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Use of LioCyx-M, Autologous Hepatitis B Virus (HBV)-Specific T cell receptor (TCR) T-cells, in Advanced HBV-related Hepatocellular Carcinoma (HCC)

Fu-Sheng Wang[1*], Fanping Meng[1], Jiehua Jin [1], Yuanyuan Li [1], Regina Wanju Wong[2], Anthony Tanoto Tan[3], Tingting Wang[2], Antonio Bertoletti[2,3,4*]

[1]Department of Infectious Diseases, Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing, China; [2]Lion TCR Pte Ltd, Singapore; [3]Emerging Infectious Diseases, Duke-NUS Medical School, Singapore;[4]Singapore Immunology Network, Agency for Science, Technology and Research (A*STAR), Singapore; *co-corresponding authors

INTRODUCTION

- Treatment outcomes for patients with unresectable hepatocellular carcinoma (HCC) who fail standard curative therapy are poor. New treatment strategies for this patient population are urgently needed to meet unmet clinical needs.
- We previously demonstrated the ability of Hepatitis-B-virus (HBV)-specific TCR engineered T cells to recognize and lyse HCC cells expressing HBV antigens derived from HBV-DNA integration in patients with liver transplant[1].
- LioCyx-M is an immunotherapeutic product composing of autologous T cells transiently modified with *in-vitro* transcribed mRNA encoding HBsAg (hepatitis B surface antigen)-specific TCR.
- The transient TCR expression makes LioCyx-M amenable to a dose escalating posology.
- Here, we tested the safety and efficacy of LioCyx-M in patients with HbsAg positive HCC.

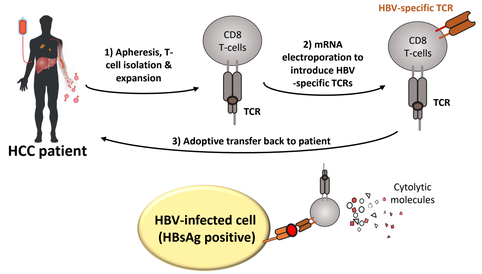


Figure 1. Workflow for LioCyx-M treatment

Peripheral blood mononuclear cells (PBMCs) are harvested from the patient via leukapheresis, followed by the activation and expansion of T cell population in vitro. Activated T cells were transduced with an HBV-specific TCR by mRNA electroporation to produce LioCyx-M. For treatment, LioCyx-M are adoptively transferred back into the same patient. These HBV-TCR redirected T cells exhibit specificity to HBV antigens expressed on the malignant cells and kill tumour cells by producing cytolytic molecules.

STUDY DESIGN

Primary endpoint
To assess the safety and tolerability of LioCyx-M in patients with HBsAg positive HCC

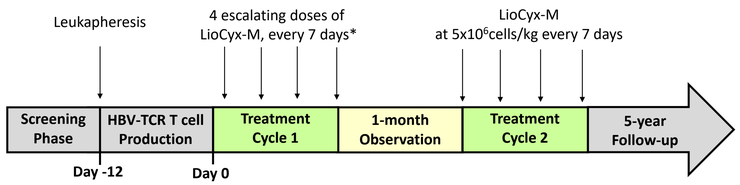
Secondary endpoint
To assess the preliminary anti-tumour efficacy of LioCyx-M in patients with HBsAg positive HCC

Safety Assessments
- Adverse events evaluated according to NCI CTC version 4.0.3

Response evaluation
- Overall Response Rate (per RECIST 1.1)
- AFP level changes from baseline.
- Serum HBsAg and HBV DNA level changes from baseline
- Overall survival

Screening Inclusion Criteria
- HCC patients at least 18 years old
- Positive test for HBsAg
- HLA profile matching with HLA-class I restriction element of TCR
- Child-Pugh < 7 points
- At least 1 month after surgical intervention or 2 weeks after TACE
- Received antiviral treatment more than 1 year prior to enrollment

Figure 2. Schematic of Study Design



*4 escalating doses
- Dose Level 1 = 1 x 10^4 cells/kg
- Dose Level 2 = 1 x 10^5 cells/kg
- Dose Level 3 = 1 x 10^6 cells/kg
- Dose Level 4 = 5 x 10^7 cells/kg

