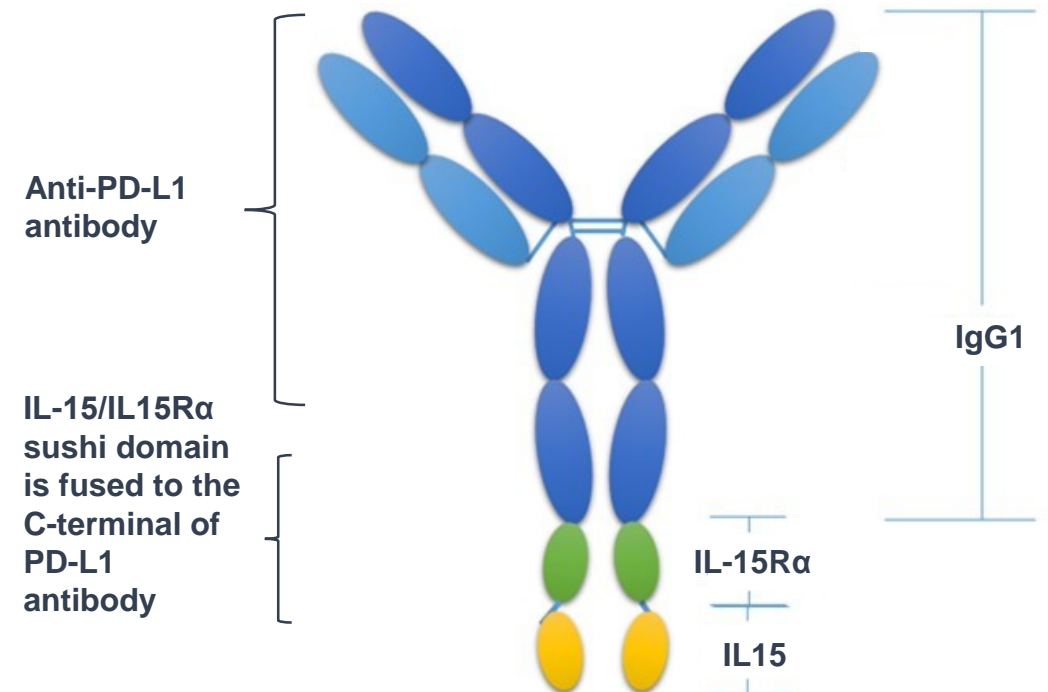
Enhanced Efficacy
Increased tumor exposure

