# HITM-SURE: Phase Ib CAR-T hepatic artery infusion trial for stage IV adenocarcinoma using Pressure-Enabled Drug Delivery technology

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HITM
HEPATIC IMMUNOTHERAPY FOR METASTASES

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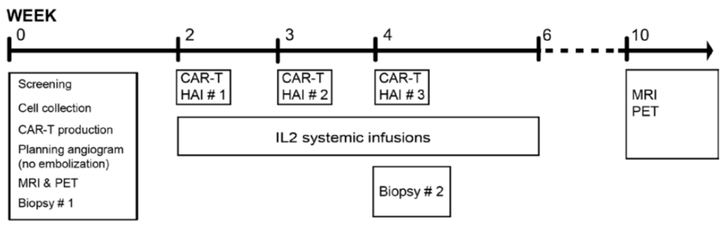
**BACKGROUND**: Prior Hepatic Immunotherapy for Metastases (HITM) phase I/Ib studies demonstrated the safety and biologic activity of anti-CEA CAR-T cell hepatic artery infusions (HAI) for CEA liver metastases (LM). Here we report preliminary HITM-SURE data using Pressure-Enable Drug Delivery (PEDD) technology for HAI to overcome high intra-tumoral pressures.

**METHODOLOGY**: Candidates had unresectable CEA+ LM and failed > 1 line of systemic chemotherapy. Enrolled patients received 3 HAI of 10^10 second generation (IgCD28TCR) anti-CEA CAR cells (Sorrento Therapeutics) via a PEDD (Surefire Medical) device and low dose IL-2 (50,000 IU/kg/day). Objectives were to evaluate the safety profile of CAR-T HAI with PEDD and to secondarily assess clinical response.




**RESULTS**: At study conclusion, 4 male and 1 female pts completed treatment—mean age 55.8 yrs (38-64) with 1-6 lines of prior chemotherapy. There was an average of 7.4 LM with an average maximal diameter of 2.8 cm. Mean CAR expression was 68.1% and production time of 11.8 d. *In vitro* targeted cytotoxicity was 41%. Reduction in serum CEA was observed in all pts during the study period (avg decrease 44%, range 13-67%). Compared to previous HITM CAR-T HAI trials with a standard catheter, PEDD significantly increased the frequency of CAR-T 5.2-fold within LM, as detected by quantitative PCR (p=0.03). No Grade (G) 4 or 5 AEs related to CAR-T HAIs via PEDD were detected. G1/2/3 events were largely attributed to IL-2 infusion and were comparable to prior HITM studies. One pt experienced grade 3 colitis, which resolved with IL-2 dose reduction and had colon biopsies that were negative for CAR-T by PCR and immunofluorescence. Twelve-month follow-up imaging in one pt with stage IV pancreatic carcinoma revealed no evidence of LM on PET and his primary pancreatic tumor was stable. Serum and LM biopsies from this pt reveal increased expression of IFN-g and IL-6 in LM, with decreased expression of IL-17, PD-L1, IDO and GM-CSF. A second pt with stage IV pancreatic cancer had no evidence of LM on PET at 6 weeks following CAR-T infusions. Mean and median survival times were 9.3 and 7.5 months for all patients, and 10.0 and 8.4 months for subjects with stage IV pancreas cancer.

| ID | SEX | AGE | DX | Chemo (#) | # LM | Max LM (cm) | EHD | CEA (ng/ml) | CAR-T DOSES |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 52 | Pancreas | FOLFIRINOX (1) | 7 | 2.5 | No | 18.5 | 4[a] |
| 2 | M | 62 | Pancreas | FOLFIRINOX (1) | 4 | 1.1 | Lung | 6.6 | 3 |
| 3 | M | 38 | Pancreas | FOLFIRINOX, Gem/Abr (2) | 10 | 3.8 | Pancreas | 31 | 3 |
| 4 | M | 64 | Rectal | FOLFOX, FOLFIRI/Bev, FOLFIRI/Pan (3) | 10 | 3.8 | Lung Bone | 8.8 | 3 |
| 5 | F | 63 | Pancreas | Gem/Pac, Gem/NabPac, FOLFIRINOX, FOLFOX, FOLFIRI, 5-FU/LI (6) | 6 | 2.5 | Pancreas | 31.7 | 3 |
| Mean (SD) | | 55.8 (11.1) | N/A | 2.6 (2.1) | 7.4 (2.6) | 2.8 (1.1) | N/A | 19.3 (11.9) | 3.2 (0.4) |

***Table 1 – HITM-SURE Patient Characteristics.*** Five patients with stage IV, chemotherapy-resistant, CEA+ adenocarcinoma liver metastases (LM) were enrolled, four of which had primary pancreatic adenocarcinoma. Lines of chemotherapy are listed, along with the number of LM, size of the largest LM, and the presence of any extrahepatic disease (EHD) apart from the primary tumor. Serum CEA at the time of enrollment and the number of CAR-T doses given during study are listed to the right.

