ADAGENE

AACR 2023
Poster#: CT233

Initial Results of a Phase 1b/2 Study of ADG126 (a Masked Anti-CTLA-4 SAFEbody®) in Combination with Pembrolizumab (an Anti-PD-1 Antibody) in Patients with Advanced/Metastatic Solid Tumors

Daneng Li[1], Sunil Sharma[2], Kristine She[3], Wenda Li[3], Ai Li[3], Songmao Zheng[3], Guizhong Liu[3], Ogon Ndukwo[3], Dana Hu-Lowe[3], Michael Chisamore[4], Peter Luo[3], Jiping Zha[3*] and Manish R. Patel[5]

1. City of Hope Comprehensive Cancer Center, Duarte, CA; 2. Honor Health Research Institute, Scottsdale, AZ; 3. Adagene Inc., San Diego, CA; 4. Merck & Co., Inc., Rahway, NJ; 5. Florida Cancer Specialists/Sarah Cannon Research Institute (Sarasota, FL). * Presenting author

Background

- ADG126 is a fully human anti-CTLA-4 IgG1 SAFEbody® with a masking peptide that competes for antigen binding and is subject to cleavage in the tumor microenvironment (TME). This design enables ADG126 to be conditionally enriched and cleaved in the TME to provide a steady and prolonged drug exposure in the tumor while limiting peripheral circulation or off-tumor toxicity. Additionally, activated ADG126 binds to a unique and highly conserved epitope of CTLA-4 with species cross-reactivity for seamless translation studies.
- ADG126 is activated efficiently in vivo, which primes T cells via partial blockade of CTLA-4 interaction with its ligands. ADG126 depletes immunosuppressive Tregs through strong antibody-dependent cellular cytotoxicity (ADCC) specifically in the TME, and it synergizes with anti-PD-1 antibody to induce potent anti-tumor efficacy.
- In a Phase 1b/2 study, ADG126 monotherapy demonstrated a) an unprecedented safety profile (no G3 or higher TRAEs) up to 20 mg/kg Q3W with repeat dosing and b) clinical activity in heavily pre-treated patients[1]. Here we present preliminary results from dose escalation of ADG126 in combination with pembrolizumab in patients with advanced/metastatic solid tumors including cervical, colorectal, endometrial, neuroendocrine, ovarian and pancreatic carcinoma (NCT05405595).

1. Ariyapperuma et al 2023. Poster CT227 on NCT04645069 presented at AACR 2023 Conference (Orlando, FL)

ADG126 SAFEbody® Binding with CTLA-4 and In Vivo Proof of Mechanism

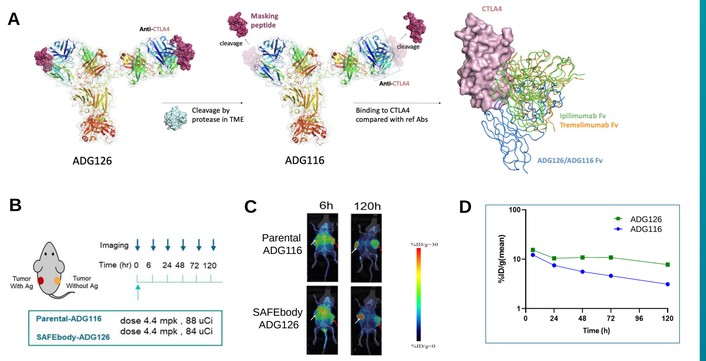
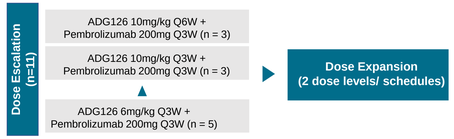


Figure 1. Simulated structure and MOA of ADG126 (**A**) ADG126 parental antibody, ADG116, binds to a unique epitope of CTLA-4 differentiated from ipilimumab and tremelimumab.(**B-D**) Nonclinical study demonstrating Zr^{89} radio-labelled ADG126 localization in the xenograft tumors (left flank tumor: with CTLA-4; right flank tumor: no CTLA-4), highly enriched in antigen dependent manner in tumor sites with prolonged half-life in vivo. The parental anti-CTLA-4 ADG116 (unmasked) was used as comparison. %ID/g: % injected dose per gram in the heart normalized against the Zr^{89} half-life.