Reduced Toxicity
Decreased systemic exposure

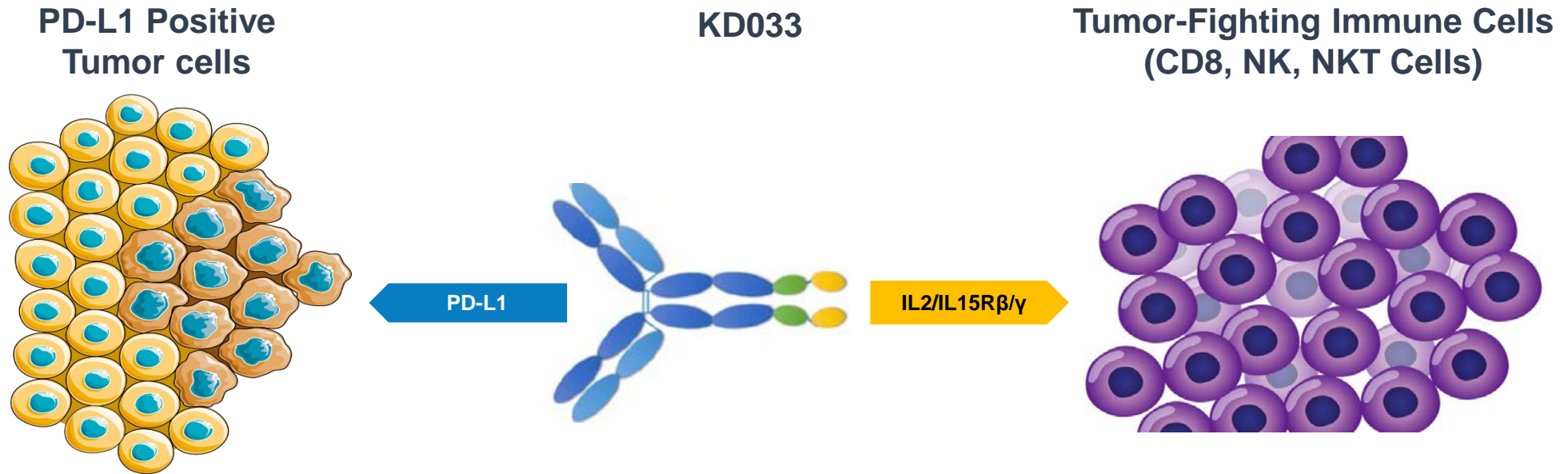
KD033: Anti-PD-L1/IL-15 Fusion Protein

- **KD033: Anti-PD-L1 antibody fused to two IL-15 cytokines**
 - **IL-15 cytokines:**
 - Stimulate immune response without immunosuppression
 - Expand tumor-fighting NK and memory CD8+ T cells to induce long-lasting responses
 - IL-15 fusion to IL-15 receptor alpha sushi domain enhances stability of the antibody complex
 - **PD-L1 antibody:**
 - Targets IL-15 to the tumor microenvironment to mitigate safety concerns

KD033 Structure



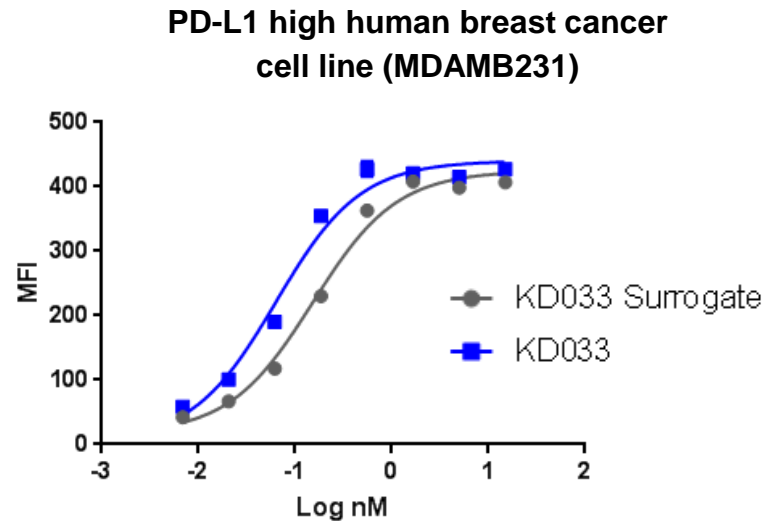
KD033 Trans-presentation Optimizes Activity of PD-L1 and IL-15



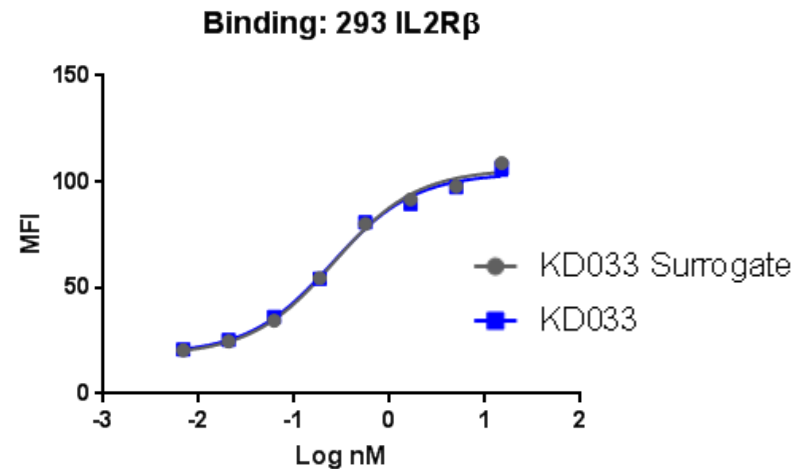
- Trans-presentation localizes immuno-stimulatory activity of IL-15 to PD-L1 positive tumors
- KD033 blocks PD-1/PD-L1 inhibitory signaling and stimulates IL2/IL15R β / γ signaling in immune cells

