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Phase I Study of LioCyx-M, Autologous Hepatitis B Virus (HBV)-Specific T cell receptor (TCR) T-cells, in Recurrent HBV-Related Hepatocellular Carcinoma (HCC) Post-Liver Transplantation

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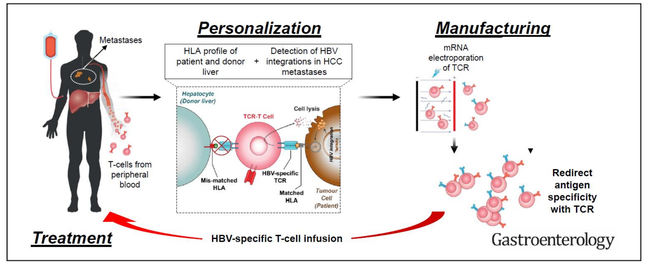
INTRODUCTION

- Although liver transplantation is the one of the curative treatment options for early-stage hepatocellular carcinoma (HCC) patients, tumor recurrence still occurs in 15 to 20% of these patients with a poor median survival [1]. Currently, there is no standard treatment for this sub-population of patients.
- We have identified unique T cell receptors (TCRs) that have the capability to recognize hepatitis B virus (HBV) antigens expressed on HBV-infected cells. Recently, we have shown in a compassionate setting with patients with HCC recurrence post-liver transplant that these cells were able to recognize and lyse hepatocellular carcinoma (HCC) cells expressing HBV antigens derived from HBV-DNA integration [2].
- LioCyx-M is an immunotherapeutic product composing of autologous T cells transiently modified with in-vitro transcribed mRNA encoding one of the four HBV antigen-specific TCRs to generate 4 product derivatives: LioCyx-M001, -M004, -M005 or -M007.
- We first determined if the patient's HLA matched the HLA-restriction of one of the TCRs, and with the use of our in-house clinical trial assay with qPCR, we were able to better match the patients to the specific TCR based on epitope expression in liver tumor.
- Here, we report our phase I study aimed to determine the feasibility, safety and preliminary efficacy of LioCyx-M in patients with recurrent HBV-related HCC post-liver transplantation.



(Tan et al, Gastroenterology 2019)

STUDY DESIGN AND PROCEDURE

Patient population

- Age 18-65
- Presence of recurrent HCC after liver transplantation
- Seropositive for HBsAg or IHC confirmation of HBsAg+ in liver sample obtained during transplantation
- Matched HLA class I profile HLA typing (HLA-C*0801, A*0201, A*1101, B*5801)
- ECOG performance status of 0-2
- Life expectancy of at least 3 months
- No major post-operative complication

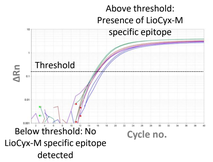
HBV positive & HLA matched

TCR epitope matching Assay

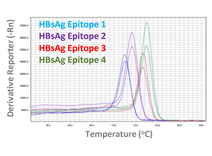
RNA extraction + cDNA synthesis

Liver tumor sample obtained during transplantation

qPCR Amplification Curve



qPCR Melt Curve Analysis



Personalized treatment

LioCyx-M1 LioCyx-M2 LioCyx-M3 LioCyx-M4

✓ HBV epitope present in tumors are recognized by TCR used in selected LioCyx-M product

Primary endpoint
To assess the safety and tolerability of LioCyx-M

Secondary endpoint
To assess the anti-tumor efficacy of LioCyx-M

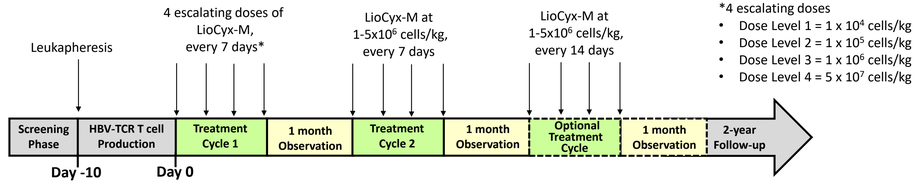
Safety Assessments

- Adverse events evaluated according to NCI CTC version 4.0

Response evaluation

- Overall Response Rate (per RECIST 1.1)
- Serum AFP level changes from baseline
- Time to progression
- Overall survival

Figure 2. Schematic of Study Design



RESULTS

Table 1. Patient Characteristics, Safety and Efficacy Data (Data cut-off on 30 April 2020)

