Study of Adoptive Transfer of Invariant Natural Killer T Cells Combined With TAE/TACE to Treat Unresectable Hepatocellular Carcinoma (HCC): Phase II Clinical Trial

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1. Background and Aims

Hepatocellular carcinoma (HCC) is the fifth most common cancer and a leading cause of cancer-related death among males and females of all ages [1]. It was estimated that in 2018, there were 840 thousand new liver cancer cases and 780 thousand liver cancer-related deaths in the world [1]. Of importance, unresectable HCC accounts for more than 70%~80% of the cases, limiting the possibility of achieving a cure in many patients [2, 3]. Currently, the prognosis of HCC is poor, with a 5-year survival of about 18% even in developed countries [4].

Transarterial embolization (TAE) or transarterial chemoembolization (TACE) is a standard therapy for intermediate-stage HCC, which is accepted as a routine practice worldwide [5, 6]. Nevertheless, different clinical characteristics of HCC, such as liver function and tumor load (different size, number, and location), will lead to different responses to TA(C)E treatment and different survival times. Furthermore, repeated TACE procedures could gradually lead to TACE refractoriness, and some patients even show TACE failure [7]. According to the Japanese Society of Hepatology (JSH) guidelines [8], TA(C)E failure is defined as an insufficient response after ≥2 consecutive TA(C)E procedures, as revealed by the response evaluation using computed tomography (CT) or magnetic resonance imaging (MRI) after 1~3 months. The median tumor doubling time after an initial response of HCC to TACE is 46 days, and >90% of the recurrent nodules have a doubling time of <3 months [9]. The recurrence rate of intrahepatic lesions after TA(C)E is 37% and 61% at 6 and 12 months, respectively [10]. Therefore, patients with HCC failed to respond to TACE,

under which circumstance is defined as TACE refractoriness, should switch to or combine with systemic therapy as soon as possible because repeated TACE is no longer beneficial for such patients [9].

The Asia-Pacific region has the highest incidence of HCC, with >50% of all the cases in the world [1]. In addition, >80% of HCC cases in China occur due to viral hepatitis and cirrhosis [11, 12]. Of note, pancytopenia is a common clinical manifestation of liver cirrhosis [13, 14]. Therefore, the number and frequency of peripheral blood lymphocytes in many patients with HCC are lower than in the normal population [15]. Furthermore, the decline of immune system function is the basis of the occurrence, development, recurrence, and metastasis of various tumors, including the decrease in anti-tumor killing and immune monitoring functions [16]. TA(C)E can induce tumor necrosis, and ischemia-reperfusion injury can induce further tumor cell damage. TA(C)E is considered to improve tumor immunogenicity by releasing antigens and stimulating cytotoxic lymphocytes (CTL) recruitment in tumors [17]. After reperfusion, natural killer T (NKT) cells are activated rapidly by CD1d [18]. Invariant NKT (iNKT) cells are enriched in the human liver, and they express a limited T-cell receptor (TCR) β spectrum and unique TCR α rearrangement (Vα24-Jα 18 in humans and Vα14-Jα18 in mice) [19]. Clinical trials have shown that activated iNKT cells can rejuvenate depleted $CD8^+$ T cells and natural killer (NK) cells [20-24]. Some of these trials activated iNKT with aGalcer-loaded monocytic dendritic cell vaccines and others adoptively transferred iNKT cells. These activated or reactivated lymphocytes can help remove residual cancer cells and prevent tumor recurrence and metastasis. Therefore, TA(C)E

combined with adoptive iNKT therapy might be an option for the treatment of HCC.

In our previous phase I trial [25], the adoptive transfer therapy of autologous iNKT cells in patients with recurrent or refractory Barcelona Clinic Liver Cancer (BCLC) B/C liver cancer demonstrated a partial clinical response and objective immune response, with very slight side effects. Therefore, we will conduct a multicenter, randomized, open trial in BCLC B/C stage patients with HCC after failure to TACE to explore the efficacy and safety of TAE combined with adoptive autologous iNKT cell therapy compared with TAE alone.

