Abstract 123P

Combination potential of EO-3021, a CLDN18.2 vc-MMAE ADC, with VEGFR2 or PD-1 inhibition in preclinical models of CLDN18.2-expressing cancers

Thomas O'Hare[1], Jaclyn Cleveland[1], Valerie Malyvanh Jansen[1], David Dornan[1]

[1]*Elevation Oncology, Inc., Boston, MA*

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INTRODUCTION

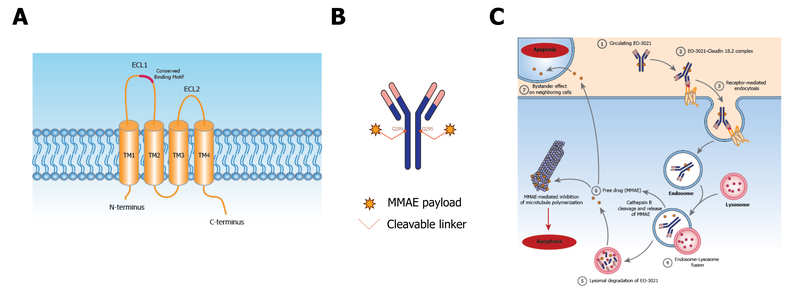

Figure 1. EO-3021, a Claudin 18.2-specific antibody drug conjugate

- Claudin 18.2 (CLDN18.2), a tight junction protein (Fig 1A) normally expressed only on gastric mucosa[1,2], is highly expressed in gastric, pancreatic, esophageal, ovarian, lung and other solid tumors
- EO-3021 is an antibody-drug conjugate (ADC) composed of a fully human IgG1 mAb targeting CLDN18.2 with a monomethyl auristatin E (MMAE) payload site-specifically conjugated at glutamine 295 (Q295) via a cathepsin B cleavable linker at a drug-antibody ratio of 2[3] (Fig 1B)
- EO-3021 selectively delivers a potent cytotoxic payload, MMAE, directly to cancer cells to disrupt microtubule networks and kills cancer cells. A bystander killing effect also occurs due to payload diffusion to neighboring tumor cells[3] (Fig 1C)
- EO-3021 monotherapy has shown promising anti-tumor activity in patients with gastric/gastroesophageal junction (GEJ) cancer that express CLDN18.2 (NCT05980416)
- Here we present preclinical studies evaluating the anti-tumor activity of EO-3021 with an anti-PD-1 or VEGFR2 inhibitor

METHODS

- PDX models of gastric adenocarcinoma (models CTG-0147, CTG-0707 and CTG-0936) were evaluated for tumor growth inhibition in response to EO-3021, isotype-MMAE control (DAR2) carrying the same site-specifically conjugated MMAE payload as EO-3021, or zolbetuximab (CLDN18.2 mAb)
- Mice were treated with EO-3021 at 0, 0.5, 1, 2, 5 and 10 mg/kg, isotype-MMAE (10 mg/kg), or zolbetuximab (10 mg/kg) by intraperitoneal injection once-weekly (qw) on days 0, 7, 14, and 21. One group was treated with a single 20 mg/kg dose of EO-3021 on day 0
- Mice bearing syngeneic MC38-B-hCLDN18.2 tumors (Biocytogen) were treated with an anti-PD-1 mAb (BioXCell; 4 mg/kg or 12 mg/kg twice-weekly (q2w)), EO-3021 (7.5 mg/kg qw), or combinations at the indicated doses
- In rechallenge experiments, MC38-B-hCLDN18.2 cells were injected in mice that achieved CRs and remained tumor-free + control mice on post-treatment Day 73. Tumor volume and body weight were measured twice a week
- Mice bearing NUGC-4-hCLDN18.2 gastric tumors (Crown Bioscience) were treated with a ramucirumab surrogate, DC101 (BioXCell; 20 mg/kg q2w), EO-3021 (2 mg/kg qw), or the combination
- CLDN18 expression was measured by IHC with VENTANA CLDN18 (43-14A) (Roche Diagnostics) on tumors from untreated mice. IHC intensity scores were assigned by a board-certified pathologist