ID	Age	Gender	Previous systemic treatment	Concomitant Immuno-suppressive drug	LioCyx-M IP received	Total dose administered	HBV TCR T cell associated AE		Best overall response	TTP	OS	Current Status
							Probably or possibly AE	Associated dose				
201-001	43	Male	Sorafenib	Tacrolimus	LioCyx-M004	10	Grade 1 Fever	5x10^6/kg	PD	1.47	11.70	Deceased
201-002	35	Male	Sorafenib	Mifu Rapamycin	LioCyx-M001	4	Nil	NA	PD	1.23	14.70	Deceased
201-003	36	Male	Lenvatinib	Sirolimus	LioCyx-M004	9	Grade 1 Fever	1-5x10^6/kg	PD	1.60	12.43	Deceased
201-004	47	Male	Nil	Tacrolimus	LioCyx-M007	4	Nil	NA	PD	0.03	3.03	Deceased
201-005	32	Female	Sorafenib; Fluorouracil +oxaliplatin	Sirolimus	LioCyx-M004	4	Grade 1 Fever	1x10^4/kg	Nil	3.33	3.33	Deceased
							Grade 1 Fever	5x10^6/kg				
201-006	28	Male	Nil	Sirolimus Tacrolimus	LioCyx-M005	12	Nil	NA	PD	1.20	N.A	Alive

AE: Adverse events; IP: Investigational product; NE: Not evaluable, OS: Overall survival, PD: Progressive disease; TTP: Time to progression

Figure 3. Swimmer plot with each bar representing the survival time for the four evaluable patients* from the start of LioCyx-M treatment to data cut-off on 30 April 2020.

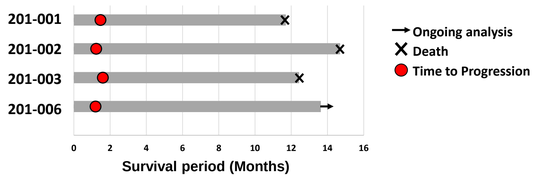
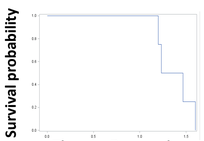
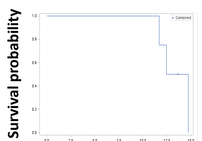


Figure 4. Kaplan-Meier curves for Time-to-Progression (TTP) (left) and overall survival (OS) (right) as of cut-off on 30 April 2020.



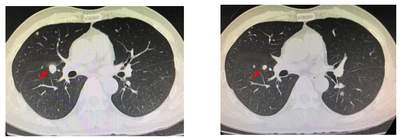
Median TTP*: 1.35 months (90% CI: 1.20, 1.60)



Median OS*: 13.57 months (90% CI: 11.70, 14.70)

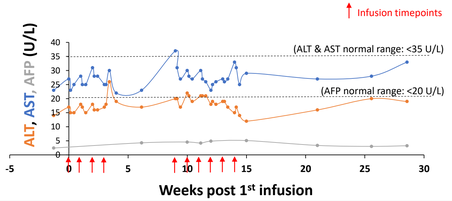
*201-004 and 201-005 were not evaluable for TTP & OS

Figure 5. CT images of 201-001 depicting a lung nodule tumor shrinkage observed 6 weeks post 1st infusion



Baseline 6 weeks post 1st infusion

Figure 6. The levels of liver enzymes (ALT & AST) and tumor biomarker AFP detected in 201-001 were within normal ranges during the course of LioCyx-M treatment and maintained up to Week 29 post 1st infusion



CONCLUSION

- Multiple infusions of LioCyx-M were well tolerated at all dose levels administrated in patients with recurrent HCC post liver transplantation.
- No serious adverse effects were observed to the transplanted liver.
- We have developed an in-house molecular qPCR screening assay to better select patients for treatment, which will potentially better position LioCyx-M as a precision medicine.
- Further assessment of LioCyx-M in Phase 2 studies is warranted.

REFERENCES

1. Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. World J Hepatol. 2019 Mar 27;11(3):261-272
2. Tan AT et al. Use of Expression Profiles of HBV DNA Integrated into Genomes of Hepatocellular Carcinoma Cells to Select T Cells for Immunotherapy, Gastroenterology. 2019; 156(6):1862-1876.e9

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