2. Study Design and Participants

This randomized, multicenter, open-labeled phase II trial will be conducted at Beijing YouAn Hospital of Capital Medical University, Beijing Shijitan Hospital of Capital Medical University, and Beijing Ditan Hospital of Capital Medical University between March 2018 and March 2020. This study will be performed according to the guidelines of the Helsinki Declaration.

3. Criteria

Inclusion Criteria:

1) 18-80 years of age, 2) TACE failure/refractory BCLC B HCC confirmed by CT, MRI, and/or histopathology, 3) life expectancy of at least 12 weeks, 4) Child-Pugh A/B，5) adequate hematological and renal functions, including white blood cell (WBC) count >3.0 × 109/L, lymphocyte count >0.8×109/L, platelet count >50×109/L, hemoglobin concentration >85 g/L, and serum creatinine

concentration of <1.5-times the upper limit of normal value (ULN), and 6) previous treatment terminated at least 4 weeks before entry to this study.

Exclusion Criteria:

1) Known history of the human immunodeficiency virus (HIV) or syphilis infection, 2) clinically serious infections, 3) history of stem cell transplant or organ allograft, 4) history of severe hypertension or cardiac disease, 5) known central nervous system (CNS) tumor, 6) autoimmune disease requiring systemic therapy with immunosuppressive agents, 7) history of allergy to immunotherapy or related drugs, 8) pregnancy or lactation, or 9) deemed not suitable for cellular immunotherapy by the investigators.

Research Suspension / Termination Criteria:

1) the patient withdrew his informed consent and asked to withdraw, 2) CT/MRI examination confirmed the occurrence of PD, according to the imRECIST, 3) unable to tolerate AEs, or serious adverse events (SAE), abnormal laboratory tests or concurrent diseases, etc, and the researchers judged that it is not in the best interests of patients to continue to participate in the study, 4) the study and treatment of patients was significantly delayed for any reason, which exceeded the scheduled treatment time ≥ 8 weeks from the time of the last administration, 5) other situations in which the researchers believe that it is necessary to stop treatment, 6) pregnancy occurred in the patient, 7) use new antineoplastic therapy, 8) the sponsor terminates the study.

Elimination Criteria:

1) the use of research drugs is not consistent with the clinical regimen, and has a significant impact on the evaluation of efficacy and safety, 2) those without any record, 3) those who did not take research drugs.

TACE Failure Criteria:

1) Intrahepatic lesion [i, two or more consecutive ineffective responses seen within the treated tumors (viable lesion >50%), even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery, on response evaluation CT/MRI after 1–3 months following adequately performed selective TACE. ii, two or more consecutive progressions in the liver (including an increase in the number of tumors compared to that before the previous TACE procedure), even after changing the chemotherapeutic agents and/or reanalysis of the feeding artery, on response evaluation CT/MRI after 1–3 months following adequately performed selective TACE]. 2) Continuous elevation of tumor markers right after TACE, even though transient minor reduction is observed. 3) Appearance of vascular invasion. 4) Appearance of extrahepatic spread.

4. Endpoints and Definitions

The primary endpoint is the PFS, i.e., the time from enrollment to disease progression according to the modified RECIST (mRECIST) guideline in trial immunotherapeutics, or death from any cause, whichever occurred first. Secondary endpoints include overall survival (OS), objective response rate (ORR), disease control rate (DCR), quality of life (QoL), and safety. Patients without any post-baseline tumor assessment are considered non-responders. Objective responses

will be confirmed at least 28 days after the initial documentation of the response.

Progression-Free Survival: Time from the date of enrollment to the date of first documentation of tumor progression.

Progression was defined using Modified RECIST (mRECIST): an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started.

Overall survival: time from the date of enrollment to the date of death from any cause.

Objective response rate: including complete response (CR) and partial response (PR) evaluated by imaging according to mRECIST for target lesions and assessed by MRI/CT. Complete Response (CR), disappearance of any intratumoral arterial enhancement in all target lesions. Partial Response (PR), at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions. Objective Response Rate = CR + PR.

Disease Control Rate: including complete response (CR), partial response (PR), and disease stabilization (SD), evaluated by imaging according to mRECIST for target lesions and assessed by MRI/CT. Complete Response (CR), disappearance of any intratumoral arterial enhancement in all target lesions. Partial Response (PR), at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target

lesions. Stable disease (SD), any cases that do not qualify for either partial response or progressive disease. Disease Control Rate = CR + PR + SD.

