ADAGENE

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Phase 1 Results Demonstrate Highly Differentiated Safety and PK Profile of ADG126, a Masked anti-CTLA-4 SAFEbody® in Patients with Advanced Solid Tumors

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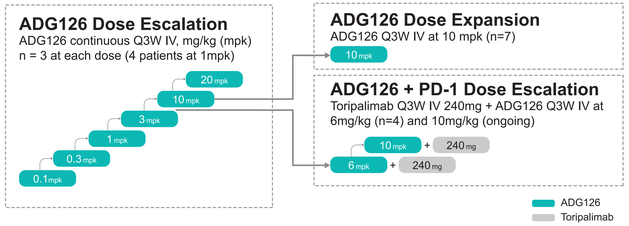
Background

The anti-CTLA-4 immunotherapy (IO) is limited in clinical efficacy due to its on-target toxicities. ADG126 is a novel anti-CTLA-4 fully human IgG1 SAFEbody® with a masking peptide blocking the antigen binding site. ADG126 is designed to be preferentially activated in the tumor microenvironment (TME), with the goal of limiting its on-target off-tumor toxicities in normal tissues and promoting prolonged exposure in the TME. Activated ADG126 binds to a unique and conserved epitope of CTLA-4 with species cross-reactivity. Nonclinical studies demonstrated that activated ADG126 potentiates T cell activation, depletes immunosuppressive Tregs through enhanced ADCC specifically in the TME. ADG126 demonstrates efficacious anti-tumor activity in multiple syngeneic murine tumor models as a single agent, as well as in combination with other immune modulatory agents.

Method

We report interim result of a first-in-human, open-label, Phase I dose escalation and dose expansion study (ADG126-1001, NCT04645069)



Primary Endpoints
Safety and tolerability

Secondary Endpoints
PK, anti-drug antibodies (ADA), ORR, DCR and DOR per RECIST 1.1

Key Inclusion Criteria: Patients with advanced / metastatic solid tumors with ECOG≤1. Prior treatment by anti-PD-1 or anti-CTLA-4 therapy are allowed
Imaging were performed every 6 weeks for the first 4 cycles, then every 9 weeks afterwards

Baseline Characteristics

- As of August 17, 2022, 26 patients had been treated by ADG126 monotherapy
- Patients were heavily pre-treated
- Tumor types included breast cancer, cholangiocarcinoma, colorectal cancer, epithelial ovarian cancer, glioblastoma, hepatocellular carcinoma, melanoma, non-small cell lung cancer, pancreatic adenocarcinoma, renal cell carcinoma, uveal melanoma, and others

Characteristics	N = 26
Age (years), median (range)	64 (41, 84)
Female, n (%)	14 (54%)
Race, n (%)	
Caucasian, n (%)	25 (96%)
Asian, n (%)	1 (4%)
ECOG, n(%)	
0	12 (46%)
1	14 (54%)
Number of regimens prior to enrollment, n (%)	
≥3	15 (58%)
Prior immunotherapy, n (%)	11 (42%)
ADG126 dose administered	
Median (range)	2 (1, 18)

ADG126 Safety Profile

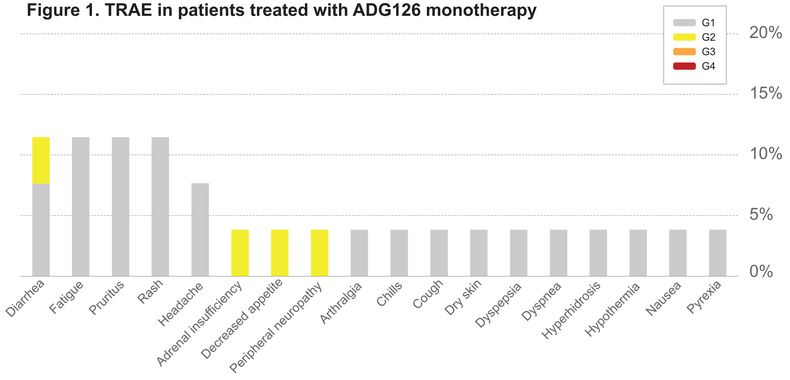
ADG126 monotherapy (N = 26)

- Well tolerated with no dose-limiting toxicities up to 20 mg/kg with repeat dosing
- The most frequent treatment-related adverse event (TRAE) (>10%) was fatigue (12%), pruritus (12%), rash (12%) and diarrhea (12%)