[a]Patient received an additional CAR-T infusion 13 months after 1st CAR-T dose.

*Abr = abraxane; Bev= bevacizumab; Gem = gemcitabine; LI = liposomal irinotecan; NabPac = Nab-paclitaxel; Pan = panitumumab; Pac = paclitaxel*

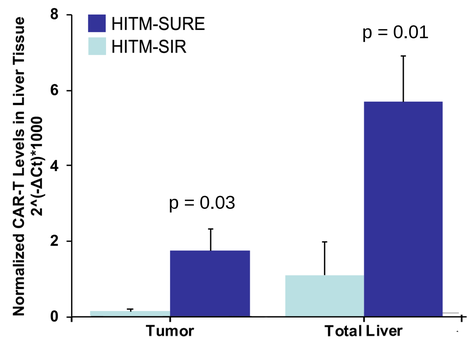



***Figure 1 – Pressure-enabled drug delivery technology results in significantly increased delivery of CAR-T.*** Quantitative PCR detection of CAR-T transgene, in tumor (left) and total liver (right) biopsy specimens obtained after standard infusion catheter (HITM-SIR) versus pressure-enabled drug delivery (HITM-SURE).

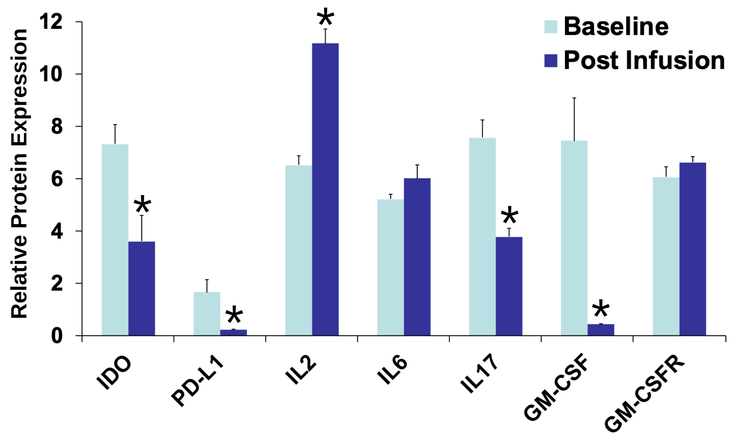
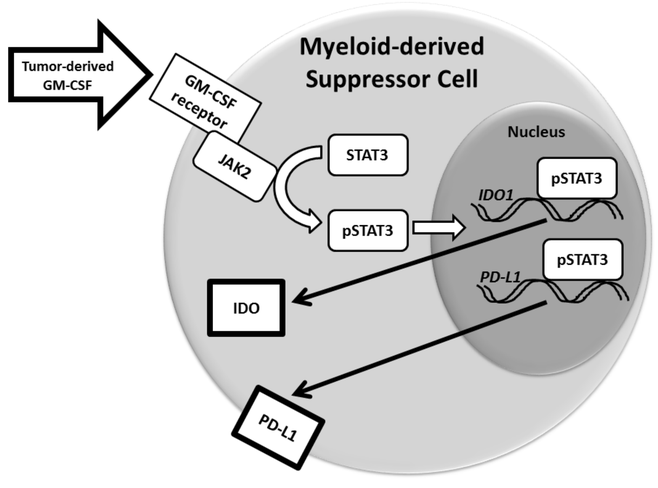



***Figure 2 – Reduced expression of immunomodulatory molecules after hepatic artery infusion of CAR-T.*** Based on pre-clinical observations, which suggest GM-CSF-STAT3 mediated upregulation of IDO and PD-L1 by MDSC in the hepatic tumor microenvironment (mechanism depicted below), we compared protein expression among baseline and post-infusion LM tumor biopsy specimens (Western blot densitometry normalized to GAPDH, above). Asterisk denotes p<0.05.