The Quality of Life (QoL) will be assessed according to the EORTC (EORTC: the European Organization for Research and Treatment of Cancer) QLQ-C30 scale between the TAE-iNKT and TAE group. And the time to deterioration of QoL, as reported by the patient, with deterioration defined as a decrease from baseline of 10 points or more on the EORTC QLQ–C30 maintained for two consecutive assessments.

Safety and side-effect profiles will be assessed based on the nature, frequency, and severity of adverse events, according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.3. Common Adverse events (AEs) occurring on or after the first treatment day through the end of this trial will be recorded according to NCI-CTCAE 4.03.

5. Drugs for research

Name of Drug

iNKT cells

Production of iNKT Cells

1) Isolate PBMCs by leukapheresis using a COM.TEC apheresis system and Lymphoprep density gradient medium.

2) Resuspend PBMCs in Corning serum-free cell medium KBM581 and stimulate with 100 ng/mL α-GalCer and 100 U/mL animal-free recombinant human

interleukin-2 for 48 hours; the rhIL-2 was replenished every other day.

3) Stimulate PBMCs with 1,000 IU/mL granulocyte-macrophage colony-stimulating factor and IL-4 for 1 week, and obtain mature, monocyte-derived DCs.

4) Sort iNKT cells by using anti-iNKT microbeads according to the manufacturer's protocol on day 7.

5) Co-culture the sorted iNKT cells with mature DCs for 14 days, and collect cells for infusion on day 21. An aliquot of cells was used for immunophenotyping and functional testing.

6) Determine the frequency of iNKT cells in T cells by using a FACSCanto II cytometer.

7) The criteria for iNKT cell administration include a negative bacterial culture, a negative mycoplasma test result, and an endotoxin level < 0.05 units/mL.

Production Standards

Inspection item	Statutory (Pharmacopoeia) standard	Internal quality control standard
Color	---	Colorless or innocent
Character	---	Transparent suspension
Identification	Flow cytometry	Cellular immunophenotype
Rate of survival cell	≥95%	≥95%
Quantity (survival cell)	---	Day7：$\geq 5*10^7$； Day 21：$\geq 1*10^8$
Microbial limit test	Aseptic, (bacteria and mold shall not be detected).	Aseptic, (bacteria and mold shall not be detected).

	Mycoplasma (not allowed to be detected). Endotoxin≤2EU/ml	Mycoplasma (not allowed to be detected). Endotoxin≤2EU/ml
Proportion	90%	90%

Dose and Administration

Intravenous infusion. From the date of cell collection, the cells will be infused on the 7th and 21st day of each month as a course of treatment for a total of three courses, the reinfusion dose is determined according to the patient's body surface area, which was about 10^8~10^9cells/m^2.

Drug Combination

Human IL-2 (25,000 IU/kg per day) will be administered (subcutaneous injection) once every other day for 1 week after iNKT cell infusion.

6. Interventions

The patients will be randomized 1:1 using a random number table to receive TAE treatment vs. the combination treatment of TAE and adoptive autologous iNKT cell infusion (TAE-iNKT). The patients in the TAE and TAE-iNKT groups will undergo TAE at weeks 0 and 4 after enrollment. TAE will be performed at the local hospitals.

In the TAE-iNKT group, iNKT cells will be administered at 1^{st}, 3^{th}, 5^{th}, 7^{th}, 9^{th}, 11^{th} weeks after enrollment. After iNKT cell infusion, a subcutaneous injection of interleukin (IL)-2 (25,000 IU/kg) will be administered once every other day for 1 week.

All target and non-target lesions will be assessed by chest, abdomen, and pelvis CT or MRI at baseline and every 4 weeks until week 16, and then every 8 weeks until

radiological progression. At the same time points, routine blood tests, tumor biomarkers, α-fetoprotein (AFP), and quality of life (QoL) will be measured.

After the end of treatment, the survival follow-up of the subjects will continue to be conducted every 3 months, while those who end treatment for reasons other than disease progression will undergo regular tumor imaging evaluation as much as possible after treatment, and survival follow-up must be carried out.

