Abstract 6300

Therapeutic potential of EO-3021/SYSA1801, a Claudin 18.2 antibody-drug conjugate, for the treatment of CLDN18.2-expressing cancers

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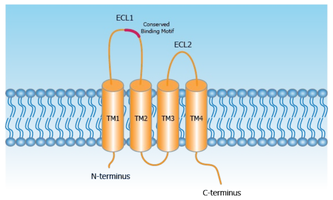
ELEVATION ONCOLOGY

INTRODUCTION

- 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
- CLDN18.2 may be exposed on epithelial surfaces in malignancy
- The ECL1 of CLDN18.2 differs from CLDN18.1 by 8 amino acids (Fig 1B)

A



B

27 45 47 56 65 80

MDQWSTQDLYNNPVTAVFNYQGLWRSCVRESSGFTECRGYFTLLGLPAMLQAVR CLDN18.2 ECL1

MDMWSTQDLYDNPVTSVFQYEGLWRSCVRQSSGFTECRPYFTILGLPAMLQAVR CLDN18.1 ECL1

Figure 1. Claudin 18.2, a tight junction protein

- EO-3021/SYSA1801 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 via a cleavable linker at a drug-antibody ratio of 2 (Fig 2A)
- EO-3021 was developed to target CLDN18.2-expressing cancer cells, minimize toxicities and maximize therapeutic index
- EO-3021 is specific for CLDN18.2 over CLDN18.1 (Fig 2B)
- Here we present preclinical data on the CLDN18.2 ADC EO-3021

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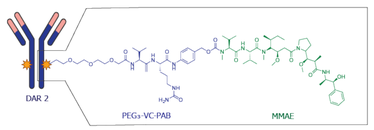

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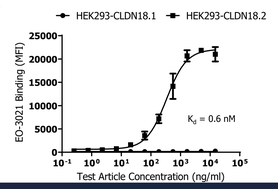

Figure 2. EO-3021 is specific for CLDN18.2

METHODS

- HEK293-CLDN18.2 cells were used to evaluate EO-3021 binding, CLDN18.2-dependent EO-3021 endocytosis, MMAE payload release, and inhibition of proliferation. HEK293 and HEK293-CLDN18.1 cells served as comparators as indicated
- EO-3021 binding was measured by flow cytometry, with median fluorescent intensity (MFI) of an Alexa Fluor 488-labeled secondary antibody used as the indicator of binding activity
- Xenograft studies evaluating tumor growth inhibition by EO-3021, EO-3021 mAb, and cisplatin or gemcitabine were done in gastric (NUGC4-CLDN18.2) and pancreatic (Patu8988S; BxPC3-CLDN18.2) models. Nu/nu mice were administered a single dose or multiple doses of treatment as indicated
- EO-3021 cross reactivity was measured by a flow cytometry binding assay in mouse, rat, cynomolgus, and human models

RESULTS

- EO-3021 and EO-3021 mAb demonstrated similar levels of ADCC (Fig 3A) and CDC (Fig 3B)

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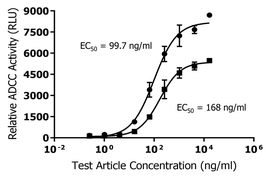
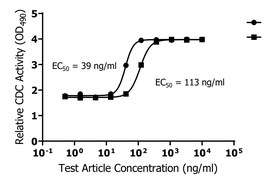


ADCC Activity in HEK293-CLDN18.2 + Jurkat/FCGR3A-NFAT

B

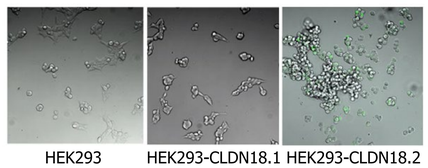


CDC Activity in CHO-K1-CLDN18.2 + human serum complement

Figure 3. EO-3021 is ADCC and CDC competent

- Endocytosis of fluorescent labeled EO-3021 (Fig 4A)
- EO-3021 impact on cell viability (Fig 4B)

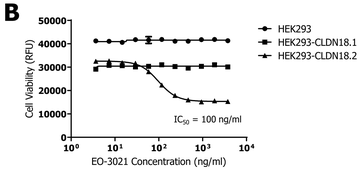
A



HEK293 HEK293-CLDN18.1 HEK293-CLDN18.2

Endocytosis EO-3021 (2 μg/ml) labeled with Zenon pHrodo iFL, 24-hour incubation

B



Cell Viability 72-hour incubation, resazurin assay

Figure 4. EO-3021-mediated endocytosis and reduction of cell viability is dependent on CLDN18.2

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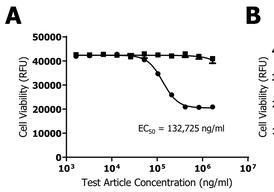

Pancreatic Cancer PATU8988S CLDN18.2 Low

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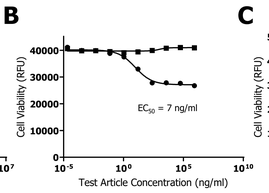
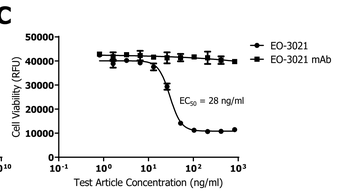


