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A Phase 1b Study of E7046 (AN0025) in Combination With Radiotherapy/Chemoradiotherapy (RT/CRT) in Preoperative Treatment of Rectal Cancer

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BACKGROUND

AN0025 (previously E7046) is a selective inhibitor of the EP4 receptor, one of the 4 known receptors for PGE2. It targets macrophages and immunosuppressive cells of myeloid lineage in tumor microenvironment[1,2,3,4]. Ionizing radiation-induced cancer cell apoptosis is accompanied by secretion of $PGE2$[5].

Preclinical studies have shown antitumor activity with AN0025 combining with RT and animal model data demonstrated antitumor memory T-cell response development by the combination.

Phase 1 study of AN0025 monotherapy showed the compound was well tolerated up to 750 mg daily. Stable disease was observed in 7 (23.3%) of 30 patients and 3 patients had metabolic responses.

Neoadjuvant treatment of high-risk rectal cancer provides the platform to test this novel agent to determine its safety and clinical activity, and the biopsy and surgical specimens for biomarker analysis may further help identify the target patient population.

This ongoing study enrolled patients into two groups, AN0025 in combination with Long Course Radio Chemotherapy (LCRT), or Short Course Radiotherapy (SCRT) followed by chemotherapy. The primary objective was to define the safety and tolerability of the combination treatment.

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

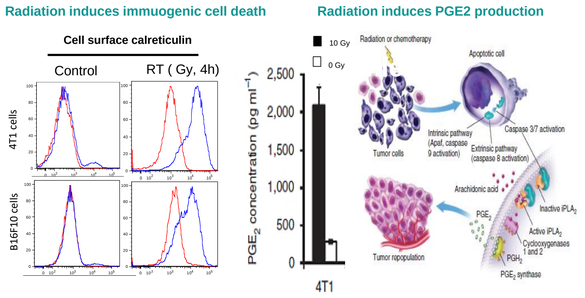
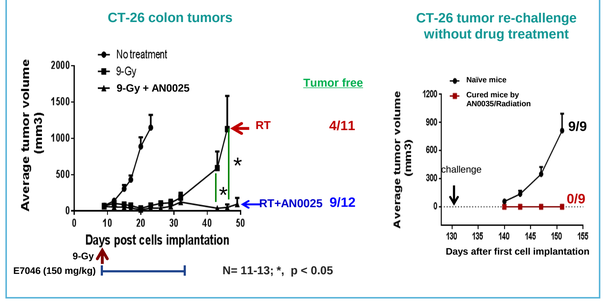
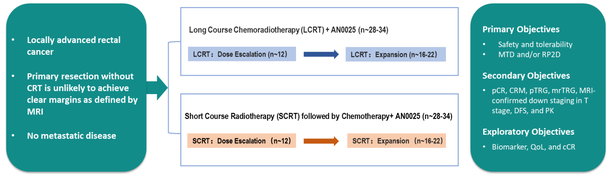


Figure 2: Preclinical Evidence



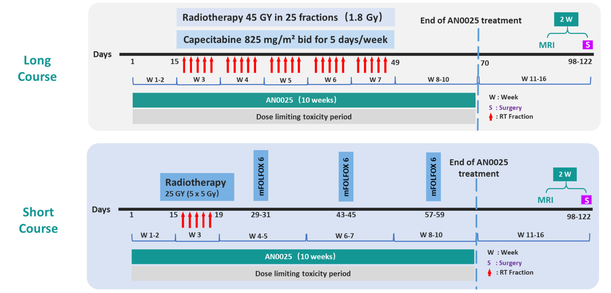
METHODS

Figure 3: PRAER1 Study Design



- Dose escalation comprised 2 dose levels, 250mg and 500mg QD for both SCRT and LCRT.
- Dose expansion approximately 16-22 subjects will receive the same treatment schedule at the RP2D

Figure 4: Study Treatment



Patient Eligibility

Key Inclusion Criteria

- Diagnosis of histologically confirmed invasive primary rectal carcinoma
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 and adequate bone marrow and liver function
- Subjects must have locally advanced rectal cancer where primary resection without CRT is unlikely to achieve clear margins as defined by MRI, with no metastatic disease
- Disease which can be encompassed within a radical radiotherapy treatment volume

Key Exclusion Criteria

- Any contraindications to MRI
- Active hydronephrosis.
- Unequivocal evidence of metastatic disease defined by CT
- Prolongation of corrected QT (QTc) interval to >480 msec when electrolyte balance is normal.
- Previous radiotherapy in the pelvic region (eg, prostate) or previous rectal surgery (eg, TME) or any investigational treatment for rectal cancer.

MRI Eligibility Criteria

Upper and Mid rectum*	Patient Eligibility
T1 – T3b	Patient NOT eligible unless mrCRM plane < 1mm or EMVI positive disease
T3c – T4a or T4b	Patient eligible regardless of mrCRM and EMVI status
Lower rectum**	**Patient Eligibility**
T2 or higher	Patient NOT eligible unless EMVI positive disease
Any T stage	Patient eligible if less than 1 mm to intersphincteric plane and anterior quadrant tumor lying <4 cm from the anal verge regardless of EMVI status

*superior extent of macroscopic tumor no higher than S1/2 junction on sagittal plane
**inferior edge less than 6 cm from the anal verge

Study Assessments

- The evaluation of rectal cancer was done by MR imaging of the rectum at baseline, before surgery, after surgery and once every year during DFS follow up period.
- MR images were assessed by the investigators for the assessment of T stage and TRG as required.
- The assessment for distant metastatic disease was done by CT scans of the chest, abdomen and pelvis at Screening, and at 3, 6, 12, 18 and 24 months after surgery during DFS follow up period to assess for local recurrence and/or new metastatic lesions.
- Clinical Complete Response (cCR) is defined as having no viable tumor on MRI and/or endoscopy as per local guidelines for 'watch and wait'.
- Excised rectal cancer specimen was fixed in formalin, sent to central lab, and assessed by histopathologist based on AJCC TNM8.
- Data were analyzed based on database cutoff of 08 Aug 2019.