Comparable Binding to Surrogate in Human Tumor and Immune Cells

KD033 and Surrogate Binding to Tumor Cells Expressing PD-L1



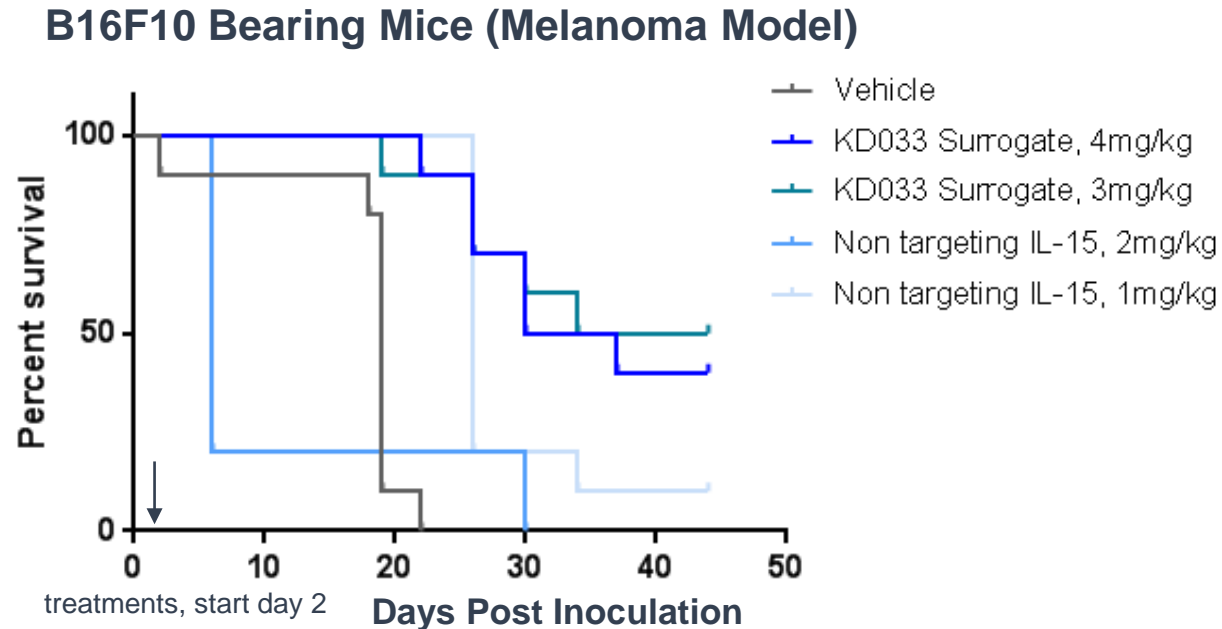
Binding of IL15 to IL2R β overexpressing cell line: a measure of IL-15 affinity



- KD033 Surrogate was generated to test pharmacology of KD033 in mouse syngeneic models
- KD033 and KD033 Surrogate bind to PD-L1 expressing human cells
- KD033 and KD033 Surrogate have high affinity binding to IL-2/IL-15R β

KD033 is Better Tolerated at a Higher Dose than Non-targeting IL-15

KD033 Surrogate Tolerability is 4-Fold Higher than Non-targeting IL-15



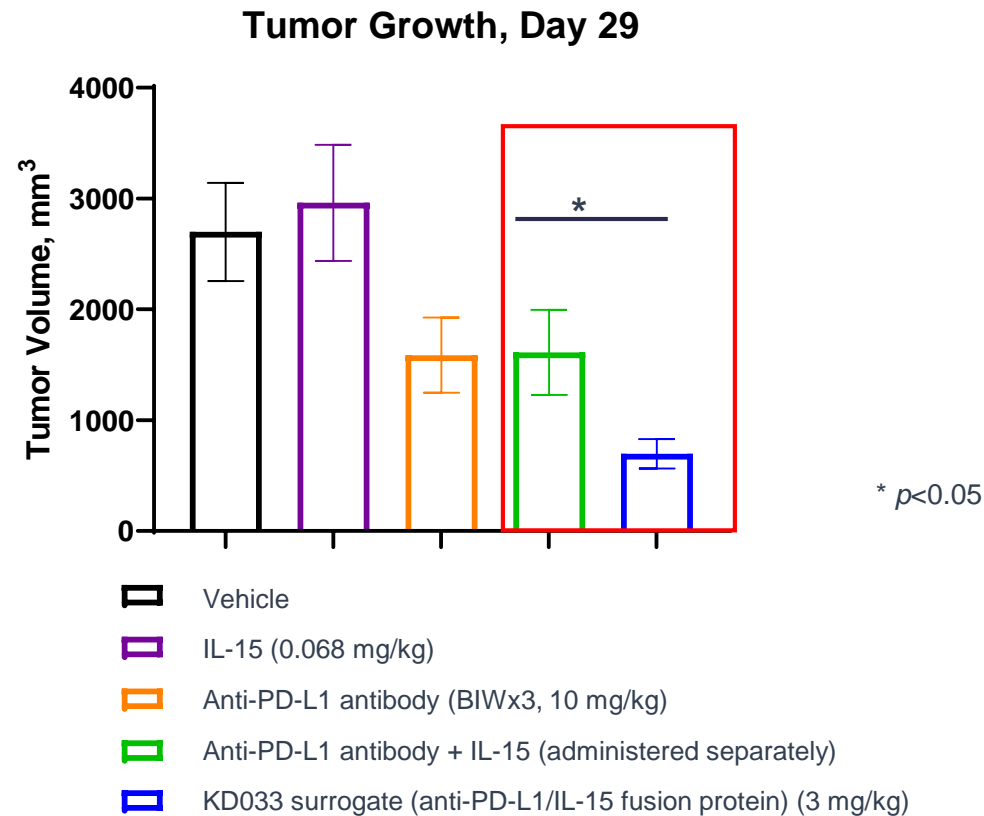
- Mice treated with non-targeting IL-15 at 2 mg/kg died 4 days after treatment (MTD is 1 mg/kg)
- KD033 surrogate is tolerated up to 4 mg/kg

