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A Phase Ib Study of AN0025 in Combination With Definitive Chemoradiotherapy (dCRT) in Unresectable Locally Advanced or Locally Recurrent Esophageal Cancer (EC)

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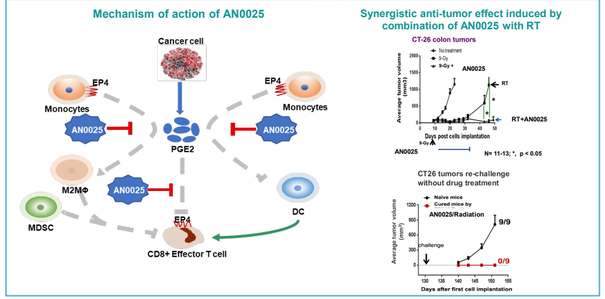
BACKGROUND

AN0025 is a highly selective and potent antagonist of the prostaglandin E2 (PGE2) receptor 4 (EP4) (PGE2-EP4). It demonstrates antitumor activity by modulating the accumulation and function of immunosuppressive myeloid cells including tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC) in the tumor microenvironment[1,2,3].

Ionizing radiation triggers the massive production of PGE2 during apoptosis in tumor cells, while the PGE2-EP4 signaling pathway contributes to the generation and maintenance of the immunosuppressive properties of the tumor microenvironment[4,5]. Therefore, the combination of AN0025 which inhibits PGE2-EP4 activity with radiotherapy (RT) is proposed to exert synergistic anti-tumor effect. Preclinical studies have demonstrated that combining AN0025 with RT exhibits strong antitumor activity, and data from animal models indicate that this combination may also promote the development of an immune memory antitumor response[6].

Additionally, the combination of AN0025 with CRT as neoadjuvant therapy has shown encouraging antitumor efficacy in locally advanced rectal cancer in a prior Ph1b clinical trial (NCT03152370). In this trial, a complete response (CR) rate of 36% was observed (4 [26.7%] of 15 patients who underwent surgery achieved pathological CR and 5 [20%] of 25 patients achieved clinical CR), further supporting the development of AN0025 in combination with CRT[7].

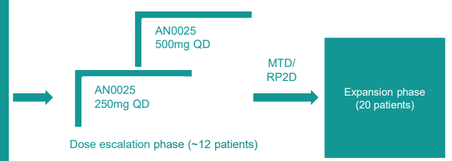
Figure 1: Rationale for Combination of AN0025 with Radiotherapy and Chemoradiotherapy (RT/CRT)



METHODS

Figure 2: Overall Study Design

- Patients with esophageal cancer/esophagogastric junction cancer of stage II to IVa base on 8th AJCC, or Stage IVb cervical/ upper thoracic esophageal cancer with supraclavicular lymph node metastases only
- Squamous cell carcinoma or adenocarcinoma
- Unresectable, no prior radiotherapy in the esophageal region, suitable for dCRT



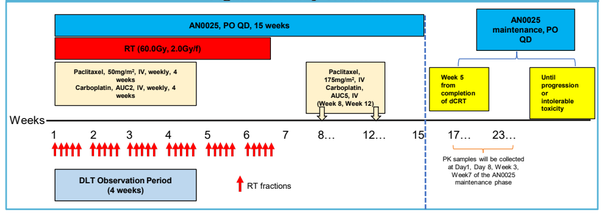
Key objectives:

Primary: safety and tolerability; DLT, MTD and/or RP2D

Secondary: preliminary efficacy per RECIST 1.1, including CRR, ORR, DCR, PFS, DOR, OS; PK profile

Exploratory: correlation between selected pharmacodynamic biomarkers and efficacy; correlation between the exposure of AN0025/metabolites and parameters related to clinical outcomes

Figure 3: Study Treatment



RESULTS

- Clinical trial information: NCT05191667. The study is being conducted in 3 research sites in China.
- Data were analyzed based on data cutoff of 23 Aug 2024.

