EO-3021: An antibody drug conjugate targeting CLDN18.2 expressing cancers

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Disclosure Information

David Dornan

I have the following relevant financial relationships to disclose:
   Employee of: Elevation Oncology, Inc.
   Consultant for: ReviR Therapeutics, Inc., Teon Therapeutics, Inc.
   Stockholder in: Elevation Oncology, Inc.

I will discuss investigational use in my presentation: EO-3021/SYSA1801/CPO102 in the Treatment of CLDN18.2 Positive Advanced Malignant Solid Tumors
Claudin 18.2 Expression Profile Confers Selectivity for Therapeutic Intervention

- Claudin 18.2 is part of a family of tight junction membrane proteins
- Claudin 18.2 expression in normal tissues is restricted to the gastric mucosa with basolateral localization
- During malignant transformation, changes in cell polarity may result in exposure of Claudin 18.2
- Claudin 18.2 is overexpressed in several types of cancers including gastric, pancreatic, esophageal, ovarian, and lung
- Claudin 18.2 expression has minimal overlap (<20%) with HER2 or PD-L1 expression in gastric cancer
- No approved therapies targeting Claudin 18.2
### Estimated Incidence of Claudin 18.2 in Solid Tumors

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated New Cancer Cases</th>
<th>Claudin 18.2 expression per disease type (IHC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>US Incidence¹</td>
<td>Global Incidence²</td>
</tr>
<tr>
<td>Gastric</td>
<td>26,500</td>
<td>1,090,000</td>
</tr>
<tr>
<td>Esophageal</td>
<td>21,500</td>
<td>604,000</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>64,000</td>
<td>496,000</td>
</tr>
<tr>
<td>Ovarian</td>
<td>20,000</td>
<td>314,000</td>
</tr>
<tr>
<td>Lung</td>
<td>238,000</td>
<td>2,207,000</td>
</tr>
</tbody>
</table>

*Any level of expression (e.g., ≥1% cells with any staining intensity of CLDN18.2)

Abbreviations: US, United States; IHC, Immunohistochemistry; PDAC, Pancreatic ductal adenocarcinoma

Examples of CLDN18.2 Targeted Therapy Modalities

**Monoclonal mAbs**
- zolbetuximab
- FL-301

**Bispecific mAbs**
- AMG-910 (CD3)
- FL-302 (CD137)
- PT886 (CD47)
- Q-1802 (PD-L1)
- TJ033721 (4-1BB)

**CAR T-cell**
- CT041
- LCAR-C18S
- LY011

**Antibody Drug Conjugates**
- EO-3021/SYSA1801/CPO102
- CMG901
- RC118
- LM302
- SOT102
- SKB315
- TORL-2-307
- JS107
- IBI343

Abbreviations: mAb, monoclonal antibody
Not an exhaustive list of all publicly disclosed programs
Mechanism of Action for Antibody Drug Conjugates

1. ADC circulates in the blood plasma
2. Antigen-ADC complex
3. Receptor-mediated endocytosis
4a. Recycling of antigen or Antigen-ADC complex
4b. Late endosome Drug release from cleavable linkers
5. Endosome-lysosome fusion
6. Lysosomal degradation Drug release from cleavable and non-cleavable linkers
7. Free drug
8. Bystander killing of neighboring cell

Modified from Tong et al. (2021) https://doi.org/10.3390/molecules26195847
EO-3021 mAb is Specific for CLDN18.2 over CLDN18.1

EO-3021 mAb:
- Fully Human mAb
- IgG1 Isotype
- Kd = 0.6 nM for CLDN18.2
- No binding to CLDN18.1

Abbreviations: ECL1, Extracellular Loop 1; ECL2, Extracellular Loop 2; IgG1, immunoglobulin G1; TM, Transmembrane
EO-3021 is ADCC and CDC Competent: Modest Differences Relative to Unconjugated mAb

Abbreviations: ADCC, antibody dependent cellular cytotoxicity; CDC, complement dependent cytotoxicity
EO-3021-Mediated Endocytosis and Reduction of Cell Viability is Dependent on CLDN18.2 Expression

**Endocytosis of Fluorescent Labeled EO-3021**

HEK293  HEK293-CLDN18.1  HEK293-CLDN18.2

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

**EO-3021 Impact on Cell Viability**

IC$_{50}$ = 100 ng/ml

Test article (ng/ml)

Cell Viability (RFU)

EO-3021 Tx (varying concentration), 72-hour incubation, resazurin assay
EO-3021 in vitro Activity More Notable in Cell Lines with Medium or High Levels of CLDN18.2 Expression

EO-3021 Promotes G2/M Cell Cycle Arrest and Activates Caspase 3/7

Cell Cycle Distribution Post-Tx

- G1
- S
- G2/M

BxPC3-CLDN18.2, 600 ng/ml Tx, 66±3 hours

Caspase 3/7 Activity Post-Tx

- EO-3021 mAb
- EO-3021

BxPC3-CLDN18.2, 24±3 hours
EO-3021 Demonstrates Bystander Effect on CLDN18.2 Negative Cells