KD033 is More Efficacious than IL-15, Anti-PD-L1, or Anti-PD-L1 + IL-15

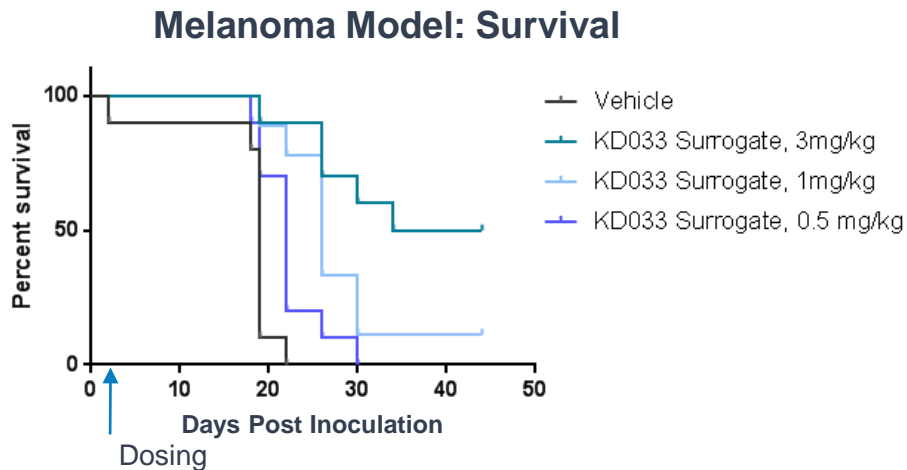
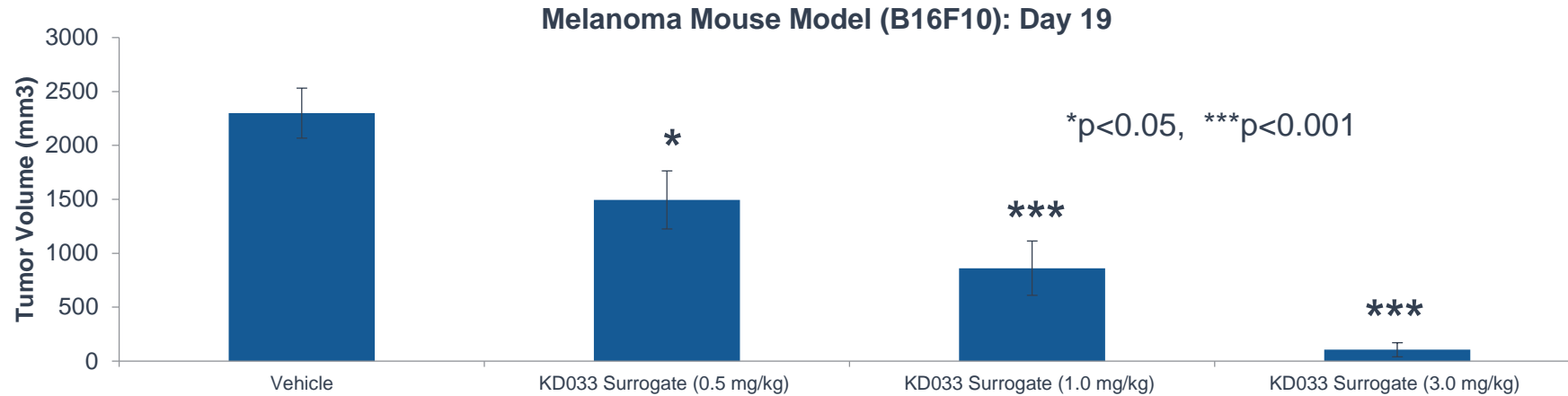
Better together:

KD033 surrogate was significantly more efficacious vs. anti-PD-L1 alone or anti-PD-L1 + IL-15 in animal studies

KD033 Surrogate Efficacy in CT26 Colon Carcinoma Model



Dose-Dependent Efficacy in PD-1/PD-L1-Resistant Melanoma Model



Group	Median Survival (Days)
Vehicle	19
KD033 Surrogate 0.5 mg/kg	22
KD033 Surrogate 1.0 mg/kg	26
KD033 Surrogate 3.0 mg/kg	39