The details of follow-up are shown in the table below:

Project / time	**Screening/ baseline period（-14d～0w）**	**The first cycle 3W±7d**	**The second cycle 6w±7d**	**Odd cycle ±7d**	**Even cycle ±7d**	**Out-of-group follow-up ±7d**
Sign the informed consent form	×					
Medical history	×					
Inclusion / exclusion criteria	×					
Physical examination and vital signs	×	×	×	×	×	×
Blood routine	×	×	×	×	×	×
Urine routine	×	×	×	×	×	×
Biochemistry (liver and kidney function, blood glucose, blood lipid)	×	×	×	×	×	×
Myocardial enzyme	×	×	×	×	×	×
Thyroid function	×	×	×	×	×	×
Five items of hepatitis B	×					
Hepatitis C antibody	×					
HBV-DNA/HCV RNA quantification	×		×		×	×
Syphilis antibody	×					
HIV antibody	×					
Digestive tumor markers, AFP	×	×	×	×	×	×
Coagulation	×	×	×	×	×	×

Autoantibody	×					
T cell subsets	×	×	×	×	×	×
Detection of cell suspension (bacteria, fungi, endotoxin)	×	×	×	×	×	
Electrocardiogram	×		×		×	×
Colour Sonography	×					×
Liver enhanced MR or CT	×		×		×	×
Imaging data of other organs	×		×		×	×
Pathological examination of tumor	×					
Drug combination	×	×	×	×	×	×
Adverse events	×	×	×	×	×	×

The Implementation of TAE

1) Select catheterization of the feeding artery by using a microcatheter.

2) Perform abdominal and hepatic arteriography.

3) Embolization with Gelfoam until near stasis of the arterial flow.

4) Determine the dose of iodized oil by the tumor size or based on whether the portal vein had a tumor thrombosis.

5) Inject the emulsion of iodized oil until the accumulation of the emulsion in the tumor and the visualization of the portal vein branches near the tumor. (If there was a significant arterioportal shunt, embolization with Gelfoam was first performed to occlude the shunt, after which the iodized oil emulsion was infused, and embolization with Gelfoam was performed.)

7. Statistical Analysis

The trial was designed to use a 2-sided 5% type I error and had 80% power to detect an improvement in PFS from 1.5 months in the TAE group to 4.5 months in the TAE-iNKT group, corresponding to a hazard ratio (HR) of 0.33 in terms of median PFS. In consideration of these assumptions, the trial design was powered for 60 patients to be randomly assigned in each group as the intention-to-treat population (allocation ratio of 1:1, n=30 patients in each group), and allowing for a drop-out rate of 20%. Sample size estimation was performed using PASS 11.

Continuous variables will be expressed as the median and IQR, and will be compared using t tests or Mann-Whitney tests. Categorical variables will be presented as the frequency and percentage, and will be compared using Fisher's exact tests. Survival and time to QoL deterioration will be estimated using the Kaplan-Meier method, and their 95% CIs will be calculated using the Brookmeyer and Crowley method. Survival differences will be compared using log-rank tests. Peripheral blood cells will be analyzed using Sidak's multiple comparison test. The overall two-sided significance level of P< .05 will be split into a two-sided significance level of P< .01 for tests of PFS, OS, ORR, DCR, and QoL according to the Bonferroni method (dividing the available total α (typically 0.05) equally among the chosen endpoints). If the PFS and/or all secondary endpoints are statistically significant at a two-sided significance level of 0.01, the curative effect of TAE-iNKT will be deemed better than that of TAE alone. All statistical analyses will be conducted using SAS software version 9.4 (SAS Institute).

8. Data Management.

Designated and trained staff act as data managers, responsible for the data management of this study, complete data collection, input, quality inspection and make data security monitoring plan in accordance with the requirements of GCP. When the following conditions are met, the data can be locked: all data have been entered into the database; all questions have been solved; the researcher has completed the signature; the analytical population has been defined and judged. After the database is locked, if the project team evaluates that it needs to be unlocked, it can reopen the lock. The process of unlocking the database should include notifying the project team, clearly defining which data errors will be changed, the reason for the change, and the date of the change, and signed by key researchers, data managers, and statistical analysts. The re-locking of the database should follow the same notification / approval process as the database lock for the first time.

