691

A Phase I study of AN4005, an orally available PD-L1 inhibitor, in patients with advanced tumors: safety and preliminary efficacy

Yanqiao Zhang, MD[1], Jinyu Lu, MD, PhD[2,*], David Levitz, MD[2], Xiaorong Dong, MD, PhD[3], Alexander Spira, MD, PhD[4], Martin Gutierrez, MD[5], Mengjie Gu, PhD[6], Xuyang Lu, PhD[6], Xuyang Song, PhD, MBA[6]

[1]Department of Gastrointestinal Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China, [2]Department of Oncology, Montefiore Einstein Comprehensive Cancer Center, New York, New York, US, [3]Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [4]Thoracic and Phase I Program, Virginia Cancer Specialists Research Institute, Fairfax, Virginia, US, [5]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, New Jersey, US, [6]Adlai Nortye Biopharma Co., Ltd., Hangzhou, China, *Corresponding author

BACKGROUND

AN4005 is an orally available, small-molecule programmed cell death ligand 1 (PD-L1) inhibitor that demonstrates antitumor activity by blocking the interaction between PD-L1 and programmed cell death-1 (PD-1) (Fig. 1). In animal studies, AN4005 demonstrated tumor growth inhibition comparable to that of anti-PD-L1 monoclonal antibody (mAb) in an immune-dependent manner (Fig. 2). We hypothesized that an oral small-molecule PD-L1 inhibitor like AN4005 may offer potential advantages over mAbs, including improved tumor penetration, better safety management, reduced immunogenicity, and patient convenience.

Figure 1: Mechanism of Action of PD-L1 Inhibitor

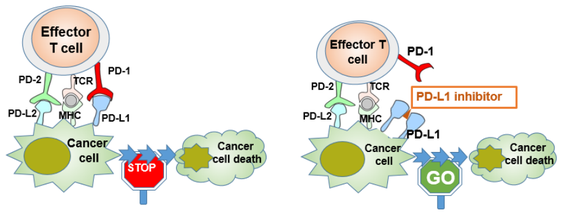
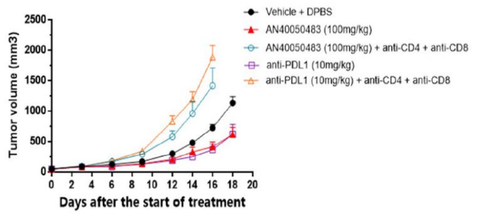


Figure 2: AN4005 exhibits an immune-dependent antitumor activity



Abbreviations: DPBS = Dulbecco's Phosphate Buffered Saline; mAb = monoclonal antibody; PDL1 = programmed death-ligand 1; TGI = tumor growth inhibition.
Note: To determine the immune dependence of AN4005 activity on TGI, anti-CD4 and -CD8 mAbs were used to deplete CD4+ and CD8+ T cells in vivo, respectively, and antitumor effect was then analyzed.

METHODS

This is an open-label, multicenter, Phase 1, first-in-human study of AN4005 in patients with advanced tumors. A traditional '3+3' design was employed for dose escalation, with sentinel patients enrolled at the starting dose of 50 mg BID. The primary objective was to investigate the safety, identification of recommended phase II dose (RP2D) and/or maximum tolerated dose (MTD). Secondary objectives included pharmacokinetics (PK) and preliminary efficacy per RECIST 1.1. Eligible patients received a single dose of AN4005, followed by multiple doses in 28-day cycles after PK sample collection from the single dose.

