Consent Patients provided written consent to perform evalutions here described.

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271 CONSISTENT HIGH-QUALITY DENDRITIC CELL VACCINES PRODUCED POST-CHEMOTHERAPY IN PATIENTS WITH ACUTE MYELOID LEUKEMIA FOR USE IN A PHASE I/II TRIAL

[1]Frauke Schnorfeil, [1]Christiane Geiger, [2]Iris Bigalke, [2]Dag Josefsen, [2]Yngvar Floisand, [2]Gunnar Kvalheim, [3]Dolores Schendel, [1]Anna Tafuri, [3]Kai Pinkernell*. *[1]Medigene Immunotherapies GmbH, Martinsried, Germany; [2]Oslo University Hospital, Oslo, Norway; [3]Medigene AG, Planegg-Martinsried, Germany*

Background A Phase I/II dendritic cell (DC) vaccine trial was completed in 20 patients with acute myeloid leukemia (AML) in complete remission or CRi after chemotherapy who were ineligible for hematopoietic stem cell transplantation (NCT02405338). The DC vaccines were designed to delay disease progression by mobilizing natural killer (NK) cells through secretion of IL-12(p70) and activating T cells by stimulation with WT-1 and PRAME, two prominent antigens in AML. DC vaccination was carried out in weeks 1, 2, 3, 4, 6 and monthly thereafter for 2 years. Two questions were prominent at the trial start. First, could mature DCs (mDCs) be efficiently prepared to accommodate the vaccine regimen, including use of separate DC-fractions for each antigen. Second, could suitable quality DC vaccines be generated from patients with myeloid disease, since all had received intensive chemotherapy, impairing hematopoiesis, such that several patients showed extended times for monocyte recovery in peripheral blood before being able to undergo apheresis for production.
Methods Immune monitoring tools were used to assess DC vaccines: multi-color flow cytometry for surface and intracellular protein staining, dual-color ELISpot for secretion of IL-10/IL-12, and chemokine-directed trans-well migration.
Results Adequate regeneration of monocytes occurred post-chemotherapy in all patients, allowing production of sufficient numbers of cryopreserved vaccine cells (2.5 or 5.0 × 106 mDCs/antigen/ampule) to be completed. In 15/20 patients one batch was sufficient to cover all vaccinations, while 5 patients with lower initial monocyte counts required an additional production.Phenotypic and functional parameters of patient DC vaccines were compared to cells of a healthy control (HC). Patient mDCs expressed CD83, CD40, CD80, CD86 and HLA-DR at frequencies/levels comparable to the HC. Both DC-fractions displayed intracellular protein antigen expression in most cells. Polarized secretion of IL-12(p70) without IL-10 was seen with few exceptions. Furthermore, mDCs displayed chemokine-directed migration. Detection of delayed type hypersensitivity responses post-vaccination at six weeks indicated the DC vaccines were active in vivo in all patients.
Conclusions DC vaccine production feasibility was clearly fulfilled and high quality mDCs were generated for every patient. Quantity and quality of DC vaccines did not differ in the patient groups that relapsed or remained in remission, nor in patients who succumbed to disease during the trial. DC vaccines were remarkably consistent, although originating from patients differing in age, AML subtype and receiving varied amounts of standard chemotherapy regimens.
Ethics Approval The study was approved by the responsible Norwegian ethics committee, approval number 2014/1677.

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272 USE OF LIOCYX-M, AUTOLOGOUS HEPATITIS B VIRUS (HBV)-SPECIFIC T CELL RECEPTOR (TCR) T-CELLS, IN ADVANCED HBV-RELATED HEPATOCELLULAR CARCINOMA (HCC)

[1]Fu-Sheng Wang, [1]Fanping Meng*, [1]Jiehua Jin, [1]Yuanyuan Li, [2]Regina Wanju Wong, [3]Anthony Tanoto Tan, [2]Tingting Wang, [4]Antonio Bertoletti. *[1]5th Medical Center, PLA General Hospital, Beijing, China; [2]Lion TCR Pte Ltd, Singapore, Singapore; [3]Duke-NUS Medical School, Singapore, Singapore; [4]Lion TCR Pte Ltd, Duke-NUS Medical School, Singapore, Singapore*

