# Phase 1 dose-finding study of a novel anti–CTLA-4 antibody ADG116 as monotherapy in patients with advanced solid tumors

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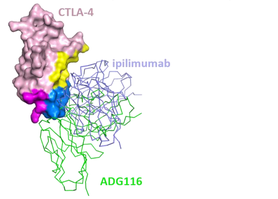
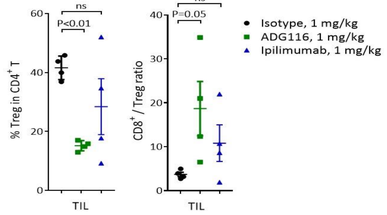
## Background

- ADG116 is a differentiated anti-CTLA-4 IgG1 antibody targeting a highly conserved epitope of CTLA-4 across different species, distinct from ipilimumab (Ipi). The broad species cross-reactivity enables us to elucidate the novel mechanisms of action that combines safer T cell activation by softer ligand blocking with enhanced Treg depletion via stronger ADCC than Ipi, giving rise to 5-fold stronger anti-tumor efficacy with improved Teff/Treg ratio than Ipi in preclinical studies. GLP toxicology study showed 3-fold safety margin over reported HNSTD for Ipi. Here we report the results from the ongoing dose escalation portion of the Phase I study of ADG116 in patients with advanced solid tumors (NCT04501276).

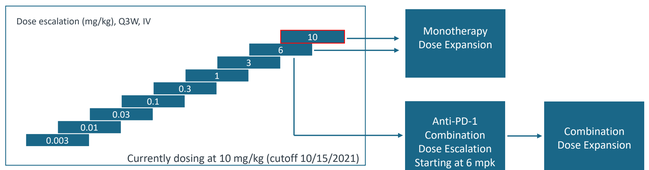



3D structures of CTLA4 and its interaction with Ipi (purple) and ADG116 (green)




Treg depletion and CD8/Treg ratios in the tumor-infiltrating lymphocytes (TIL) of treated MC38 tumors in the *hCTLA4* knock-in background

## Study Design and Patient Demographics




- This is an open-label phase 1 study in patients with advanced solid tumors who have failed multiple lines of prior therapies. ADG116 is administered once every 3 weeks until disease progression or unacceptable toxicity using a 3+3 design with DLT window of 21 days.
- As of October 15, 2021, the data cutoff date, 25 enrolled patients with advanced metastatic disease have been treated across 15 different tumor types, 68% of which are IO insensitive tumors. Dose has been escalated up to 10 mg/kg and cohort expansion was initiated at 6 mg/kg. 17 patients (68%) received 3 or more lines of prior systemic therapies; 6 patients (24%) with prior immunotherapy treatment.

**Table 1: Patient Profiles**

| Subject ID | Dose (mg/kg) | Prior tx # | Prior IO # | Duration (day) | Dose # |
|---|---|---|---|---|---|
| 1 | 0.003 | 2 | Pembro | 37 | 2 |
| 2 | 0.01 | 11 | 0 | 87 | 3 |
| 3 | 0.03 | 5 | Nivo | 29 | 2 |
| 4 | 0.03 | 2 | Pembro | 128 | 4 |
| 5 | 0.03 | 5 | 0 | 24 | 1 |
| 6 | 0.1 | 8 | 0 | 22 | 1 |
| 7 | 0.1 | 4 | Nivo | 43 | 2 |
| 8 | 0.1 | 1 | 0 | 33 | 2 |
| 9 | 0.3 | 2 | 0 | 84 | 4 |
| 10 | 0.3 | 4 | 0 | 31 | 2 |
| 11 | 0.3 | 3 | 0 | 48 | 3 |
| 12 | 1 | 5 | 0 | 40 | 2 |
| 13 | 1 | 2 | 0 | 174 | 5 |

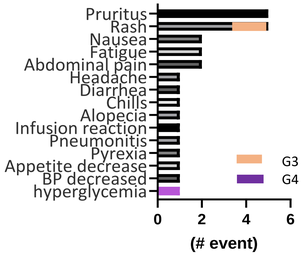
| Subject ID | Dose (mg/kg) | Prior tx # | Prior IO # | Duration (day) | Dose # |
|---|---|---|---|---|---|
| 14 | 1 | 7 | 0 | 85 | 4 |
| 15 | 3 | 3 | Pembro | 37 | 2 |
| 16 | 3 | 7 | 0 | 40 | 2 |
| 17 | 3 | 4 | 0 | 13 | 1 |
| 18 | 3 | 4 | 0 | 87 | 4 |
| 19 | 6 | 3 | 0 | 116+* | 4+ |
| 20 | 6 | 3 | 0 | 39 | 2 |
| 21 | 6 | 5 | 0 | 45 | 3 |
| 22 | 10 | 3 | 0 | 38+* | 2+ |
| 23 | 10 | 3 | Nivo, 2x | 37 | 2 |
| 24 | 10 | 2 | 0 | 36 | 2 |
| 25 | 6 (Exp) | 2 | 0 | 34+* | 2+ |

* Still on treatment

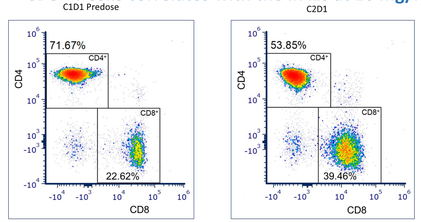
## Safety, Tolerability and Early Efficacy