Thorn et al, *Cancer Gene Therapy* (2016) **23,** 188-198.

| ID | TdEff CAR+ (%) | Viability (%) | Production Time[a] (days) | Anti-CEA Cytotoxicity (% lysis) |
|---|---|---|---|---|
| 1 | 60.9% | 81.8% | 10 | 24.4 |
| 2 | 59.6% | 90.0% | 15 | 47.4 |
| 3 | 64.7% | 86.7% | 9 | 47.2 |
| 4 | 73.7% | 89.6% | 14 | 27.2 |
| 5 | 81.8% | 85.4% | 11 | 58.9 |
| Mean± StDev | 68.1±9.4% | 86.7±3.4% | 11.8±2.6 | 41±14.7 |

***Table 2 – CAR-T Production Metrics and Quality Assessment.*** CAR-T transduction efficiency (TdEff), viability, production time, and in vitro killing of CEA+ target tumor cells by anti-CEA CAR-T measured by LDH release.

[a]Days post-transduction required to reach cell number target of > 30 x $10^9$

This study was approved by the Roger Williams Medical Center Institutional Review Board, approval number 16-350-74.
Funded in part by the Colorado Office for Economic Development and International Trade.

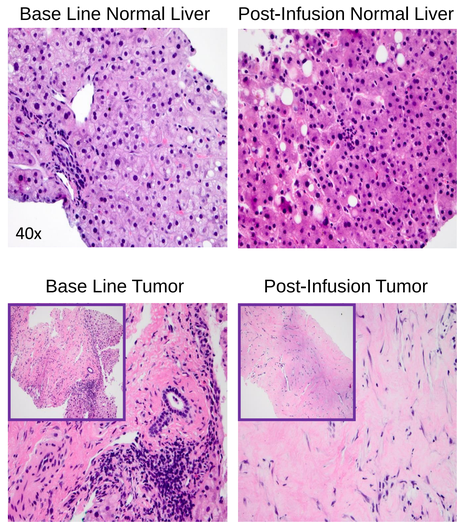



***Figure 3 (above) – Post-infusion Tumor Fibrosis.*** Core needle biopsies of normal liver (top) and liver metastasis (bottom), taken from Patient 1 before (left) and after CAR-T HITM-SURE infusions (right). H&E staining shows increase in necrosis/fibrosis in tumor but not normal liver. 40X and 20X inset.

***Table 4 (right) – HITM-SURE Adverse Event Reporting.*** AEs listed by severity (1-4), where shaded boxes represent AE that prompted dose reduction in IL-2 infusion. Yellow signifies 25% dose reduction, orange is 50% reduced dose, and those in red had IL-2 temporarily discontinued, but was later resumed.

| Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | |
|---|---|---|---|---|---|
| 1 | | 2 | | | Abdominal Cramping |
| 1 | | 2 | | | Abdominal Distention |
| | | 2 | | 1 | Acute Kidney Injury |
| | | | 1 | | Alopecia |
| | | 1 | 3 | | Anemia |
| | 2 | | | | Anorexia |
| | | | | 3 | Ascites |
| 1 | 1 | 1 | 1 | 1 | Coagulopathy |
| | | 3 | 2 | | Colitis |
| | | 3 | | | Cytokine Release Syndrome |
| 3 | | 2 | | | Dehydration |
| | | | | 1 | Depression |
| 2 | 2 | | 2 | 1 | Diarrhea |
| | | | 1 | | Elevated Creatinine |
| 2 | 1 | 1 | | | Elevated Alkaline Phosphatase |
| 2 | 1 | 2 | 1 | 2 | Fatigue |
| 3 | 2 | 2 | 1 | 2 | Fever |
| | | | | 1 | Hallucinations |
| 2 | | 3 | | 1 | Hyperbilirubinemia |
| | 1 | | NA | NA | Hypereosinophilia |
| 3 | | | | | Hyperglycemia |
| | | | 1 | | Hypernatremia |
| 3 | 3 | | 3 | 3 | Hypertension |
| 2 | 2 | 2 | | 2 | Hypoalbuminemia |
| | | 1 | | | Hypocalcemia |
| 3 | 1 | 1 | 1 | 1 | Hypokalemia |
| 1 | | 1 | | 1 | Hypomagnesemia |
| 3 | 1 | 3 | | 1 | Hyponatremia |
| 3 | | 4 | | | Hypophosphatemia |
| 2 | | 3 | | 2 | Hypotension |
| | 3 | | 1 | 3 | Hypoxia |
| | | | 3 | | Leukocytosis |
| | | | | 1 | Leukopenia |
| 1 | 1 | 2 | 1 | 1 | Lower Extremity Edema |
| | | | 1 | | Nausea |
| | | | 1 | | Pleural Effusion |
| | | | | 3 | Pneumonia |
| 2 | | | | | Pulmonary Edema |
| 2 | | | | | Rigors |
| | | 3 | | | Septic Shock |
| 1 | 2 | 1 | | 1 | Tachycardia |
| 1 | 2 | 1 | | 2 | Thrombocytopenia |
| 2 | | 1 | 1 | | Transaminitis |
| | | | | 3 | Urinary Tract Infection |
| | 1 | | | | Vomiting |
| | | | | 1 | Wound Complication (Groin) |

