Initial Safety of AFP SPEAR T-Cells in Patients with Advanced Hepatocellular Carcinoma

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3183

Introduction

- AFP is an abundant serum protein in the fetus but is transcriptionally repressed shortly after birth
- Reappearance of AFP in the circulation of adults is associated with liver regeneration, hepatitis, chronic liver diseases, or malignant growth[1]
- Elevation of serum AFP is associated with poor prognosis in HCC[2]
- HCC is the third highest cause of cancer-related death globally[3]
- Despite increasing systemic treatment options for patients with advanced HCC, there remains considerable unmet need for new therapies

Objectives

- Evaluate safety and anti-tumor activity in patients with HCC who are being treated with genetically engineered affinity-enhanced autologous SPEAR T-cells (ADP-A2AFP) directed toward the HLA-A*02-restricted AFP peptide FMNKFIYEI[a] in an ongoing phase 1 trial (NCT03132792)
- Present initial safety data from 2 patients from Cohort 1 in this ongoing trial

Methods

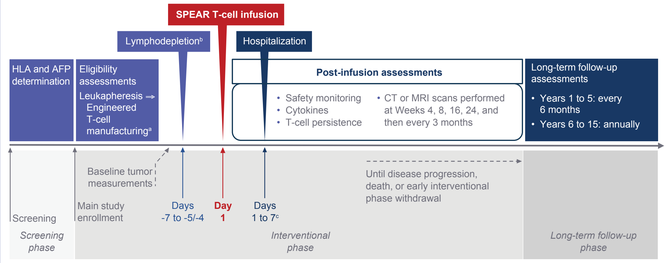
- This is a first-in-human study in HCC patients who were not amenable to transplant, resection, or loco-regional therapy and failed/intolerant/ refused standard-of-care treatment
- Patients must be HLA-A*02:01[+] or HLA-A*02:642[+]
- Evidence of tumor AFP expression is required; based on a protocol amendment, AFP expression can be based on serum AFP level >400 ng/mL or by IHC at ≥1+ staining in ≥20% of HCC tumor cells
  - The original protocol criteria (by which the 2 patients treated were identified) required IHC at ≥2+ staining in ≥40% of HCC tumor cells
- Non-cancerous liver tissue must have ≤5% of cells staining for AFP by IHC
- Additional key inclusion criteria are Child-Pugh score ≤6, ECOG ≤1, and adequate organ function
- Up to 20 patients will be enrolled using a modified 3+3 design

Table 1. Dose escalation

Cohort	No. of Patients	Transduced Cell Doses	Lymphodepletion Regimen	Interval for Safety Review
1	2–6	1 × 10⁹ (range: 0.8–1.2 × 10⁹)	Cy: 500 mg/m²/d × 3 days Flu: 20 mg/m²/d × 3 days	21-day stagger between patients
2[a]	3–6	1 × 10⁹ (range: 0.5–1.2 × 10⁹)	Cy: 500 mg/m²/d × 3 days Flu: 20 mg/m²/d × 3 days	7-day stagger[b]
3	3–6	5 × 10⁹ (range: 1.2–6.0 × 10⁹)[d]	Cy: 600 mg/m²/d × 3 days Flu: 30 mg/m²/d × 4 days[c]	7-day stagger[b]
	Expansion phase: up to 12 patients in total in Cohort 3	5 × 10⁹ (range: 1.2–10.0 × 10⁹)	Cy: 600 mg/m²/d × 3 days Flu: 30 mg/m²/d × 4 days	No stagger[d]

[a]Current stage of study; the SRC approved advancing to Cohort 2 with 2 patients treated in Cohort 1 who completed the DLT observation period
[b]If in Cohort 1 or Cohort 2, 1 out of 3 patients experiences a DLT requiring expansion of an additional 3 patients (n=6), the subsequent observation period in Cohort 2 or Cohort 3 will be increased from 7 days to 14 days for the next 3 patients treated
[c]For patients considered to be at higher risk for refractory thrombocytopenia (eg, cirrhosis and platelet count <100) or have other comorbidities, the low-dose lymphodepletion regimen may be used after approval by the sponsor
[d]Stagger between patients will continue until 3 patients have received the high-dose regimen without DLTs as determined by the SRC

Figure 1. Study design



[a]T-cell selection; lentiviral gene transfer of affinity-enhanced TCR; T-cell expansion
[b]See Table 1
[c]14 days in the UK

Results for Cohort 1 (Data cut-off November 9, 2018)