RESULTS

Table 1: Patient Characteristics

Number of patients		250 mg n=14	500 mg n=14	All n=28
Age	Median, yr (range)	62.5 (41, 74)	55.5 (39, 74)	58.5 (39, 74)
Race	White Asian	13 1	14 0	27 1
Sex	Male Female	10 4	10 4	20 8
ECOG PS	0 1	12 2	5 9	17 11
T stage	T3c-T4b	6	10	16
EMVI+	Yes	8	9	17

EMVI: Extramural venous invasion

Table 2: Patient Disposition

	250 mg	500 mg	All
Treated	14	14	28
DLT Evaluable	13	12	25
Completed Neoadjuvant treatment as per protocol	13	12	25
Discontinued from Neoadjuvant treatment	1	2	3
Reason for discontinuation			
Adverse Event*	1	1	2
Subject Decision	0	1	1

*Patient 1: abdominal pain (Gr1), vomiting (Gr2), hypokalemia (Gr3), Fatigue (Gr3); patient 2: pharyngeal mucositis (Gr2)

Table 3: AN0025 Treatment-Related AEs

	250 mg n=14		500 mg n=14		All n=28	
TRAEs, patients (%)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any	12 (85.7%)	1 (7.1%)	7 (50.0%)	1 (7.1%)	19 (67.9%)	2 (7.1%)
Serious	1 (7.1%)*	0	0	0	1 (3.6%)	0
Occurred in ≥ 3 patients						
Fatigue	5 (35.7%)	1 (7.1%)	3 (21.4%)	0	8 (28.6%)	1 (3.6%)
Diarrhea	2 (14.3%)	0	2 (14.3%)	1 (7.1%)	4 (14.3%)	1 (3.6%)
Nausea	3 (21.4%)	0	0	0	3 (10.7%)	0
Decreased appetite	2 (14.3%)	0	1 (7.1%)	0	3 (10.7%)	0
Headache	2 (14.3%)	0	1 (7.1%)	0	3 (10.7%)	0
Paraesthesia	2 (14.3%)	0	1 (7.1%)	0	3 (10.7%)	0

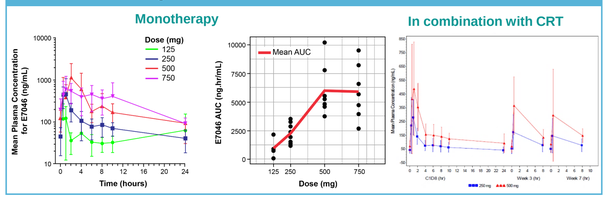
* One patient had serious TRAEs (abdominal pain, vomiting, and fatigue).

Table 4: Preliminary Efficacy

	250 mg QD			500 mg QD			TOTAL
	LCRT (N=7)	SCRT (N=7)	All (N=14)	LCRT (N=7)	SCRT (N=7)	All (N=14)	All (N=28)
Completed 10 weeks of treatment and with evaluable scans	7	6	13	6	6	12	25
mrTRG							
TRG1	1	1	2	0	0	0	2
TRG2	1	2	3	1	2	3	6
TRG3	1	1	2	3	3	7	8
TRG4	4	2	6	2	1	3	9
Subjects with a cCR	1	4	5	0	0	0	5
Watch& Wait	1	4	5	0	0	0	5
Subjects undergo surgery*	4	1	5	4	6	10	15
Subjects with a pCR*	0	1	1	2	1	3	4
Subjects with a CRM negative resection*	2	1	3	4	5	9	12
pTRG*							
TRG1	0	1	1	2	1	3	4
TRG2	0	0	0	0	1	1	1
TRG3	4	0	4	2	2	4	8
TRG4	0	0	0	0	2	2	2

* 2 patients had central histopathology review completed after data cutoff..

Figure 5: Clinical Pharmacokinetics of AN0025



CONCLUSIONS

- AN0025 was well tolerated in combination with chemoradiation in both 250 mg and 500 mg treatment arms. No DLTs have been observed.
- PK profile of AN0025 in combination with CRT is similar to monotherapy.
- Preliminary efficacy results are encouraging and support the development of AN0025 in combination with chemoradiation and short course radiotherapy with consolidation chemotherapy.
- Additional follow-up data and biomarker analyses will guide future development of this combination in rectal cancer.

Acknowledgments

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Disclosure

M.P. Saunders reports personal fees for meetings/chairing/speaking from Servier, Merck, Amgen, Sanofi, outside the submitted work. J. Ng has nothing to disclose. V. Bhagawati-Prasad: Employee of Eisai. N. Lautermilch, M. Rashford, J. Jin: Employees of Adlai Nortye. S. Formenti: Research Grants: Bristol Myers Squibb, Varian, Janssen, Regeneron, Eisai, Merck, Celldex. Honoraria: Bristol Myers Squibb, Varian, Elekta, Janssen, Regeneron, GlaxoSmithKline, Eisai, AstraZeneca, Merck, Viewray, Bayer. R. Glynne-Jones: Advisory Board: Eisai, Sanofi, Servier, Amgen, during the conduct of the study.

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