Table 2. TRAE

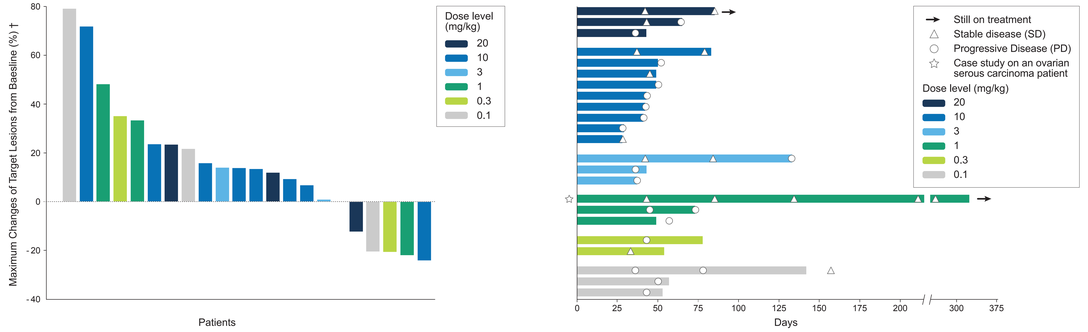
	G1	G2	G3-5
TRAE (n, %)	6 (23%)	4 (15%)	0

Figure 1. TRAE in patients treated with ADG126 monotherapy



Clinical Activity Assessment

ADG126 demonstrates single-agent anti-tumor efficacy with disease control rate of 39% among 23 evaluable patients*



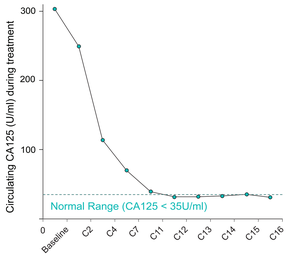
† One PD patient with one non-evaluable target lesion post-treatment was excluded from the waterfall plot. * patients with at least one valid post baseline tumor assessment.
For the swimmer plot, bar ends at EOT.

Case study: A Major CA125 Response* in an Ovarian Serous Carcinoma Patient

- Previously received curative salpingo-oophorectomy and 5 lines of systemic therapies§
- Treatment ongoing with 18 cycles of ADG126 at 1 mg/kg
- 90% reduction in CA125 from 303 to 31 U/ml (normal < 35 U/ml) at the end of C16
- 22% decrease in target lesions at the end of C16

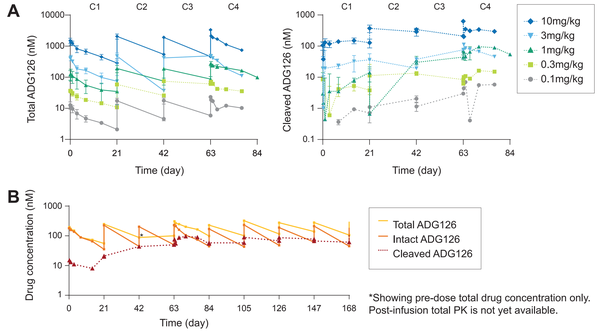
		Baseline	End of C2	End of C7	End of C16
Target Lesion	TL1 - Lymph Node	17 mm	13 mm	12 mm	12 mm
	TL2 - Lymph Node	15 mm	15 mm	13 mm	13 mm
	Sum (% from baseline)	32 mm	28 mm (-13%)	25 mm (-22%)	25 mm (-22%)
Non-Target Lesion		Present	Present	Present	Present
New Lesion		NA	No	No	No
Overall Response		NA	SD	SD	NA
CA125 in U/ml (% from baseline)		303	249 (-18%)	70 (-77%)	31 (-90%)

§Carboplatin + paclitaxel + bevacizumab (1L), carboplatin + gemcitabine (2L), carboplatin + pegylated liposomal doxorubicin (3L), olaparib + bevacizumab (4L) and paclitaxel-nab + niraparib (5L)
C = treatment cycle
*Reference: CA 125 definitions agreed by GCIG November 2005



ADG126 Pharmacokinetics (PK)

- Plasma PK of total and intact ADG126 were approximately linear with dose
- Cleaved ADG126 on average accumulated ≥3-fold (C4 vs C1) during repeat dosing



*Showing pre-dose total drug concentration only. Post-infusion total PK is not yet available.

Plasma PK of total and cleaved ADG126 in the first 4 cycles in (A) 20 patients with PK data and (B) an ovarian serous carcinoma patient (case study). Total ADG126 and intact ADG126 was measured by LC-MS using signature peptides. Cleaved ADG126 is calculated as total ADG126 minus intact ADG126. C = treatment cycle

Conclusions

- ADG126 (anti-CTLA-4 SAFEbody®) is well tolerated with repeat and continuous dosing up to 20 mg/kg, which is an unprecedented high dose level for anti-CTLA-4 class of molecules. This supports proof-of-concept for the SAFEbody® precision masking technology to improve safety margin
- PK of total and intact ADG126 was approximately linear with dose, with significant accumulation (≥3-fold) of the cleaved species, the active moiety of ADG126, contributing to ~1.5-fold longer half-life of total ADG126 compared with its parental antibody
- In heavily pre-treated patients, ADG126 monotherapy shows promising efficacy signals with 39% disease control rate. One ovarian serous carcinoma patient has shown a major CA125 response with 90% reduction following 16 cycles (~ 1 year) of monotherapy and still remains on treatment on the 18th cycle
- Evaluation of the combination of ADG126 with anti-PD-1 therapy is ongoing

Dr. Gary Richardson has received clinical research funding from Adagene for the role of site principal investigator. Contact: gary.richardson@ocv.net.au
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