Table 3. Adverse events and serious adverse events

	AEs (N=2)					AEs Related[c] to T-Cells (N=2)				
	Any Grade[a]	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Activated partial thromboplastin time prolonged	2	1	1	0	0	0	0	0	0	0
Alopecia	2	1	1	–	–	0	0	0	0	0
Anemia	2	1	0	1	0	0	0	0	0	0
Leukopenia	2	0	0	1	1	0	0	0	0	0
Neutropenia	2	0	1	0	1	0	0	0	0	0
Thrombocytopenia	2	1	0	0	1	0	0	0	0	0
Abdominal pain[b]	1	0	0	1	0	0	0	0	0	0
ALT increased	1	1	0	0	0	1	1	0	0	0
AST increased	1	0	1	0	0	1	1	0	0	0
Bile duct obstruction[b]	1	0	0	1	0	0	0	0	0	0
Blood alkaline phosphatase increased	1	0	0	1	0	1	1	0	0	0
Cholangitis	1	0	0	1	0	0	0	0	0	0
Cognitive disorder	1	1	0	0	0	1	1	0	0	0
Fatigue	1	1	0	0	0	0	0	0	0	0
Headache	1	1	0	0	0	0	0	0	0	0
Hyperbilirubinemia	1	0	0	0	1	0	0	0	0	0
Jaundice	1	0	0	0	0	0	0	0	0	0
Lymphopenia	1	0	0	0	1	0	0	0	0	0
Mental status changes	1	0	0	0	0	0	0	0	0	0
Muscular weakness	1	0	1	0	0	1	0	1	0	0
Musculoskeletal pain	1	0	1	0	0	0	0	0	0	0
Nausea	1	1	0	0	0	0	0	0	0	0
Pain in extremity	1	0	1	0	0	1	0	1	0	0
Pyrexia	1	1	0	0	0	1	1	0	0	0
Rash	1	1	0	0	0	0	0	0	0	0
Thrombophlebitis superficial	1	1	0	0	0	0	0	0	0	0
Vomiting	1	1	0	0	0	0	0	0	0	0

[a]There were no Grade 5 AEs; patients are counted once for each term under the most severe grade; AEs with missing severity are only included in Any Grade column. [b]SAE. [c]Related based on investigator assessment

Table 2. Cohort 1 patient characteristics

Patient	Age	Sex	Underlying Liver Disease	Previous Treatments	Lymphodepletion and Dose
1	61	M	HCV cirrhosis treated with antiviral agent and RNA negative	Gemcitabine/ cisplatin, sorafenib, tislelizumab, palliative TACE of large liver lesion	500 mg/m² Cy + 15 mg/m² Flu[a] × 3 days 100 million transduced cells
2	17	M	None	Doxorubicin/ cisplatin, gemcitabine/ oxaliplatin, pembrolizumab, AutoSynVax, avastin, thalidomide/ temodar, XRT lung metastases	500 mg/m² Cy + 20 mg/m² Flu × 3 days 100 million transduced cells

[a]Flu dose reduced due to renal insufficiency per protocol

Table 4. Baseline and peak liver chemistries after T-cell infusion through Week 8

Patient	ALT, U/L		AST, U/L		Alk Phos, U/L		Total Bili, mg/dL	
	BL	Peak	BL	Peak	BL	Peak	BL	Peak
1	14	67	35	65	71	223	0.4	0.9
2	24	60	37	54	87	100	0.6	1.0

BL, baseline

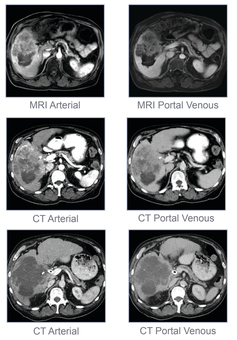
Table 5. Serum AFP expression

Study Time Point	Patient 1 AFP, ng/mL	Patient 2 AFP, ng/mL
Baseline	12,665	25,092
Week 2	29,616	29,229
Week 4	28,012	37,869
Week 8	23,240	48,158
Week 12	16,489	NA[a]
Week 16	18,602	NA[a]
Completion/withdrawal (time)	29,784 (Week 18)	41,186 (Week 12)

NA, not applicable
[a]Patient 2 completed/withdrew at Week 12

Figure 2. Patient 1 baseline imaging and post-treatment results

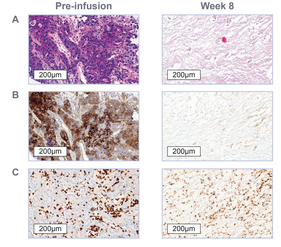
- Week 4: scan shows SD (+5.7%)
- Week 12: scan shows SD (+7.5%) with increasing necrosis
- Week 16: patient had PD; target lesions increased (+15.8%) and new lesions were detected



