

540P A phase Ib 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 and targets macrophages and immunosuppressive cells of myeloid lineage in tumor microenvironment. Preclinical studies have shown potent antitumor activity with AN0025 combining with RT and animal model data suggested antitumor memory T-cell response development by the combination. Neoadjuvant treatment of high-risk rectal cancer provides the platform to test such novel agents to clarify safety and efficacy and provide biopsy and surgical specimens for biomarker analysis.

Methods: This is a multicenter, open-label, Phase Ib study in patients (pts) with poor prognosis locally advanced rectal cancer as defined by standard MRI. This ongoing study enrolled pts into two groups, AN0025 in combination with Long Course Radiotherapy (LCRT), or Short Course Radiotherapy (SCRT) followed by chemotherapy. The dose escalation design comprised 2 dose levels, 250mg and 500mg QD for both SCRT and LCRT. Treatment duration was 10 weeks followed by surgery at week 14-16. Pre-surgery MRI was done at week 11-13. Primary objective was safety and tolerability of AN0025 + CRT.

Results: As of 23 Apr 2019, 27 pts were enrolled. 14 pts were treated in 250 mg cohort with 7 pts in LCRT and in SCRT. No DLT was observed among 13 evaluable pts in this dose level. 500mg cohort is ongoing, 13 pts enrolled. Overall, 18 (66.7%) pts had treatment-related AEs (TRAE), most commonly fatigue (25.9%), diarrhea (14.8%), nausea (11.1%), decreased appetite (11.1%), headache (11.1%), and paraesthesia (11.1%). 2 pts experienced grade 3 TRAEs (diarrhea and fatigue) and 1 pt had serious TRAEs (abdominal pain, vomiting, and fatigue). Median age was 59, 74% were male, 41% had ECOG 1, 56% with T stage T3c-T4b, and 63% were EMVI+. For 250 mg cohort, pre-surgery MRI showed 6/13 pts had downstaging in T stage (3 each in LCRT and SCRT) and mrTRG 1-2 rate was 46% (43% and 50% in LCRT and SCRT respectively). Clinical responses led to 5/13 pts (38%) managed by a watch-and-wait approach.

Conclusions: AN0025 was well tolerated in combination with chemoradiation and preliminary efficacy results are encouraging. Additional safety and efficacy data will be presented.

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