Significant Tumor Growth Inhibition (TGI)

Nonclinical Efficacy Screening of KD033 in 10 Syngeneic Models

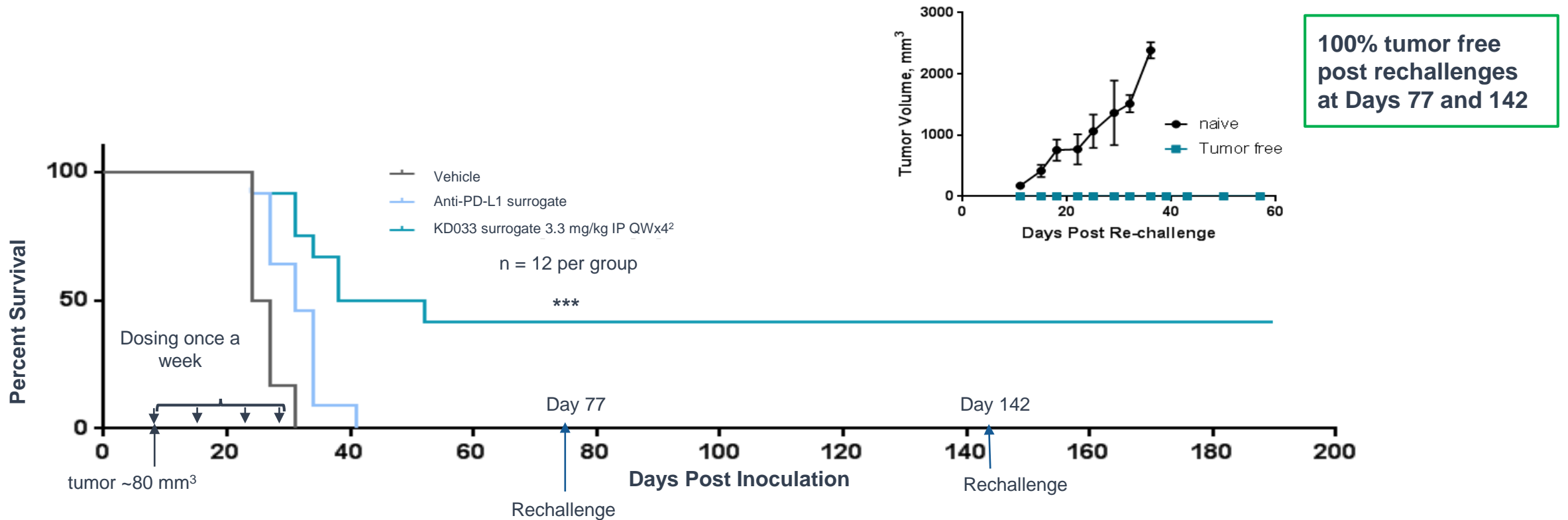
Model	Tumor Type	Single-dose KD033 surrogate treatment
		TGI (%)
CT26-WT	Colorectal	79
MC38	Colorectal	72
MBT-2	Bladder	63
H22	Liver	58
A20	Lymphoma	46
RM-1	Prostate	44
Pan02	Pancreatic	37
B16F10	Melanoma	34
B16BL6	Melanoma	32
LL/2	Lung	28

- Single-Dose KD033 Surrogate Treatment 3mg/kg, tumor volume ~100mm³
- Purple indicates syngeneic models used as tool models; dark blue indicates significantly better efficacy than historical anti-PD-L1 efficacy