Methods

This is a Phase 1b/2, open-label, multicenter dose escalation study to evaluate the safety, tolerability, PK and preliminary efficacy of ADG126 + pembrolizumab (Pembro).



- Primary endpoints: safety and tolerability.
- Secondary endpoints: PK, ADA, ORR, DCR, DOR and PFS per RECIST 1.1.

DL = dose level; mTPI = modified Toxicity Probability Interval; Q3W = once every 3 weeks; Q6W = once every 6 weeks.

Patient Baseline Characteristics

- As of March 9, 2023, 11 patients (Pts) had been treated with ADG126 (6 mg/kg Q3W and 10 mg/kg Q3W or Q6W) + Pembrolizumab (200mg Q3W) in dose escalation
- Patients were generally heavily pre-treated (**Table 1**)
- Tumor types consist of ovarian, colorectal, pancreatic and endometrial cancer, etc., and most of them (82%) are mostly considered as "cold" tumors

Table 1. Baseline Characteristics of Patients

Characteristics	N = 11
Age (years), median (range)	61 (26 -75)
Female, n (%)	9 (82%)
Race, n (%)	
Caucasian, n (%)	7 (64%)
Black or African American, n (%)	1 (9%)
Other	3 (27%)
ECOG, n (%)	
0	6 (55%)
1	5 (45%)
Prior lines of therapy before enrollment, n (%)	
≥3	9 (82%)
Prior immunotherapy, n (%)	2 (18%)

Clinical Safety Assessments

- No DLTs, with the most frequent TRAEs as follows: fatigue (3 Pts), diarrhea (2 Pts), nausea (2 Pts) and vomiting (2 Pts).
- Most TRAEs are Grade (G) G1 and G2. Two Pts had G3 TRAEs: one G3 diarrhea as late onset toxicity (C8 in 6 mg/kg Q3W cohort) and one G3 adrenal insufficiency after DLT (C3 in 10 mg/kg Q6W cohort). No G4/5 events.
- The safety profile is comparable to that of Pembro monotherapy.

Table 2. Frequencies of TRAEs of ADG126 + Pembro

TRAE by Cohort	Cohort N	G1 (%)	G2 (%)	G3 (%)	G4/5
ADG126 6mg/kg Q3W	5	0	2 (40%)	1 (20%)	0
ADG126 10mg/kg Q3W or Q6W	6	3 (50%)	2 (33%)	1 (17%)	0

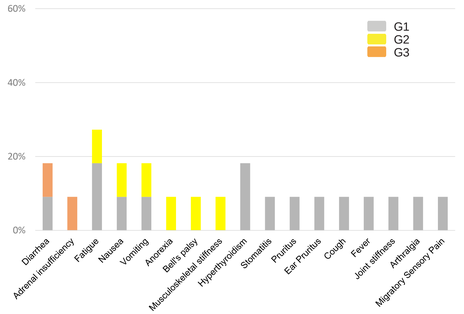
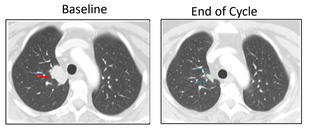


Figure 2. Summary of TRAEs and frequency for the dose escalation phase (n=11) of the study

Clinical Case Studies

Case#1: PR in a Patient of Metastatic Endometrial Cancer

- Advanced adenocarcinoma of endometrium (MSI-H) with lung metastasis
- Previously received carboplatin + paclitaxel × 6 cycles followed with anastrozole as a maintenance therapy until new lung metastasis lesion developed
- ADG126 10mg/kg Q3W + Pembro 200mg Q3W
- PR with a 33% and a 37% target lesion reduction at the end of C2 and C4, respectively



Curtesy of Tammy Lamb, M.D. Florida Cancer Specialists

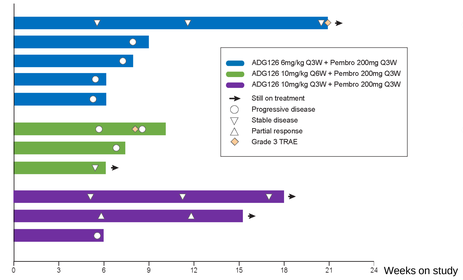
	Lesion #	Location	Baseline	End of C2	End of C4
Target lesion	TL#1	Lung, Right	27 mm	18 mm	17mm
	Sum		27 mm	18 mm	17mm
Non-target lesion		N/A	N/A	N/A	N/A
New lesion				No	No
Overall response				**PR (-33%)**	**PR (-37%)**