REFERENCES

1. Türechi et al. Gene. 2011; 83-92
2. Sahin et al. Clin Cancer Res. 2008; 14(23)
3. Dan et al. Cancer Res (2023) 83 (7_Supplement): 6300

RESULTS

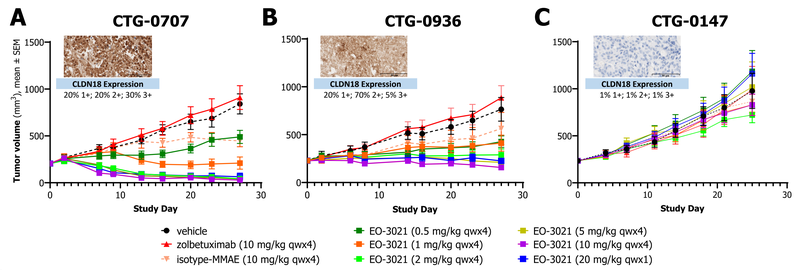

Figure 2. EO-3021 induces tumor regression in PDX models of gastric cancer that are non-responsive to zolbetuximab

- In high CLDN18.2 expressing gastric cancer models, EO-3021 induces complete tumor regression relative to isotype control; zolbetuximab (10 mg/kg qwx4) exhibited no anti-tumor effect (Fig 2A, 2B)
- At concentrations as high as 10 mg/kg qwx4, EO-3021 has no anti-tumor effect in the gastric cancer model that expresses low or no CLDN18.2 (Fig 2C)

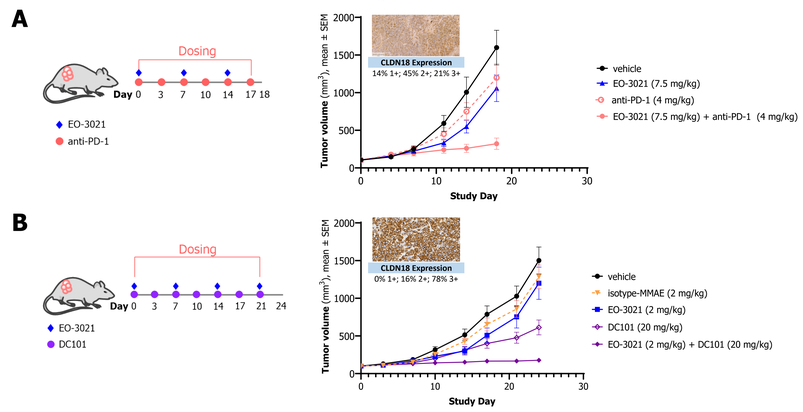

Figure 3. EO-3021 in combination with an anti-PD-1 mAb (MC38-B-hCLDN18.2 syngeneic model) or ramucirumab surrogate DC101 (NUGC-4-hCLDN18.2 gastric xenograft model) displayed superior anti-tumor activity over single agent

- The combination of EO-3021 + anti-PD-1 mAb exhibited superior anti-tumor activity over single agent EO-3021 or anti-PD-1 mAb (n=12 mice per treatment group) (Fig 3A). At Day 18, the combination resulted in an average tumor growth inhibition of 79.9% compared to 33.8% for EO-3021 ($p < 0.0008$) and 25.0% for anti-PD-1 ($p < 0.0001$)
- EO-3021 + ramucirumab surrogate (DC101) displayed superior anti-tumor activity over single agent EO-3021 or DC101 (n=10 mice per treatment group) (Fig 3B). At Day 24, the combination resulted in an average tumor growth inhibition of 88.2% compared to 20.1% for EO-3021 ($p < 0.0002$) and 59.2% for DC101 ($p < 0.0001$)