Table 1: Patient Demographics and Baseline Characteristics

Number of patients		250 mg n=5	500 mg n=7	All n=12
Age in years, median (range)		61 (52, 64)	64 (56, 70)	61.5 (52, 70)
Race	Asian	5 (100%)	7 (100%)	12 (100%)
Sex	Male	5 (100%)	6 (86%)	11 (92%)
	Female	0	1 (14%)	1 (8%)
ECOG PS	0	5 (100%)	5 (71%)	10 (83%)
	1	0	2 (29%)	2 (17%)
Tumor category	Locally advanced	5 (100%)	6 (86%)	11 (92%)
	Locally recurrent	0	1 (14%)	1 (8%)
Histology	Squamous cell carcinoma	5 (100%)	7 (100%)	12 (100%)
T stage	T2	1 (20%)	1 (14%)	2 (17%)
	T3-T4b	4 (80%)	6 (86%)	10 (83%)
N stage	N1-2	4 (80%)	6 (86%)	10 (83%)
	N3	1 (20%)	1 (14%)	2 (17%)
M stage	M0	5 (100%)	6 (86%)	11 (92%)
	M1	0	1 (14%)	1 (8%)
Measurable disease	Yes	2 (40%)	6 (86%)	8 (67%)
	No	3 (60%)	1 (14%)	4 (33%)

Safety profile:

- Twelve (100%) patients experienced at least 1 treatment-emergent adverse event (TEAE), 10 (83%) patients experienced at least 1 TEAE with Grade ≥ 3.
- Eleven (92%) patients experienced at least 1 AN0025-related AE, 2 (17%) patients experienced at least 1 Grade ≥ 3 AN0025-related AE.
- Seven (58%) patients experienced 9 serious adverse events (SAEs), none of which were deemed related to AN0025.
- Two (17%) patients experienced AEs leading to dose reduction of chemotherapy. No patients experienced AEs leading to dose reduction of radiotherapy or AN0025.
- Nine (75%), 5 (42%), and 3 (25%) patients experienced at least 1 AE leading to dose interruption of AN0025, chemotherapy, and radiotherapy, respectively.
- One (8%) patient had AE that led to discontinuation of radiotherapy. No patients had AEs that led to discontinuation of AN0025 or chemotherapy.
- No DLT occurred at either dose level, and the maximum tolerated dose (MTD) was not reached.

Table 2: AN0025-Related AEs

	250 mg n=5		500 mg n=7		All n=12	
TRAEs, patients (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	5 (100%)	1 (20%)	6 (86%)	1 (14%)	11 (92%)	2 (17%)
Occurred in ≥ 2 patients with any grade or in ≥ 1 patient with Grade ≥ 3						
Weight decreased	3 (60%)	1 (20%)	3 (43%)	0	6 (50%)	1 (8%)
Anemia	4 (80%)	0	0	0	4 (33%)	0
White blood cell count decreased	3 (60%)	0	0	0	3 (25%)	0
Diarrhea	2 (40%)	0	1 (14%)	0	3 (25%)	0
Asthenia	1 (20%)	0	1 (14%)	0	2 (17%)	0
Esophageal fistula	0	0	1 (14%)	1 (14%)	1 (8%)	1 (8%)

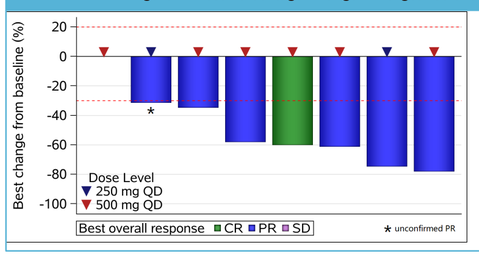
Table 3: Preliminary Efficacy: Best Overall Response (BOR) per RECIST v1.1