9. Handling of Adverse Events during and after the Study.

Researchers should follow up, observe and record the outcome of all adverse events, and follow patients who drop out of the study because of adverse events until the adverse events are completely relieved. Researchers must determine whether adverse events are related to research drugs and provide evidence to support this judgment.

In all clinical or laboratory examinations, abnormal items of clinical significance should be filled in the form of adverse events and followed up at least once a week until normal or reached the baseline level.

Measures to Deal with Expected Adverse Events

1) Fever: patients may have different degrees of fever, doctors will give symptomatic antipyretic treatment.

2) Allergic reaction: a small number of patients may have allergic reaction, such as skin pruritus, urticaria, chest tightness and so on.

3) Digestive tract symptoms: patients may have digestive tract symptoms of nausea, vomiting and various stomach discomfort, and doctors will give gastric mucosal protective agents, acid suppressants, gastric motility drugs or antiemetic drugs according to the situation.

If any serious adverse event occurs in the course of clinical research, the researcher shall report the serious adverse event to the ethics committee of the research unit and the applicant unit of clinical research within 24 hours of knowing the serious adverse event. At the same time, researchers must fill in the form of serious adverse events and record the time, severity, duration, measures taken and outcome of serious adverse events.

10. Follow-up and Medical Measures after the End of the Study.

After the completion of this study, the subjects may still have the end events of the disease itself, such as the progression of liver cancer and the deterioration of liver function. We will closely observe and follow up, communicate with patients in time, and put forward objective medical suggestions. Therefore, the regular return visit of the subjects will be very important, because it will help to detect the progress of these

diseases in the early stage, so that the clinical follow-up doctors can take timely and effective treatment measures to improve the prognosis.

11. Data Preservation.

The original data of the examination results (including the test sheet) are owned by the researchers. The CRF shall be in triplicate, one copy shall be retained by the bidding unit, one copy by the participating unit and one copy by the statistical unit. Demographic data, related medical history, physical examination, a series of laboratory tests and combined medication and adverse events take the CRF table and hospital case system data as the original data, in which the part related to the privacy of the subjects is only reflected in the original medical records.

Researchers should properly preserve research documents in accordance with relevant requirements. Important documents should be kept until 5 years after the end of the clinical study.

12. References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2018;68(6):394-424. doi:https://doi.org/10.3322/caac.21492
2. Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of Hepatocellular Carcinoma. *Surgical Oncology Clinics*. 2015;24(1):1-17. doi:10.1016/j.soc.2014.09.001
3. Jelic S, Sotiropoulos GC. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2010;21:v59-v64. doi:10.1093/annonc/mdq166
4. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*. 2021;71(3):209-249. doi:https://doi.org/10.3322/caac.21660
5. Kokudo N, Takemura N, Hasegawa K, et al. Clinical practice guidelines for hepatocellular

carcinoma: The Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. *Hepatology Research*. 2019;49(10):1109-1113. doi:https://doi.org/10.1111/hepr.13411

6. Chang PY, Huang CC, Hung CH, et al. Multidisciplinary Taiwan Consensus Recommendations for the Use of DEBDOX-TACE in Hepatocellular Carcinoma Treatment. *Liver Cancer*. Oct 2018;7(4):312-322. doi:10.1159/000487608

7. Takayasu K, Arii S, Ikai I, et al. Prospective Cohort Study of Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma in 8510 Patients. *Gastroenterology*. 2006;131(2):461-469. doi:10.1053/j.gastro.2006.05.021

8. Kudo M, Matsui O, Izumi N, et al. Transarterial Chemoembolization Failure/Refractoriness: JSH-LCSGJ Criteria 2014 Update. *Oncology*. 2014;87(suppl 1)(Suppl. 1):22-31. doi:10.1159/000368142

9. Woo HY, Jang JW, Choi JY, et al. Tumor doubling time after initial response to transarterial chemoembolization in patients with hepatocellular carcinoma. *Scandinavian Journal of Gastroenterology*. 2010/03/01 2010;45(3):332-339. doi:10.3109/00365520903456573

10. Terzi E, Golfieri R, Piscaglia F, et al. Response rate and clinical outcome of HCC after first and repeated cTACE performed “on demand&#x201d. *Journal of Hepatology*. 2012;57(6):1258-1267. doi:10.1016/j.jhep.2012.07.025

11. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nature Reviews Gastroenterology & Hepatology*. 2019/10/01 2019;16(10):589-604. doi:10.1038/s41575-019-0186-y

12. Ding C, Fu X, Zhou Y, et al. Disease burden of liver cancer in China from 1997 to 2016: an observational study based on the Global Burden of Diseases. *BMJ Open*. 2019;9(4):e025613. doi:10.1136/bmjopen-2018-025613

13. Lv Y, Yee Lau W, Wu H, et al. Causes of peripheral cytopenia in hepatitic cirrhosis and portal hypertensive splenomegaly. *Experimental Biology and Medicine*. 2017;242(7):744-749. doi:10.1177/1535370217693113

14. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before Procedures in Patients with Cirrhosis and Thrombocytopenia. *New England Journal of Medicine*. 2012;367(8):716-724. doi:10.1056/NEJMoa1110709

15. Taussig MD, Irene Koran ME, Mouli SK, et al. Neutrophil to lymphocyte ratio predicts disease progression following intra-arterial therapy of hepatocellular carcinoma. *HPB*. 2017;19(5):458-464. doi:10.1016/j.hpb.2017.01.013

16. Miller Jacques FAP, Sadelain M. The Journey from Discoveries in Fundamental Immunology to Cancer Immunotherapy. *Cancer Cell*. 2015;27(4):439-449. doi:10.1016/j.ccell.2015.03.007

17. Girardi E, Zajonc DM. Molecular basis of lipid antigen presentation by CD1d and recognition by natural killer T cells. *Immunological Reviews*. 2012;250(1):167-179. doi:https://doi.org/10.1111/j.1600-065X.2012.01166.x

18. Nair S, Dhodapkar MV. Natural Killer T Cells in Cancer Immunotherapy. Review. *Frontiers in Immunology*. 2017-September-22 2017;8(1178)doi:10.3389/fimmu.2017.01178

19. Salio M, Silk JD, Jones EY, Cerundolo V. Biology of CD1- and MR1-Restricted T Cells. *Annual Review of Immunology*. 2014;32(1):323-366. doi:10.1146/annurev-immunol-032713-120243

20. Motohashi S, Ishikawa A, Ishikawa E, et al. A Phase I Study of In vitro Expanded Natural Killer T Cells in Patients with Advanced and Recurrent Non–Small Cell Lung Cancer. *Clinical Cancer Research*. 2006;12(20):6079. doi:10.1158/1078-0432.CCR-06-0114

21. Kunii N, Horiguchi S, Motohashi S, et al. Combination therapy of in vitro-expanded natural killer T cells and α-galactosylceramide-pulsed antigen-presenting cells in patients with recurrent head and neck carcinoma. *Cancer Science*. 2009;100(6):1092-1098. doi:https://doi.org/10.1111/j.1349-7006.2009.01135.x

22. Yamasaki K, Horiguchi S, Kurosaki M, et al. Induction of NKT cell-specific immune responses in cancer tissues after NKT cell-targeted adoptive immunotherapy. *Clinical Immunology*. 2011/03/01/ 2011;138(3):255-265. doi:https://doi.org/10.1016/j.clim.2010.11.014

23. Exley MA, Friedlander P, Alatrakchi N, et al. Adoptive Transfer of Invariant NKT Cells as Immunotherapy for Advanced Melanoma: A Phase I Clinical Trial. *Clinical Cancer Research*. 2017;23(14):3510. doi:10.1158/1078-0432.CCR-16-0600

24. Toyoda T, Kamata T, Tanaka K, et al. Phase II study of α-galactosylceramide-pulsed antigen-presenting cells in patients with advanced or recurrent non-small cell lung cancer. *Journal for ImmunoTherapy of Cancer*. 2020;8(1):e000316. doi:10.1136/jitc-2019-000316

25. Gao Y, Guo J, Bao X, et al. Adoptive Transfer of Autologous Invariant Natural Killer T Cells as Immunotherapy for Advanced Hepatocellular Carcinoma: A Phase I Clinical Trial. *The Oncologist*. 2021;26(11):e1919-e1930. doi:https://doi.org/10.1002/onco.13899