Background We have demonstrated the ability of Hepatitis-B-virus (HBV)-specific T cell receptor (TCR) bioengineered T cells to recognize and lyse Hepatocellular carcinoma (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 HBV-specific TCR. The transient TCR expression makes LioCyx -M amenable to a dose escalating posology.
Methods The primary endpoint of this phase 1 trial is to assess the safety and tolerability of LioCyx-M in patients with advanced HBV-HCC without curative treatment options. Eligible patients were diagnosed with Barcelona clinic liver cancer stage B or C HCC (Child-Pugh < 7 points), receiving >1 year antiviral treatment prior to enrollment. These patients had matching HLA class I genotypes which present HBV encoded antigen. Peripheral blood was collected from each patient prior to each dose for LioCyx-M manufacturing. Patients received 4 escalating doses of 1×10^4 cells/kg, 1×10^5 cells/kg, 1×10^6 cells/kg, 5×10^6 cells/kg bodyweight (BW) in the first treatment cycle, each intravenously administered weekly. Patients underwent 1-month safety assessment post the 4th infusion, according to Common Terminology NCI CTCAE Version 4.0.3. If there were no dose associated toxicities, patients were eligible to continue administration of LioCyx-M at dose of 5×10^6 cells/kg BW weekly. Tumor response per RECIST 1.1 criteria and survival time were assessed.
Results At data cutoff (30 April 2020), eight patients were enrolled, with a median age of 53 (range: 49 - 67). These patients received a median number of 6 (range: 4 - 12) infusions of LioCyx-M. 1 patient developed Grade 3 elevations in alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST) and bilirubin after receiving LioCyx-M at dose level of 1×10^5 cells/kg BW. Another patient had Grade 1 transient fever after receiving LioCyx-M at dose level 5×10^6 cells/kg BW in the 4th, 5th and 6th infusions. No treatment-related adverse events (trAEs) such as cytokine release syndrome or neurotoxicity were observed. No fatal trAEs were observed. The median time to progression was 1.9 months (range: 0.2 - 9.5 months). The median overall survival was 34 months (range: 3 - 38.2 months).
Conclusions The encouraging clinical outcome and tolerable safety highlight the good benefit-risk profile of LioCyx-M. Therefore, further exploration of efficacy of LioCyx-M treatment for advanced HBV-HCC is warranted in a Phase 2 proof-of-concept clinical study.
Acknowledgements Funding: Lion TCR.
Trial Registration NCT03899415
Ethics Approval The study was approved by Fifth Medical Center of Chinese PLA General Hospital's Ethics Board, approval number R2016185DI010.

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273 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

[1]Wenjie Chen, [1]Jintao Cheng*, [1]Xiaofang Zheng, [1]Fan Yang, [2]Royce Fam, [3]Sarene Koh, [3]Lu-En Wai, [2]Tingting Wang, [4]Antonio Bertoletti, [1]Qi Zhang. *[1]3rd Aff Hospital, Sun Yat-Sen University, Guangzhou, China; [2]Lion TCR Pte Ltd, Singapore, Singapore; [3]Lion TCR Pte Ltd, A*STAR, Singapore, Singapore; [4]Lion TCR Pte Ltd,Duke-NUS Medical School, Singapore, Singapore*

Background LioCyx-M is an immunotherapeutic product based on autologous T cells transiently modified with in vitro transcribed mRNA encoding HBV-specific T-cell receptors (TCR). We have previously shown, in a compassionate setting, the ability of LioCyx-M cells to recognize and lyse hepatocellular carcinoma (HCC) expressing HBV antigens derived from HBV-DNA integration in patients with HCC recurrence post-liver transplant.[1] Here, we report our phase I study aimed to determine the feasibility, safety and preliminary efficacy of LioCyx-M in recurrent HBV-related HCC post-liver transplantation

Methods Eligible patients with HBsAg-positive recurrent HCC as well as HLA-matched to selected TCRs were enrolled in this study. All patients underwent leukapheresis prior to treatment and peripheral blood mononuclear cells (PBMC) were collected for LioCyx-M manufacturing. During the 1st treatment cycle, patients received 4 escalating doses of 1×10^4 cells/kg, 1×10^5 cells/kg, 1×10^6 cells/kg, 5×10^6 cells/kg bodyweight (BW) intravenously every 7 days. Adverse events were evaluated by Common Terminology Criteria for Adverse Events Version 4.0. In the second treatment cycle, one infusion of LioCyx-M at dose of 1–5 $\times$ 10^6 cells/kg BW was intravenously administrated every 7 days for 4 weeks. The anti-tumour efficacy of LioCyx-M was evaluated per RECIST 1.1 criteria and survival was followed-up during the study.