Figure 3: Overall Study Design

N=31~36
Advanced tumors (solid tumors and lymphomas)

Key inclusion criteria:

- ECOG 0-1
- Advanced unresectable or metastatic solid tumors, or relapsed/refractory lymphomas
- No standard therapy available

Food effect assessment using RP2D

Primary objective

- Safety, tolerability, MTD and/or RP2D

Secondary objectives

- Pharmacokinetics (PK)
- Food effect on PK
- Preliminary efficacy: CRR, ORR, DCR, PFS, DOR (RECIST 1.1 for solid tumors, or Lugano for lymphoma); OS

Exploratory objectives

- Preliminary efficacy assessed by iRECIST or LYRIC
- Biomarkers, Pharmacodynamics (PD), PK/PD correlation
- Efficacy by PD-L1 expression

RESULTS

- Trial Registration: ClinicalTrials.gov identifier NCT04999384.
- The study is currently being conducted in research sites in both US and China.
- Data were analyzed based on cohorts up to 1000mg QD dose level and data cutoff of 14 Oct 2024.

Table 1: Number of Patients per Tested Dose Level

Dose level	50 mg BID	100 mg BID	200 mg QD	300 mg QD	600 mg QD	1000 mg QD	Total
Number of patients treated	2	4	3	4	6	6	25

BID, twice daily; QD, once daily.

Table 2: Patient Demographics and Baseline Characteristics

Demographics and Baseline Characteristics		Total N = 25 (%)
Age in years, median (range)		57 (28 – 78)
Primary Tumor Type	Colon Cancer NSCLC Ovarian Cancer Uterine Cancer Gastric Cancer Other	7 (28%) 3 (12%) 3 (12%) 3 (12%) 3 (12%) 6 (24%)
Sex	Male Female	9 (36%) 16 (64%)
Race	Asian White Black or African American Not reported or not specify	15 (60%) 5 (20%) 2 (8%) 3 (12%)
ECOG PS at baseline	0 1	10 (40%) 15 (60%)
Prior IO treatment	Yes No	11 (44%) 14 (56%)
Prior lines of systemic therapies	0 1 2 ≥3	2 (8%) 2 (8%) 5 (20%) 16 (64%)

Safety profile:

- Twenty-three (92%) patients experienced at least 1 treatment-emergent adverse event (TEAE), 9 (36%) patients experienced at least 1 TEAE with Grade ≥ 3.
- Twenty (80%) patients experienced at least 1 AN4005-related AE, 2 (8%) patients experienced Grade 3 AN4005-related AE. No Grade 4 or 5 AN4005-related AEs were observed.
- Eight (32%) patients experienced 15 serious adverse events (SAEs), 1 (4%) patient experienced 1 SAE assessed by investigator as related to AN4005.
- No patients experienced AEs leading to dose reduction of AN4005. Nine (36%) patients experienced at least 1 AE leading to dose interruption of AN4005. Four (16%) patients had AE that led to discontinuation of AN4005.
- Immune-related AEs (irAEs) were reported in 2 patients (8%) and manageable.
- No dose-limiting toxicities (DLTs) occurred at any dose level, and the MTD was not reached.

Table 3: Treatment-Related Adverse Events (TRAEs) Reported in ≥2 Patients with any Grade or in ≥1 Patient with Grade≥3

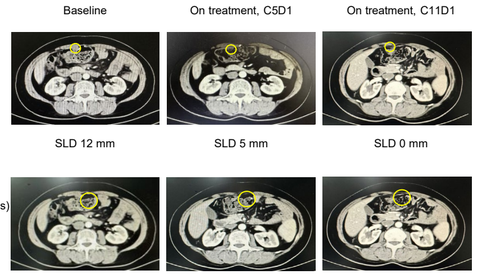
Preferred Term, n (%)	Total (N=25)	
	Any Grade	Grade≥3
Any TRAEs	20 (80%)	2 (8%)
Aspartate aminotransferase increased	4 (16%)	1 (4%)*
Nausea	4 (16%)	0
Vomiting	4 (16%)	0
Alanine aminotransferase increased	3 (12%)	1 (4%)*
Anaemia	3 (12%)	0
Decreased appetite	3 (12%)	0
Gamma-glutamyltransferase increased	3 (12%)	0
Blood alkaline phosphatase increased	2 (8%)	0
Blood bilirubin increased	2 (8%)	0
Gastrooesophageal reflux disease	2 (8%)	0
Hypoalbuminaemia	2 (8%)	0
Proteinuria	2 (8%)	0
Peripheral neuropathy	1 (4%)	1 (4%)**

*One (4%) patient in the 100 mg BID cohort experienced Grade 3 alanine aminotransferase increased and Grade 3 aspartate aminotransferase increased. These events were also considered irAEs by the Investigator.
**One (4%) patient in the 200 mg QD cohort experienced Grade 3 peripheral neuropathy which was also reported as an SAE. However, the Sponsor could not establish a causal association of the event with AN4005, due to confounders in this case.