RESULTS

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

ID	Age	Gender	ECOG score	BCLC stage	Presence of Macrovascular invasion	Presence of Extrahepatic spread	Number of previous systemic treatment	Total dose administered	HBV TCR T cell associated AE		Best overall response	PFS	TTP	OS	Current Status
									Probably or possibly AE	Associated dose					
B001	49	Male	1	C	Yes	Yes	1/sorafenib	12	• 1 G3 ALT increase; • 1 G3 GGT increase; • 1 G3 AST increase; • 1 G3 bilirubin increase	1x10^5/kg	SD	3.10	3.10	N.A	Lost to follow up
B002	51	Male	1	B	No	No	1/sorafenib	7	Nil	Nil	SD	2.97	2.97	33.57	Death
B003	59	Male	2	C	Yes	Yes	2/Afatinib, sorafenib	4	Nil	Nil	PD	0.93	0.93	3.53	Death
B004	48	Male	1	C	Yes	Yes	1/sorafenib	4	Nil	Nil	PD	0.90	0.90	2.53	Death
B005	46	Male	1	C	No	Yes	Nil	4	Nil	Nil	SD	9.53	9.53	N.A	Alive
B006	67	Male	1	A	No	No	Nil	4	Nil	Nil	NE	14.50	14.50	N.A	Alive
B007	56	Male	2	C	No	Yes	1/sorafenib	6	Nil	Nil	PD	0.23	0.23	6.83	Death
B008	59	Male	1	C	No	Yes	1/sorafenib	8	3 Grade 1 fever	5×10^6/kg	NE	2.60	2.60	N.A	Alive

AE: Adverse events; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCLC: Barcelona Clinic Liver Cancer; G: Grade; GGT: Gamma-glutamyl transferase (GGT); NA: Not applicable; NE: Not evaluable, OS: Overall survival, PD: Progressive disease; SD: Stable disease; TTP: Time to progression

Figure 2. Swimmer plot with each bar representing the survival time for each patient from the start of LioCyx-M treatment to data cut-off on 30 April 2020.

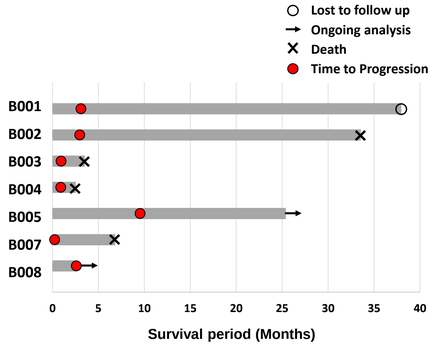
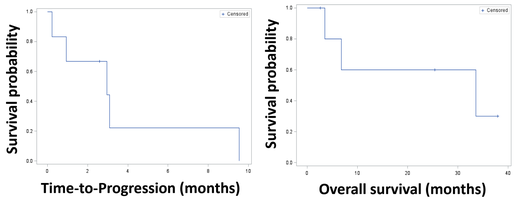


Figure 3. Kaplan-Meier curves for Time-to-Progression (TTP) (left) and overall survival (right) as of cut-off on 30 April 2020.

Median Time-to-Progression*: 2.97 months (90% CI: 0.23, 9.53)

Median Overall Survival*: 33.57 months (90% CI: 2.53, NA)



*Median TTP and OS are calculated based on 7 evaluable patients, except B006.

Figure 4. CT images Depicting the Cross-Sectional Area of Tumor Nodules Detected in Measured at Indicated Timepoints for B001

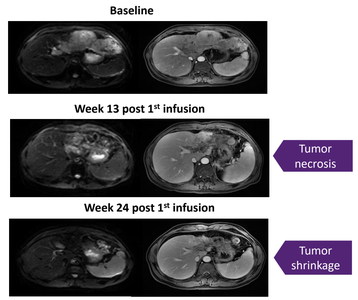
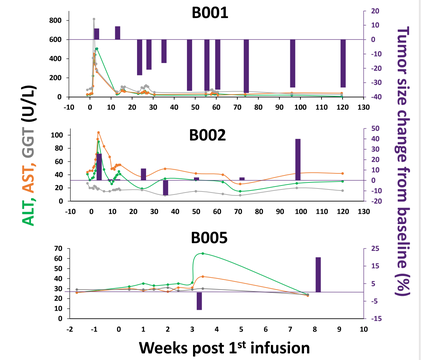


Figure 5. Liver enzymes levels changes (left axis) and liver tumour size changes compared to baseline in percentage (right axis) in 3 representative patients (B001, B002 & B005)



CONCLUSION

- **LioCyx-M infusions were well-tolerated with only 1 grade 3 SAEs observed.**
- **Best responses were stable disease (SD) with duration of stable disease ≥ 3 months in 3 patients out of 6 evaluable patients.**
- **Tumor shrinkage at liver is accompanied by transient elevation of liver enzymes post 1st infusion, indicating the on-target effects of LioCyx-M.**

REFERENCES

1. 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

CONTACT US: clinicaltrials@liontcr.com