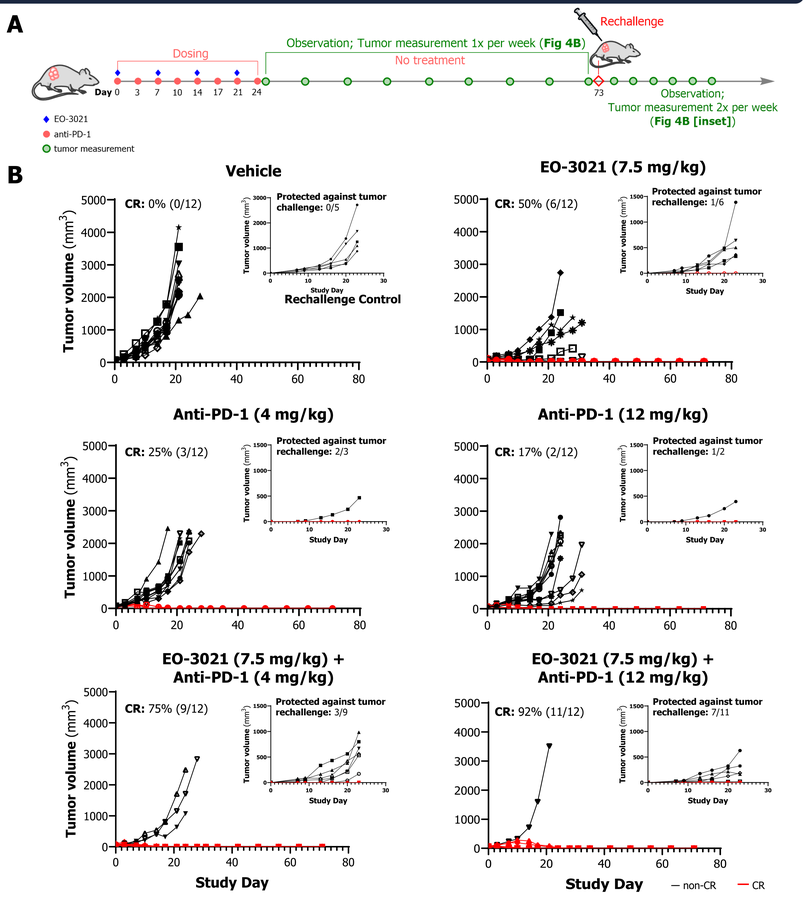

Figure 4. The combination of EO-3021 + anti-PD-1 induces CRs and protects against tumor rechallenge in syngeneic model MC38-B-hCLDN18.2

- Schematic for EO-3021 + anti-PD-1 experiments (Fig 4A)
- EO-3021 + anti-PD-1 mAb induced durable CRs* at a higher frequency (75%, EO-3021 + anti-PD-1 (4 mg/kg); 92%, EO-3021 + anti-PD-1 (12 mg/kg)) than single agent EO-3021 (50%) or single agent anti-PD-1 (25%, 4 mg/kg; 17%, 12 mg/kg) (Fig 4B). The combination yielded superior protection against rechallenge with MC38-B-hCLDN18.2 cells [graph inset] compared to single agent EO-3021

CONCLUSIONS

- EO-3021 demonstrated notable in vivo anti-tumor activity and superiority over zolbetuximab in gastric (CTG-0707, CTG-0936) PDX models with varying levels of CLDN18.2. The minimal efficacious dose that demonstrated tumor regressions was 2 mg/kg (model CTG-0707) or 5 mg/kg (model CTG-0936); minimal anti-tumor activity was observed in model CTG-0147, which had little to no detectable CLDN18.2
- EO-3021 administered in combination with an anti-PD-1 or VEGFR2 (DC101) inhibitor resulted in more robust tumor growth inhibition compared to the single agents
- EO-3021 administered in combination with an anti-PD-1 in the syngeneic MC38-B-hCLDN18.2 model induced durable CRs, some of which protected against tumor rechallenge, indicating potential induction of a robust immunogenic cell death response
- A Phase 1 study is ongoing to evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of EO-3021 in adult patients with solid tumors likely to express CLDN18.2 (NCT05980416); results from preclinical studies support the planned clinical evaluation of EO-3021 in combination with ramucirumab or a PD-1 inhibitor

*CR defined as no measurable tumor for 2 consecutive measurements

Abbreviations: ADC, antibody-drug conjugate; CR, complete response; ECL1, Extracellular Loop 1; ECL2, Extracellular Loop 2; IgG1, immunoglobulin G1; IHC, immunohistochemistry; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; qw, once-weekly; q2w, twice-weekly

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Contact: tohare@elevationoncology.com