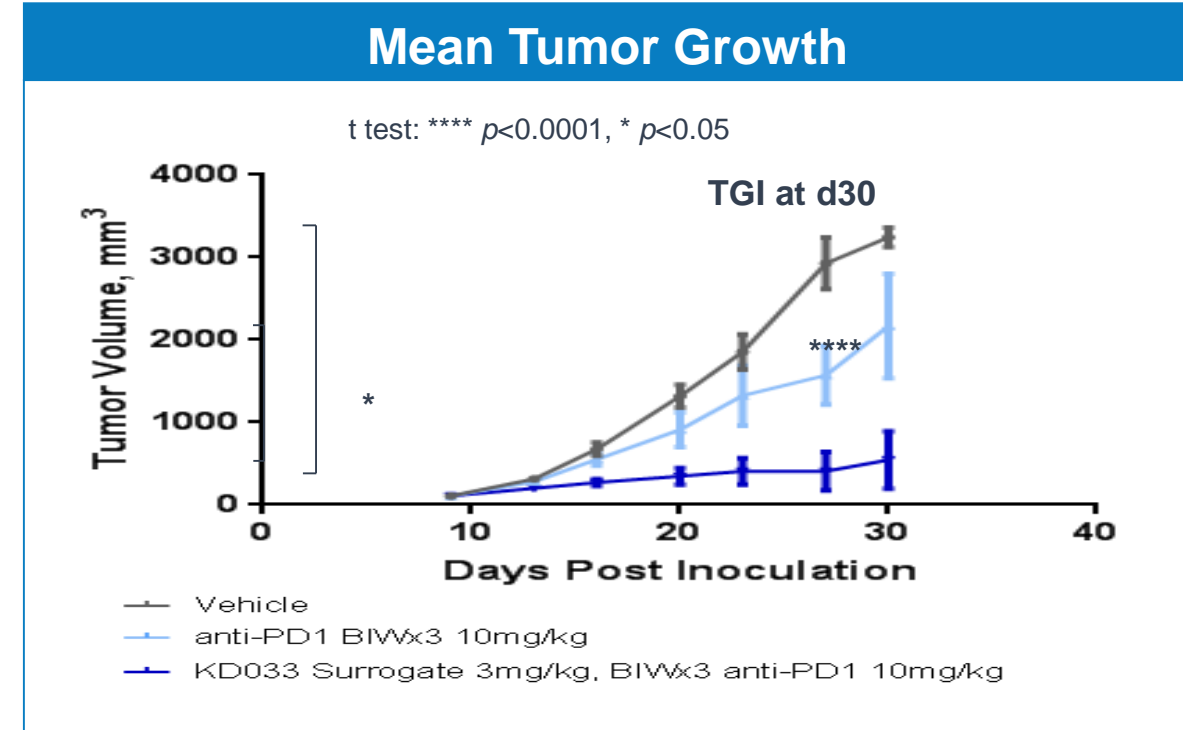
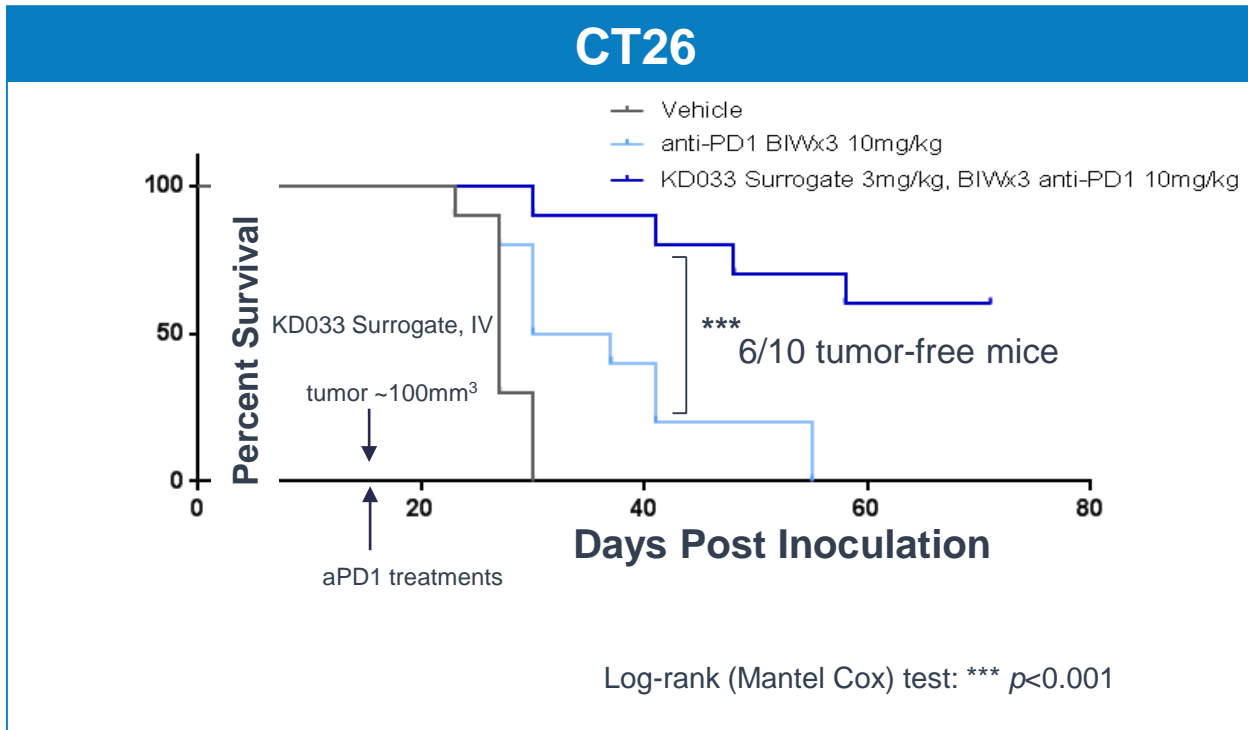
KD033 Triggers Tumor Cell Killing Memory