Results Six patients were enrolled, with a median age of 35.5 (range: 28 - 47). These patients received a median number of 6.5 doses of LioCyx-M therapy (range: 4 - 12). Only fever was observed as treatment-related AEs. Grade 1 fever was observed at dose levels of 1 $\times$ 10^4 cells/kg BW (n=1) and 1–5 $\times$ 10^6 cells/kg BW (n=3) respectively. No cytokine release syndrome- and neurotoxicity-like AEs were observed. Out of 4 patients evaluable for tumor response, the median of time to progression was at 1.3 months (range: 1.2 - 1.6 months). The median overall survival was 14 months (range: 4 - 22 months). At data cutoff (30 April 2020), one patient was still alive and 5 were deceased.

Conclusions Our data showed that multiple infusions of LioCyx-M are well tolerated at all dose levels administrated in recurrent HCC post liver transplantation, with no adverse effect to the transplanted liver. This calls for further assessment in a Phase 2 study.

Acknowledgements Funding: Lion TCR.

Trial Registration NCT02719782

Ethics Approval The study was approved by Sun Yat-Sen Third Affiliated Hospital's Ethics Board, approval number [2015]2-157.

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274 TUMORAL AND PERIPHERAL IMMUNOPHENOTYPE OF REFRACTORY VS RELAPSE TO PD-(L)1 BLOCKADE IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

[1]Maria Ascierto*, [2]Matthew Hellmann, [1]Nathan Standifer, [1]Song Wu, [1]Han Si, [1]Chris Morehouse, [1]Marlon Rebelatto, [1]Shaad Abdullah, [1]Rajiv Raja, [1]Jean-Charles Soria, [1]Caroline Germa, [1]Carl Barrett. *[1]Astrazeneca, Gaithersburg, MD, USA; [2]MSK, New York, NY, USA*

Background Despite the encouraging successes of immune checkpoint inhibitors, many patients do not benefit and are either refractory or relapse. The mechanisms of refractory or relapsed disease following PD-(L)1 blockade are largely unknown. To identify characteristics associated with refractory or relapsed disease we explored the immune and genomic landscape of samples derived from NSCLC patients who previously received PD-(L)1 blockade and had blood and fresh tumor biopsies collected at the time of progression.

Methods Patient response categories were defined prospectively; 'refractory' defined as progression within 16 weeks of initiating PD-(L)1 and 'relapse' defined as initial clinical benefit (CR, PR, SD) followed by progression. RNAseq (n=52) and PD-L1 IHC (n=22) were performed on tumor tissue. Immune profiling of whole blood was assessed using flow cytometry or Biomark HD (Fluidigm) gene expression panel (n=54 and n=62, respectively). Differential gene expression was defined as unadjusted $p<0.05$ and fold-difference >1.5. Pathways analysis was conducted by David tool. Patient samples were collected during screening for clinical trial of second line immunotherapy. Written informed consent was obtained from the patients for publication of this abstract.

Results In patients with NSCLC previously treated with PD-(L)1 blockade, tumors of relapsed patients were characterized by increased expression of genes associated with interferon signaling (e.g. CXCL9, SPIC, IFNg), immune suppression (e.g. ARG1, TGFB), immune exhaustion (e.g. ADORA2A), and increased PD-L1 expression (by gene expression and IHC). Refractory disease was associated with increased cadherin signaling and calcium-dependent-cell-adhesion gene expression pathways. In the periphery, reduced quantities of B cells and activated (HLA-DR+ or CD38+) or proliferating (Ki67+) CD8+ T cells were observed in refractory patients.

Conclusions The tumor and peripheral compartments of patients with NSCLC previously treated with PD-(L)1 blockade differ based on prior response. Relapsed patients tend to have signals of sturdy immune activation and chronic inflammation thus ultimately leading to immune exhaustion. These results may help inform rational therapeutic strategies to overcome resistance to PD-(L)1 blockade in NSCLC.

Trial Registration NCT02000947

Ethics Approval Research on human samples here analyzed have been performed in accordance with the Declaration of Helsinki.

Consent Written informed consent was obtained from the patient for publication of this abstract.

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