Number (%) of patients	Measurable disease at baseline n = 8	No measurable disease at baseline n = 4 ***	All n = 12
Complete response (CR)	1 (13%)	0	1 (8%)
Partial response (PR)	6* (75%)	N/A	6* (50%)
Stable disease (SD)	1 (13%)	N/A	1 (8%)
Progressive disease (PD)	0	1 (25%)	1 (8%)
Non-CR/non-PD	N/A	3 (75%)	3 (25%)
Confirmed overall response rate (cORR) **	6 (75%)	---	---
Unconfirmed overall response rate (uORR) **	7 (88%)	---	---
Disease control rate (DCR)	8 (100%)	3 (75%)	11 (92%)

N/A = not applicable. *One patient had an unconfirmed PR. **cORR is 50% (1/2) at 250 mg and 83% (5/6) at 500 mg, uORR is 100% (2/2) at 250 mg and 83% (5/6) at 500 mg. ***Primary esophageal lesions are non-measurable.

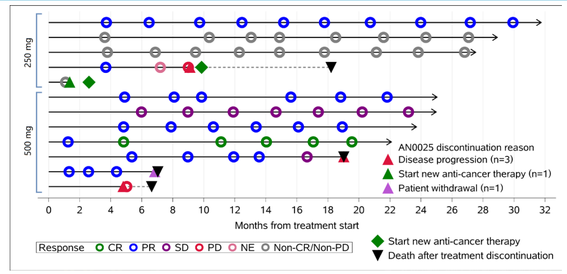
- Among the 8 patients with measurable disease at baseline, 1 (12%) achieved confirmed CR, 6 achieved PR, including 5 confirmed PRs, giving an unconfirmed overall response rate (ORR) of 88% (7/8) and a confirmed ORR of 75% (6/8).
- Among the 4 patients without measurable disease at baseline, 3 (75%) achieved non-CR/non-PD, including 1 patient who transformed to be operable and achieved pathologic complete response (pCR) confirmed by post-surgery pathology.
- The disease control rate (DCR) was 92% (11/12).

Figure 4: Best Percentage Change in Target Lesions



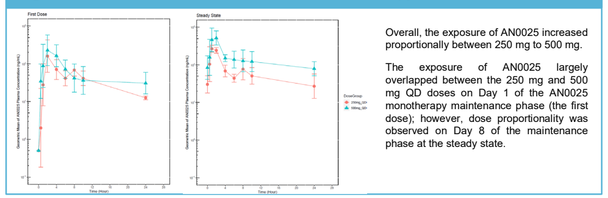
Best change from baseline is available for 8 patients who had measurable lesions at baseline and had at least one post-treatment tumor assessment. It is measured as the largest percentage reduction in sum of longest diameters of the target lesions.

Figure 5: Time on Treatment and Tumor Response Assessment



- The median follow-up was 19.3 months, with 7 patients remaining on study treatment and a maximum time on treatment of 29.9 months.
- The median progression-free survival (PFS) was not reached, with an 18-month PFS rate of 73%. The 18-month overall survival (OS) rate was 82%.

Figure 6: Pharmacokinetics Profile of AN0025 Monotherapy in the Maintenance Phase



Overall, the exposure of AN0025 increased proportionally between 250 mg to 500 mg.

The exposure of AN0025 largely overlapped between the 250 mg and 500 mg QD doses on Day 1 of the AN0025 monotherapy maintenance phase (the first dose); however, dose proportionality was observed on Day 8 of the maintenance phase at the steady state.

CONCLUSIONS

- **AN0025 in combination with dCRT was well tolerated in both 250 mg and 500 mg QD dose levels in Chinese patients with unresectable locally advanced/locally recurrent esophageal cancer. No DLTs were observed.**
- **AN0025 PK approached linearity at both 250 mg and 500 mg QD.**
- **Preliminary efficacy results are encouraging and support the development of AN0025 as an immune modulator with CRT.**

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Acknowledgments

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Disclosure

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