Gastric Cancer NCI-N87-18.2 CLDN18.2 Medium HER2 Amplified

C

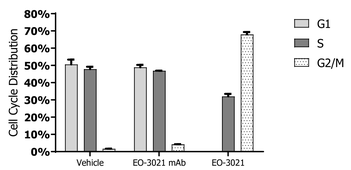


Pancreatic Cancer BxPC3-18.2 CLDN18.2 High

Figure 5. EO-3021 *in vitro* activity is more notable in cell lines with medium or high levels of CLDN18.2 expression

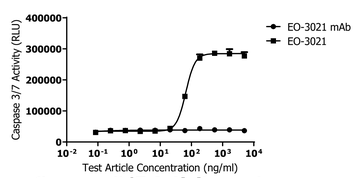
- EO-3021, but not EO-3021 mAb, exhibited potent activity across cell lines with low, medium, and high CLDN18.2 expression (Fig 5) and promoted G2/M cell cycle arrest (Fig 6A) and apoptosis (Fig 6B) in BxPC3-CLDN18.2 pancreatic cancer cells

A



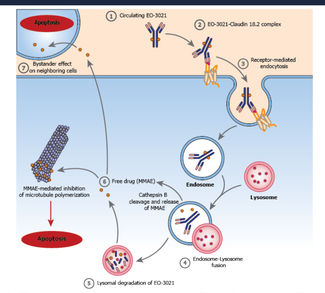
Cell Cycle Distribution post treatment in BxPC3-CLDN18.2, 600 ng/ml, 66-hour treatment

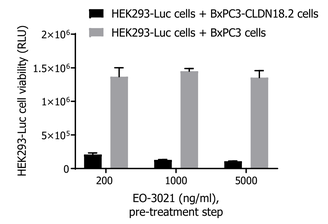
B



Caspase 3/7 Activity post treatment in BxPC3-CLDN18.2, 24-hour treatment

Figure 6. EO-3021 promotes G2/M cell cycle arrest and activates caspase 3/7





EO-3021 Internalization and Bystander Effect HEK-293-Luc cells co-cultured with EO-3021 pretreated BxPC3-CLDN18.2 (Ag positive) or BxPC3 (Ag negative) cells for 96 hours

Figure 7. EO-3021 demonstrates bystander effect on CLDN18.2 negative cells

- EO-3021 induced tumor regressions with a single dose across low, medium, and high CLDN18.2-expressing *in vivo* models and outperformed SOC chemotherapy. EO-3021 mAb did not induce tumor regressions across *in vivo* models

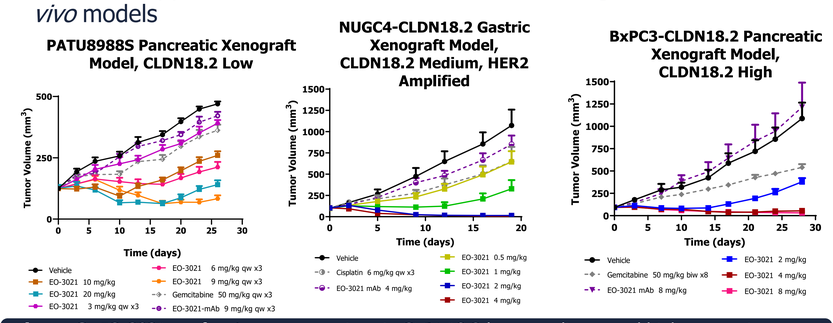
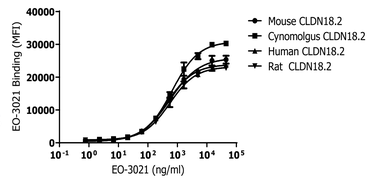


Figure 8. EO-3021 confers tumor regressions in CLDN18.2 low-, medium-, and high-expressing xenograft models

- EO-3021 mAb is cross reactive with major toxicology species
- NHP PK is dose proportional
  - $t_{1/2}$: ~7 days
- General toxicology profile across species is consistent with either MMAE payload or CLDN18.2 targeting in the stomach
- Pharmacology/toxicology profiling suggests EO-3021 can achieve doses in humans that results in anti-tumor activity



EO-3021 mAb Cross Reactivity

Figure 9. Nonclinical toxicology and PK summary of EO-3021

CONCLUSIONS

- EO-3021 demonstrated *in vivo* antitumor activity and outperformed SOC in gastric and pancreatic cancer models
- Results from *in vitro* and *in vivo* studies highlight the promising therapeutic potential of EO-3021 for patients with CLDN18.2-expressing cancers
- A Phase 1 study is ongoing in China to evaluate SYSA1801 in patients with CLDN18.2 positive advanced solid tumors (NCT05009966)
- Elevation Oncology plans to initiate a Phase 1 study of EO-3021 (SYSA1801) in the US in H2 2023

REFERENCES

1. Türechi et al. Gene. 2011; 83-92.
2. Sahin et al. Clin Cancer Res. 2008; 14(23).
3. Schuler MH et al. J Clin Oncol. 2017. 35:15_suppl 4038-4038.

Abbreviations: ADC, antibody-drug conjugate; ADCC, antibody dependent cellular cytotoxicity; Ag, antigen; CDC, complement dependent cytotoxicity; ECL1, Extracellular Loop 1; IgG1, immunoglobulin G1; Luc, luciferase; mAb, monoclonal antibody; MFI, median fluorescent intensity; MMAE, monomethyl auristatin E; NHP, non-human primates; PK, pharmacokinetics; RLU, relative light units; RFU, relative fluorescence units; SOC, standard of care; $t_{1/2}$, half-life

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