- Most treatment-related AEs (TRAEs) were Grade 1/2, with rash (20%) and pruritus (20%) being most common, very well tolerated up to 6 mg/kg.
- In the 10 mg/kg cohort, a Grade 4 DLT event (hyperglycemia) and Grade 3 rash occurred (post Oct 15th data cutoff date).
- Subject #23, a 74 year-old male with renal cell carcinoma who relapsed on nivolumab, enrolled in the 10 mg/kg cohort and developed treatment-related newly onset type I diabetes with Grade 4 hyperglycemia. CD8+ T cells were increased after the 1st cycle of the treatment, showing that ADG116 is highly active for triggering T cell activation.
- Subject #22, a 77 year-old male with pancreatic cancer with three prior therapies shows 22% reduction of his target lesions based on his CT scan images.

### Treatment-Related Adverse Events




### Subject #23 RCC patient with significant increase in CD8+ T cells correlates with the irAEs at 10 mg/kg

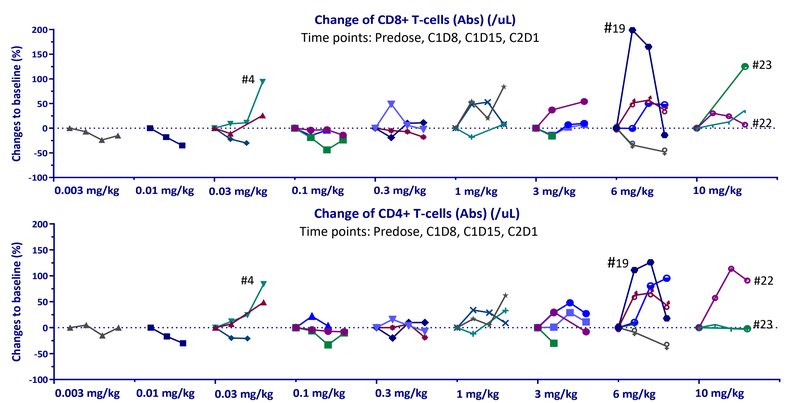



### Subject #22 pancreatic cancer with 22% tumor shrinkage after 2 cycles at 10 mg/kg

| Patient #22 (pancreatic cancer) | | Baseline | 1st Tumor assessment |
|---|---|---|---|
| Target lesions | TL1-Pancreas | 35 mm | 29 mm |
| | TL-2 Liver | 15 mm | 10 mm |
| Non-target lesion | Portal vein lymph node | Present | Disappear |
| Change in target lesions | -22% | | |

## Pharmacodynamic Biomarkers

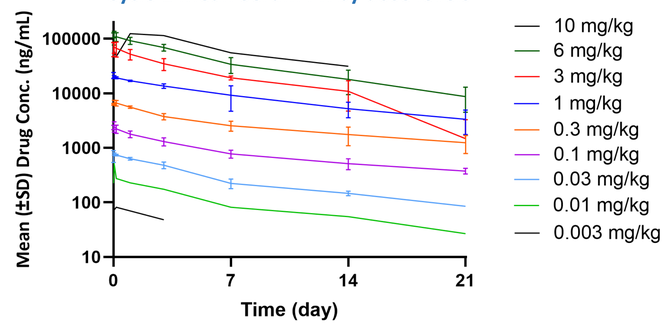
### Increased CD8 and CD4 T cells by ADG116 treatment




- Dose-dependent increase in peripheral CD8 and CD4 T cells post ADG116 treatment, indicating immune activation by targeting CTLA-4 target/pathway.
- The Patients #4 (urothelial cancer), #19 (ovarian cancer) and #22 (pancreatic cancer), with increased CD8 and/or CD4 T cells, showed stable disease, with 22% reduction in the target lesions of Patient #22.

## Pharmacokinetics

### Cycle 1 Mean Serum PK by dose levels




- The serum pharmacokinetics (PK) of ADG116 monotherapy after IV infusion was assessed using Non-compartmental Analysis and population PK modeling approaches.
- Dose-dependent, and approximately linear PK (based on $C_{max}$ and $AUC_{0\text{-}21d,cycle1}$) was observed for ADG116 with its mean terminal half-life estimated ~10 days up to 10mg/kg.
- For patients with PK data from multiple Q3W treatment cycles, limited accumulation (e.g.,<2-fold mostly) for $C_{trough}$ and $C_{max}$ was observed.

## Conclusions

- ADG116 is well tolerated up to 6 mg/kg, showing most treatment-related AEs (TRAEs) as Grade 1 with a few Grade 2 in patients with advanced metastatic solid tumors. The 10 mg/kg cohort is ongoing.
- Four prolonged stable diseases (17%, 4/24) were observed in these heavily pre-treated patients including cold tumors. Of special note is a 22% tumor reduction for a pancreatic cancer patient at 10 mg/kg with only Grade 1 TRAE.
- ADG116 shows strong dose-proportional increase in PD markers for T cell activation and in drug exposures with a half-life supporting Q3W dosing.
- ADG116 has achieved the RP2D range for single and combination uses based on PD biomarkers in peripheral blood and safety manifested as irAEs.
- Monotherapy dose expansion is ongoing at 6mg/kg. Combination with anti-PD-1 Ab or anti-CD137 agonist Ab (ADG106) is planned thereafter.

## Acknowledgements & Disclosure

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