Abbreviations: Ag, antigen

HEK-293-Luc cells co-cultured with either BxPC3-CLDN18.2 (Ag positive) or BxPC3 (Ag negative) cells and Tx for 96 hours
Single Dose of EO-3021 Confers Tumor Regressions in CLDN18.2 High Expressing Xenograft Model

BxPC3-CLDN18.2 Pancreatic Xenograft Model
CLDN18.2 High

Nu/nu mice were administered single dose of Tx, unless otherwise indicated. Dosing initiated on Day 0.
Single Dose of EO-3021 Confers Tumor Regressions in CLDN18.2 Medium Expressing Xenograft Model

**NUGC4-CLDN18.2 Gastric Xenograft Model**

CLDN18.2 Medium, HER2 Amplified

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**Graph Description:**

- **Y-axis:** Tumor Volume (mm³)
- **X-axis:** Time (days)
- **Legend:**
  - Vehicle
  - EO-3021 0.5 mg/kg
  - EO-3021 1 mg/kg
  - EO-3021 2 mg/kg
  - EO-3021 4 mg/kg
  - Cisplatin 6 mg/kg qw x3
  - EO-3021 mAb 4 mg/kg

**Legend Note:**

- Mice were administered single dose of Tx, unless otherwise indicated. Dosing initiated on Day 0.
Single Dose of EO-3021 Confers Tumor Regressions in CLDN18.2 Low Expressing Xenograft Model

Nu/nu mice were administered single dose of Tx, unless otherwise indicated. Dosing initiated on day 0.
Nonclinical Toxicology and PK Summary of EO-3021

- EO-3021 mAb is cross reactive with major toxicology species
- NHP PK is dose proportional with $t_{1/2} \sim 7$ days
- General toxicology profile across species (cyno and rat) is consistent with either MMAE payload or CLDN18.2 targeting in the stomach
- Pharmacology/toxicology integrated data suggest EO-3021 can achieve doses in humans that result in anti-tumor activity

### EO-3021 mAb Cross Reactivity

<table>
<thead>
<tr>
<th>Test article (ng/ml)</th>
<th>EO-3021 Binding (MFI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse CLDN18.2</td>
<td></td>
</tr>
<tr>
<td>Cynomolgus CLDN18.2</td>
<td></td>
</tr>
<tr>
<td>Human CLDN18.2</td>
<td></td>
</tr>
<tr>
<td>Rat CLDN18.2</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: MMAE, monomethyl auristatin E; NHP, non-human primates; PK, pharmacokinetics; $t_{1/2}$, half-life
EO-3021/SYSA1801 Activity in a Patient with Gastric Cancer

- **Patient:** 47-year-old female with gastric cancer
- **Metastases:** lymph nodes
- **Prior therapy:** XELOX (oxaliplatin + capecitabine) with immunotherapy
- **EO-3021 treatment:** 1.0 mg/kg IV Q3W x 12 cycles (ongoing)
- **Target Lesion:** Retroperitoneal lymph node
- **RECIST v1.1:** Best overall response of confirmed partial response (66.7% maximal tumor reduction)
- **Duration of response:** ~11 months (ongoing)
- **Clinical Trial:** Phase I (NCT05009966)

EO-3021 is under investigation in a clinical trial and has not been approved for any indication by a regulatory administration.
EO-3021 Summary

- Antibody drug conjugate composed of a fully human IgG1 CLDN18.2 selective mAb conjugated at Q295 with a vcMMAE linker payload to give DAR2
- Promotes cell killing of cell lines expressing CLDN18.2 and a consequential bystander effect on CLDN18.2 negative cells
- Robust in vivo activity in xenografts with varying levels of CLDN18.2
  - Single dose tumor regressions in models with varying levels of CLDN18.2 with a lower minimal efficacious dose in models with medium and high levels of CLDN18.2 relative to models with low CLDN18.2
- Pharmacology/toxicology integrated data suggest EO-3021 can achieve doses in humans that results in anti-tumor activity
- Confirmed PR (66.7% reduction) with 11 months (and ongoing) duration of response in a patient living with metastatic gastric cancer in an ongoing Phase I clinical trial (NCT05009966)
- Elevation Oncology sponsored Phase I trial to initiate in US 2H 2023
Acknowledgements

CSPC
- Mo Dan
- Xiwu Hui
- Yancui Wang
- Can Yuan
- Yang Zhang
- Xiaoyan Wang
- Charles Wang

Elevation Oncology
- Thomas O’Hare
- Jaya Srivastava
- Valerie Jansen
- Shawn Leland
- Joe Ferra

Peking University Cancer Hospital & Institute
- Yakun Wang
- Jifang Gong
- Lin Shen