Clinical results of a phase 1 trial evaluating a HER2 directed CAR-T product selective for the tumor microenvironment (TME) in patients with GI and other solid tumor malignancies

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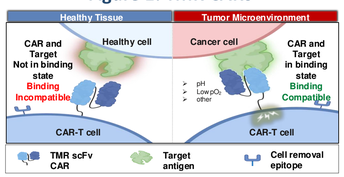
BACKGROUND

HER2 is amplified in many solid malignancies and expression is frequently retained following multiple lines and modalities of HER2 targeted therapy. The shared expression of HER2 in healthy and malignant tissue, raises the risk of on-tumor off-target toxicity (OTOTT) with HER2 targeted therapies. Exploiting the unique attributes of the the tumor microenvironment for tumor metabolism regulated (TMR) CARs may safely expand the universe of solid tumor targets.

TMR CARs:

- Address exposure dependent risk of OTOTT
- Reversibly exploit metabolically distinct characteristics within the tumor microenvironment for improved binding selectivity
- Designed to improve the therapeutic index, permitting increased exposure in the setting of "over-expressed" tumor associated antigens

Figure 1: TMR CARs



METHODS

Trial Design

This Phase 1, dose escalation, basket trial (NCT04511871) evaluated the safety, tolerability, pharmacokinetics, and efficacy of the autologous CAR-T product CCT303-406 in 12 Pts with HER2 IHC 3+ / FISH 2+, Stage IV, r/r solid tumors (gastric, esophageal, colorectal, breast)

- Dose cohorts of 3E5 (n=3), 1E6 (n=3), or 1E7 (n=6) CAR-T cells/kg were evaluated with a 28-day in-patient DLT observation period
- Cell product was manufactured from whole blood with a 12-day closed process (release day 17)
- Lymphodepletion regimen of 500 mg/m^2 Cy and 30 mg/kg Flu x 3 days

Figure 2: CCT303-406 Trial Design for Patients with HER2+ Malignancies

Screening

Key Eligibility Criteria

18-70 years

- Stage IV advanced solid tumor malignancies that have failed standard of care treatment
  - Relapsed malignancies confirmed by histology
  - Measurable lesion ≥15 mm
- HER2 IHC 3+ / FISH 2+
- ECOG performance status 0 or 1

Objectives

Primary Endpoints

28 days

- Dose limiting toxicities by cohort

Secondary

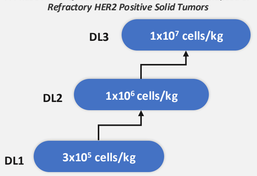
52 weeks

- ORR, incidence, severity and duration of adverse events, PK by cohort

Completion of 12-patients through primary endpoint triggers safety, efficacy and durability evaluation

Design

A Phase I Trial of CCT303-406 in Patients With Relapsed or Refractory HER2 Positive Solid Tumors



Pts = Patients ; r/r = Relapsed Refractory; DLTs = Dose Limiting Toxicities; Cy = Cyclophosphamide; Flu = Fludarabine; ORR = Overall Response Rate; PK = Pharmacokinetics; DL1,2,3 = Dose Level

Table 1: Demographics and Baseline Characteristics

	Subjects (N = 12)
Median age (range), years	51.2 (30-69)
Sex, n (%)	
Female	4 (33)
ECOG PS 0 or 1, n (%)	
1	11 (92)
HER2 positive IHC 3+, n (%)	9 (75)
Patients with prior HER2-directed therapies, n (%)	
HER2 Antibody	10 (84)
HER2 Antibody Drug Conjugate	4 (33)
HER2 Tyrosine Kinase Inhibor	9 (75)
PD1/PDL1 Antibodies	5 (42)