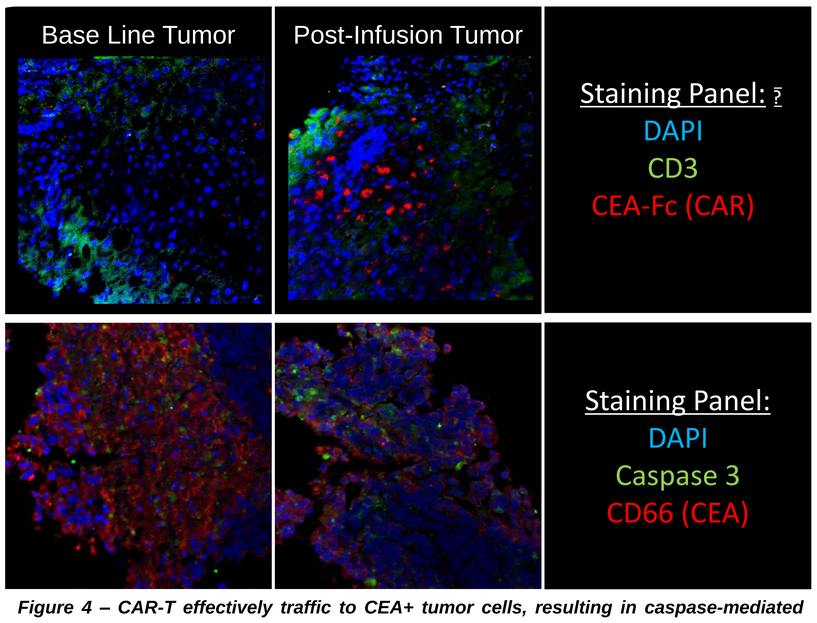



***Figure 4 – CAR-T effectively traffic to CEA+ tumor cells, resulting in caspase-mediated apoptosis.*** Immunofluorescence microscopy of liver tumor biopsies at baseline (left) and post-CAR-T treatment (right). Upper panels from Patient 1 demonstrate trafficking of CAR-T to tumor after infusion. Lower panels from Patient 5 demonstrate decreased frequency of CEA+ tumor cells and ongoing apoptosis.

| ID | mRECIST Liver | mRECIST Total | irRC Liver | irRC Total | Post-Tx PET | Vital Status | Overall Survival (mo) |
|---|---|---|---|---|---|---|---|
| 1 | SD | SD | PR | SD | CR | AWD | 19.3 |
| 2 | PD | PD | PD | PD | PD | DOO | 9.1 |
| 3 | PD | PD | PD | PD | PD | DOD | 7.5 |
| 4 | PD | PD | PD | PD | PD | AWD | 6.4 |
| 5 | PD | PD | PD | PD | CR | DOD | 3.9 |
| Stable disease (SD), Partial response (PR), Progressive disease (PD) Alive with disease (AWD), Death by disease (DOD), Death by other cause (DOO) | | | | | | | Mean OS 9.3 Median OS 7.5 |

***Table 5 – Overall Survival and Treatment Responses by mRECIST and irRC Criteria.***

**CONCLUSION**: Early results from the HITM-SURE study indicate that HAI of CAR-T using PEDD is well tolerated and results in encouraging activity against CEA+ LM. The median OS compares favorably with prior HITM studies and presently approved second/third line regimens. Final results will inform design and device choice for larger studies. NCT02850536