- **KD033 induced immune system memory:**
 - Mice treated with KD033 surrogate survived tumor rechallenges at Day 77 and Day 142 post inoculation

KD033 Surrogate Treatment in MC38 Colon Adenocarcinoma Mouse Model



Synergistic Efficacy with Combined with Anti-PD-1

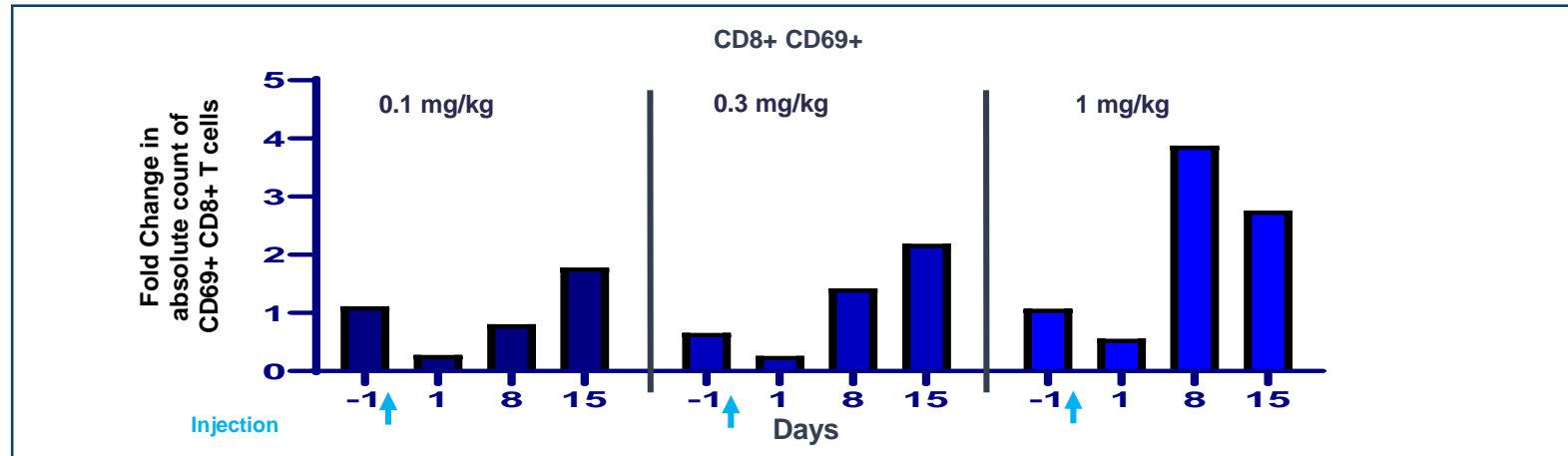


- Adding anti-PD1 therapy to KD033 surrogate demonstrated strong anti-tumor activity (6/10 tumor-free mice)
- Combination of KD033 surrogate and anti-PD1 demonstrated acceptable safety

Activates Lymphocytes and Induces Proliferation of CD8⁺ T and NK Cells in PBMCs

Sustained T, CD8 and NK cell activation and proliferation in cynomolgus monkeys after a single dose of KD033