ECOG PS = Eastern Cooperative Oncology Group Performance Status

RESULTS

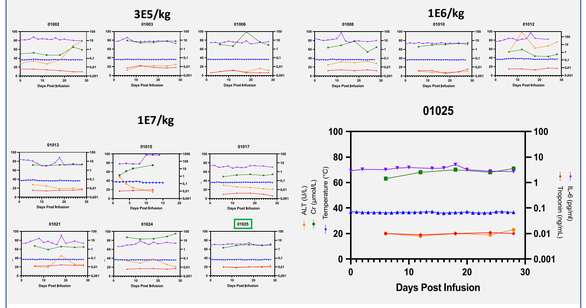
Safety & Pharmacokinetics

Table 2: Serious Adverse Events by Cohort

	Cohort 1	Cohort 2	Cohort 3
Dose (cells/kg)	3x10^5 N=3	1x10^6 N=3	1x10^7 N=6
CRS	0 (0.0%)	0 (0.0%)	1 (16.7%)
ICANS	0 (0.0%)	0 (0.0%)	0 (0.0%)
DLT	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with AE leading to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with AE leading to study discontinuation	0 (0.0%)	0 (0.0%)	0 (0.0%)

CRS = Cytokine Release Syndrome; ICANS = Immune Effector Cell-associated Neurotoxicity Syndrome; AE = Adverse Events

Figure 3: In-patient Longitudinal Safety Assessments



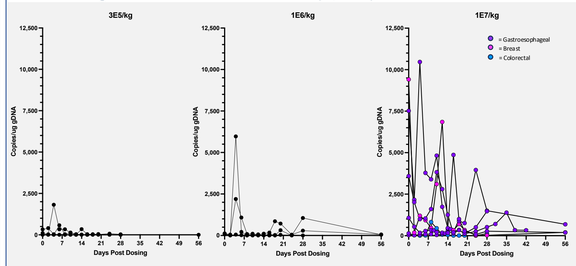
ALT = Alanine Transaminase; Cr = Creatinine

CCT303-406 safety:

- No DLTs, No SAEs, No AEs leading to death or study discontinuation
- 1 patient developed CRS (Grade 2) and recovered
- Lymphodepletion-related Grade 3 or higher AEs included white blood cell count decrease, lymphocyte count decrease
- 2 patients with investigational product-related Grade 3 or Higher AEs
  - ➢ Patients had longitudinal assessment of on-target, off-tumor toxicity for organs of special interest during in-patient observation

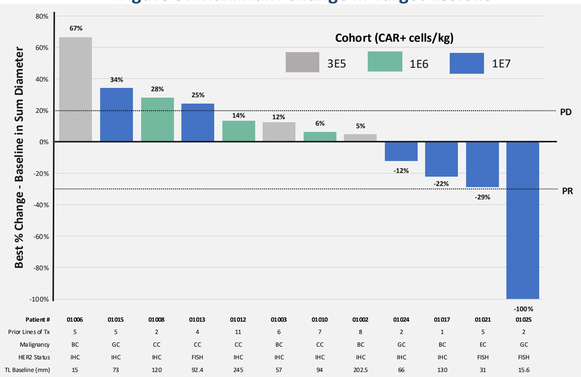
SAE = Serious Adverse Events

Figure 4: Pharmacokinetics (QPCR) Data Per Patient



Efficacy

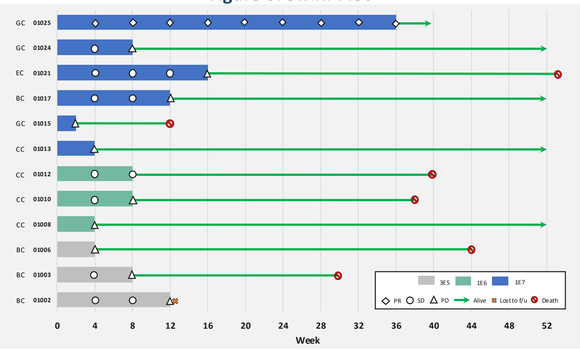
Figure 5: Maximum Change in Target Lesions



Patient #	01006	01015	01008	01013	01012	01003	01010	01002	01024	01017	01021	01025
Prior Lines of Tx	5	5	2	4	11	6	7	8	2	1	5	2
Malignancy	BC	GC	CC	CC	CC	BC	CC	BC	GC	BC	EC	GC
HER2 Status	IHC	IHC	IHC	FISH	IHC	IHC	IHC	IHC	IHC	IHC	FISH	FISH
TL Baseline (mm)	15	73	120	92.4	245	57	94	202.5	66	130	31	15.6