- Best response by investigator assessment was:
  - SD at 12 weeks in Patient 1
  - SD at 4 weeks in Patient 2

Figure 3. Pre-infusion and post-treatment Week 8 biopsies from Patient 1

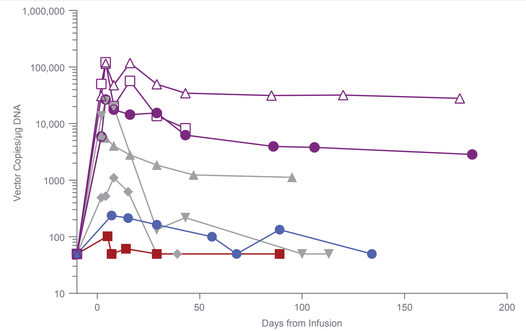
- (**A**) H&E staining shows 80% tumor cells and 1% necrotic cells pre-infusion: Week 8 biopsy shows diffuse tissue necrosis with cholestasis and necrotic cells suspicious for necrotic tumor cells; no viable tissue is present
- (**B**) AFP is present pre-infusion (25% 1+, 40% 2+; 25% 3+); post-infusion shows only background staining of the necrotic tissue, and is non-diagnostic
- (**C**) CD3 staining shows numerous T-cells and T-cell aggregates within the pre-infusion tumor tissue and the post-treatment necrotic tissue



- Pre- and post-treatment biopsies from Patient 2 were also assessed from liver tumor (pre) and metastatic tissue (post)
  - Pre- and post-treatment tumor tissue had few infiltrating CD3 cells and no evidence of necrosis
  - AFP expression was detectable pre- and post-treatment

Figure 4. Persistence of transduced T-cells in the peripheral blood as measured by qPCR

- ADP-A2AFP–treated patients are presented in comparison with patients in a dose-escalation trial utilizing an affinity-enhanced TCR targeting MAGE-A4 (ADP-A2M4; NCT03132922); ADP-A2M4 patients received a more potent lymphodepletion regimen (Cy 600 mg/m² + Flu 30 mg/m² × 3 days)
  - ADP-A2AFP at 100 million transduced cells
  - ADP-A2M4 at 100 million transduced cells
  - ADP-A2M4 at 1 billion transduced cells



Conclusions

- ADP-A2AFP at the 100 million transduced cell dose showed no evidence of clinically significant hepatotoxicity in the first 2 patients
  - Grade 4 hyperbilirubinemia first reported at Week 9 due to bile duct obstruction
- SAEs included abdominal pain and bile duct obstruction, both considered unrelated to ADP-A2AFP (as of November 9, 2018)
- No protocol-defined DLTs were reported
- Most AEs were consistent with those typically experienced by cancer patients undergoing cytotoxic chemotherapy or other cancer immunotherapies
- The SRC approved advancing to Cohort 2 after treating 2 patients based on overall benefit:risk
- Imaging and post-treatment biopsy for Patient 1 showed evidence of a tumor necrosis with lymphocytic infiltration, concurrent with a transient decrease in serum AFP
- ADP-A2AFP gene-modified SPEAR T-cells were detectable in the peripheral blood at low levels
- Higher dose lymphodepletion will be explored in Cohort 3
- One patient in Cohort 2 has been treated with 1 billion transduced cells with no SAEs reported and no evidence of liver toxicity as of Week 2

Abbreviations

AE, adverse event; **AFP,** alpha-fetoprotein; **Alk phos,** alkaline phosphatase; **ALT,** alanine aminotransferase; **AST,** aspartate aminotransferase; **Bili,** bilirubin; **Cy,** cyclophosphamide; **DLT,** dose-limiting toxicity; **ECOG,** Eastern Cooperative Oncology Group; **Flu,** fludarabine; **HCC,** hepatocellular carcinoma; **HCV,** hepatitis C virus; **HLA,** human leukocyte antigen; **IHC,** immunohistochemistry; **PD,** progressive disease; **qPCR,** quantitative polymerase chain reaction; **SAE,** serious adverse event; **SD,** stable disease; **SPEAR,** specific peptide enhanced affinity receptor; **SRC,** Safety Review Committee; **TACE,** transarterial chemoembolization; **TCR,** T-cell receptor; **XRT,** radiation (x-ray) therapy

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