Case#2: Tumor Shrinkage in a Cervical Cancer Patient Previously Progressed on Pembrolizumab

- Advanced cervical cancer (stage IV squamous carcinoma) with mediastinal lymph node metastasis
- PD-L1 CPS score = 1, TMB high: 24 Muts/Mb
- Previously received 2 lines of therapies:
  - Carboplatin/paclitaxel/bevacizumab x 6 cycles
  - Pembrolizumab monotherapy × 9 cycles
- ADG126 10mg/kg Q3W + Pembro 200mg Q3W
- SD with 13% sum target lesion reduction at end of C6

	Lesion #	Location	Baseline	End of C2	End of C4	End of C6
Target lesion	TL#1	Lymph node (Subcarinal)	25 mm	25 mm	21mm	17mm
	TL#2	Lymph node (Pre-carinal)	29 mm	29 mm	30mm	30mm
	Sum		54 mm	54 mm	51 mm	47 mm
Non target lesion		Lymph node (Right Supra-clavicular)	Present	Present	Present	Present
New lesion				No	No	No
Overall response				**SD (+0%)**	**SD (-5.6%)**	**SD (-13%)**

Patient Clinical Activity Assessments



- Partial response (PR) has been observed in a patient who received ADG126 (10 mg/kg Q3W) + Pembro (200 mg Q3W) (see Case Study #1).
- ORR = 17% and DCR = 50% among the 6 Pts who received ADG126 10mg/kg Q3W or Q6W + Pembro 200mg Q3W.

Figure 3. Swimmer plot for Pts treated with ADG126 + Pembro. As of this data-cut, 4 Pts were still receiving treatment. All Pts had at least 2 cycles of treatment, with the longest treatment in Cycle 8.

Biomarker Modulation in the Periphery

ADG126 monotherapy induces limited increase of the peripheral IFN-γ. The magnitude of IFN-γ modulation is more pronounced under ADG126 + Pembro combination therapy.

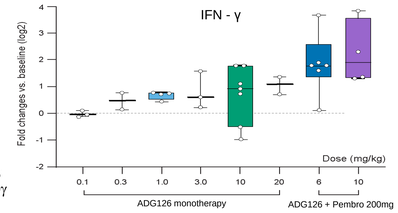


Figure 5. Serum IFN-γ levels upon treatment by ADG126 monotherapy or in combination with Pembro. Serum IFN-γ were quantified using Mesoscale Discovery (MSD) Technologies' V-Plex Proinflammatory Panel 1.

Conclusions

- In this dose escalation study, the anti-CTLA-4 SAFEbody ADG126 in combination with pembrolizumab is well-tolerated up to 10 mg/kg Q3W or Q6W and with repeat dosing beyond 4 cycles.
  - The safety profile of ADG126 + Pembro is comparable to that of Pembro monotherapy.
  - No DLTs and G4/5 TRAEs. Only two G3 TRAEs appeared after repeat dosing (C8 and C3).
- Clinical activity includes 1 PR (confirmed at end of Cycle 2), and 1 SD (13% reduction at end of Cycle 6) were observed in the 10mg/kg, Q3W cohort (n=3). The latter is a PD-L1 low / TMB-H patient who had progressed on prior Pembro therapy.
- Dose-dependent serum IFN-γ modulations observed for ADG126 + Pembro is greater than ADG126 monotherapy, supporting combinational therapy for greater efficacy.
- Taken together, the best-in-class safety profile and encouraging clinical activity of ADG126 in combination with pembrolizumab opens a wide range of opportunities for combination therapy with other therapeutic agents.
- Currently the dose expansion of ADG126 plus pembrolizumab in selected patient populations is underway.

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. The study is funded by Adagene Inc. Contact ir@adagene.com. Dr. Daneng Li receives research funding from Adagene Inc. We would like to acknowledge Drs. Wenqing Song, Jiagui Qu and Xin Wang for their technical support.