Preliminary efficacy:

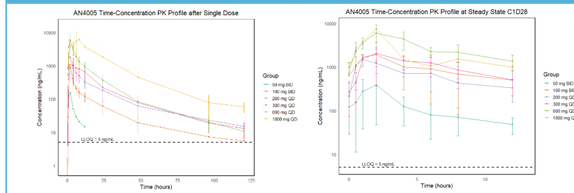
- Overall disease control rate (DCR) was 42% (10 in 24 efficacy-evaluable patients).
- One responder was observed at 300 mg QD cohort who received a confirmed complete response (CR).
  - ✓ Demographics and baseline characteristics: 50-year-old Asian female, diagnosed with Stage IIIc colon cancer at initial diagnosis, metastatic disease to peritoneum (Stage IV) at baseline, with high microsatellite instability (MSI-H) / PD-L1 TPS 30%.
  - ✓ Prior therapies: left colon extended radical resection followed by adjuvant chemotherapy; two lines of anti-PD-(L)1 mAbs at metastatic setting, achieved partial response (PR) in both lines. However, the intravenous therapy was interrupted due to the COVID-19 pandemic and the disease progressed.
  - ✓ This case highlights the value of an oral PD-L1 inhibitor.

Figure 4: CT imaging of Target Lesion and Non-Target Lesion of the Responder



Abbreviations: SLD, sum of longest diameters of target lesions; NA, not applicable; PR, partial response; CR, complete response; C, cycle; D, day.

Figure 5: Pharmacokinetics Profile of AN4005 Monotherapy in Patients with Advanced Tumors



AN4005 exposure increased in a dose-dependent manner over the range of 50 mg BID to 1000 mg QD.

CONCLUSIONS

- **AN4005 demonstrated favorable safety and tolerability in patients with advanced tumors.**
- **The preliminary efficacy of AN4005 in a tumor type known to be responsive to anti-PD-(L)1 therapy is encouraging and warrants further investigation in anti-PD-(L)1-naive patients.**
- **Based on an overall evaluation of safety, clinical benefit, and PK, the 600mg QD and 1000mg QD dose levels have been selected for further evaluation in the future expansion cohorts.**

Ethics Approval

The study protocol was approved by institutional review boards (IRB) or independent ethics committees (IEC) at participating centers. All patients enrolled gave informed consent before participating. The IRB/IEC approval numbers were: IRB Tracking Number 20213975 (WCG IRB); Event ID # 189834 (BRANY IRB); NXVCS21.53 (Salus IRB); IEC Number 2022-78 (Harbin Medical University Cancer Hospital); IEC Number 2022-0251 (Union Hospital, Tongji Medical College, Huazhong University of Science and Technology).

Acknowledgments

We thank the patients and their caregivers for participating in this trial. We also thank the investigators and their support staff who generously participated in this work. This study is sponsored by Adlai Nortye Biopharma Co., Ltd.

Disclosure

Yanqiao Zhang, Jinyu Lu, David Levitz, Xiaorong Dong, Alexander Spira, and Martin Gutierrez have nothing to disclose. Mengjie Gu, Xuyang Lu, and Xuyang Song: Full-time employees of Adlai Nortye. Xuyang Lu and Xuyang Song: Shareholders of Adlai Nortye.

yanqiaozhang@ems.hrbmu.edu.cn

Sponsored by Adlai Nortye Biopharma Co., Ltd.