Increase in Activated CD8⁺ T Cells Observed After KD033 Infusion



Increase In Cell Numbers Observed At Day 7 Post Infusion

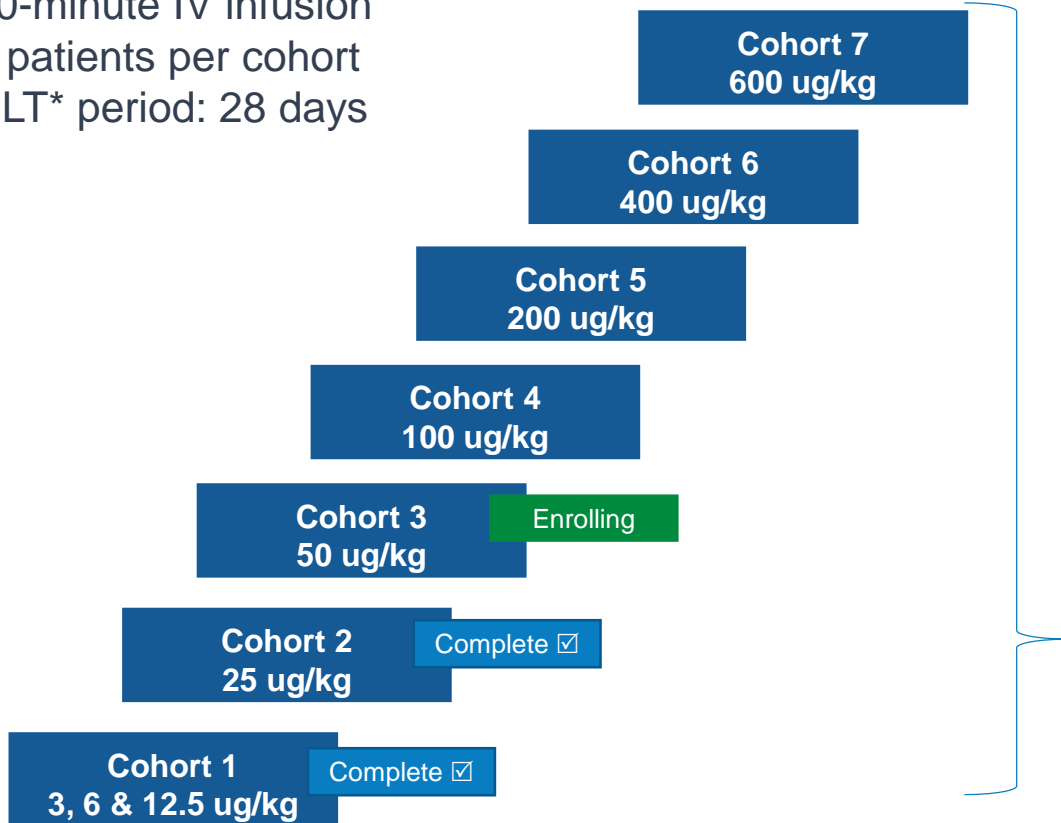
	Total T	CD8 ⁺ T	NK	NKT-Like
0.1 mg/kg	1	1	1.3	1.5
0.3 mg/kg	2.3	2.8	2.5	3
1 mg/kg	6.1	8.1	5.1	5.8

Values represent fold increases in lymphocyte cell numbers

KD033-101: Phase 1a/1b Clinical Trial

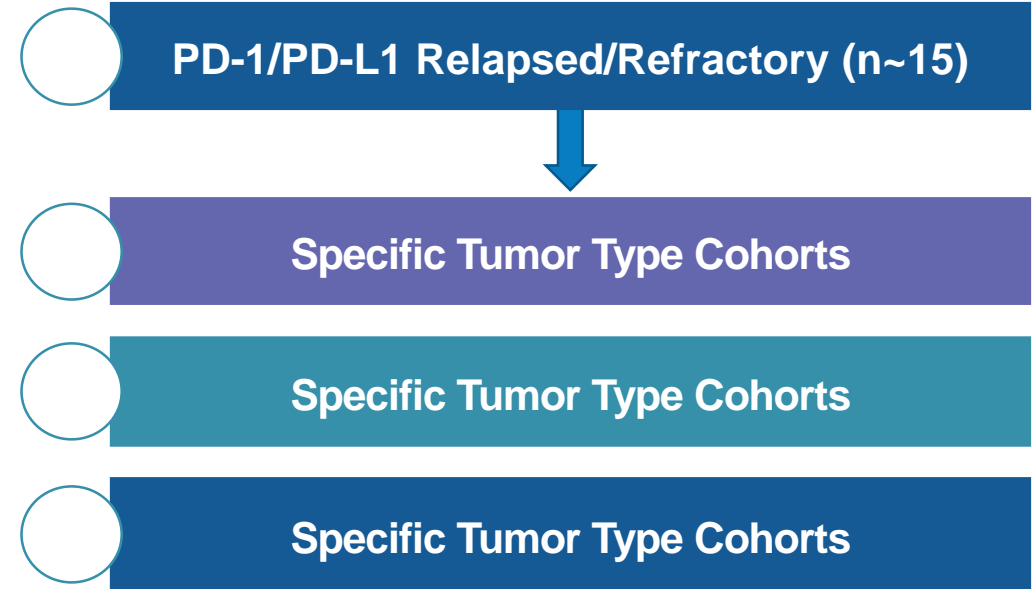
Phase 1a: Escalation (KD033 monotherapy)

- Subjects with metastatic or locally advanced solid tumors
- Dosing every 2 weeks as a 30-minute IV infusion
- 3 patients per cohort
- DLT* period: 28 days



Recommended Phase 2 Dose (MTD*)

Phase 1b: Expansion (KD033 +/- Anti-PD-1 Antibody)



Endpoints

- Safety
- Efficacy
- Pharmacokinetics (PK)
- Anti-drug antibodies (ADA)
- Pharmacodynamics (PD)

Initial safety data to be presented at ASCO (June 2021);
Additional clinical data in Q4 2021

*Dose-limiting toxicity
*Maximum tolerated dose