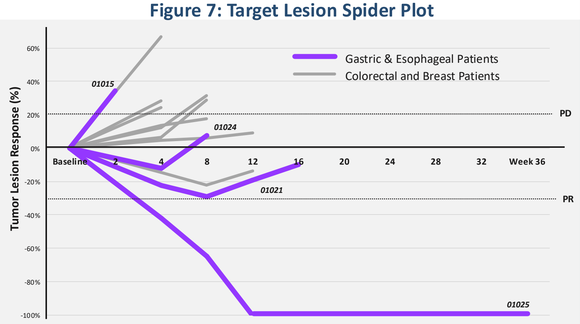
Tx = Therapy; BC = Breast Cancer; GC = Gastric Cancer; CC = Colorectal Cancer; EC = Esophageal Cancer; PD = Progressive Disease; PR = Partial Response; TL = Tumor Lesion

Figure 6: Swim Plot



PR = Partial Response; SD = Stable Disease; PD = Progressive Disease

Figure 7: Target Lesion Spider Plot



Gastric Cancer Patient (01025):

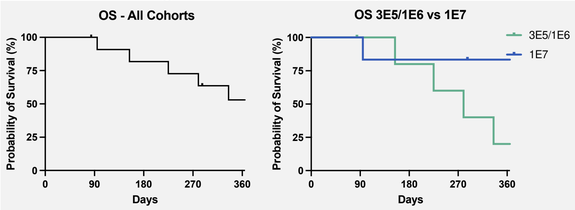
- Prior Tx included – oxaliplatin+trastuzumab+tegafur+sintilimab (14 cycles), FS-1502 (trastuzumab monomethyl auristatin F, investigational)
- Achieved a deep PR sustained for 36 weeks (ongoing)
- Demonstrated a 100% reduction in the SLD of target lesions

Esophageal Cancer Patient (01021):

- Prior Tx included – docetaxel+oxaliplatin, tegafur, trastuzumab+tegafur, pyrotinib+capecitabine, dasitamab vedotin
- Near-maximal reduction in SLD for nodal lesions at 8 weeks
- No evidence of HER2 amplification detected in ctDNA at disease progression (week 16)
- Loss of HER2 amplification upon progression suggests a possible resistance mechanism unrelated to initial HER2 status

SLD = Sum Of Longest Diameter; ctDNA = Circulating Tumor DNA

Figure 8: Overall Survival by Cohort



OS = Overall Survival

Exploratory analysis of 3E5/1E6 vs 1E7 OS

CONCLUSIONS

- Treatment with the autologous tumor metabolism regulated HER2 targeted CAR-T therapy CCT303-406 caused encouraging signals of efficacy in GE patients
  - ➢ Durable response (PR, ongoing at 36 weeks) was observed in a GC patient
  - ➢ Antitumor activity in an EC patient followed by tumor progression with evidence of loss of HER2 expression from ctDNA
- No MTD or DLTs were identified at doses up to 1E7 cells/kg
- ORR was 8% and 25% (PR) for GE cancer patients
- Median PFS was 8 weeks
- 12-month OS rate was 45.5% (5/11) overall and 80% (4/5) for the 1E7/kg dose cohort
- DOR has not been reached at 36 weeks of follow-up
- 1E7/kg was the maximum feasible dose based upon manufacturing considerations with peripheral blood starting material. Strategies that eliminate the limitations of autologous cellular therapy have been implemented with in vivo based CAR generation and ancillary transgenes to further develop this promising approach to solid tumors
- These data support the further clinical investigation of CCT303-406 in patients with HER2+ GE malignancies
- CARs with binding restricted to the tumor microenvironment may have widespread utility to more safely target antigens shared between malignant and healthy tissue

PFS = Progression Free Survival; DOR = Duration Of Response; MTD = Maximum Tolerated Dose; GE = Gastroesophageal

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