OPEN ACCESS

Original research

Clinical results of an HBV-specific T-cell receptor-T-cell therapy (SCG101) in patients with HBV-related hepatocellular carcinoma treated in an investigator-initiated, interventional trial

Xiang'an Wu ,[1] Dongmei Quan ,[2] Wei Li,[3] Karin Wisskirchen ,[4] Wei Wu ,[2] Yuhong Zhou ,[3] Yun-Peng Liu ,[5] Xueshuai Wan ,[1] Xiaorui Wang ,[6] Xuxu Zhang ,[7] Lu Yang ,[7] Mengyao Zheng ,[7] Ke Zhang ,[6] Ulrike Protzer ,[8,9] Shunda Du ,[1] Xiujuan Qu [5]

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/gutjnl-2025-335456).

For numbered affiliations see end of article.

Correspondence to
Prof Ulrike Protzer; protzer@tum.de;
Prof Shunda Du; dushd@pumch.cn and Prof Xiujuan Qu; qu_xiujuan@hotmail.com

X'aW, DQ and WL contributed equally.

Received 2 April 2025
Accepted 12 July 2025

Check for updates

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

To cite: Wu X, Quan D, Li W, *et al*. *Gut* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/gutjnl-2025-335456

ABSTRACT

Background SCG101 is an autologous T-cell therapy specifically targeting hepatitis B virus (HBV) using a natural, high-affinity T-cell receptor that is stably expressed.

Objective We evaluated the safety, pharmacokinetics, pharmacodynamics and efficacy of SCG101 in patients with HBV-related hepatocellular carcinoma (HCC) in an investigator-initiated trial.

Design Six human leucocyte antigen (HLA)-A*02:01-positive, serum hepatitis B surface antigen (HBsAg)-positive and hepatitis B e antigen-negative patients with advanced HBV-HCC, who had failed one to three prior systemic therapies, received SCG101 at doses of 5×10^7 or 1×10^8 TCR-T$^+$ cells/kg three days after lymphodepletion.

Results Within 1 week, all patients experienced a significant but transient alanine aminotransferase elevation paralleled by a 76±57 fold expansion of T cells detected in peripheral blood. No neurotoxicity, but a cytokine release syndrome reaching up to grade 3 was observed. However, these side effects were not dose-limiting and could be managed with corticosteroids, anti-interleukin-6 and/or vasopressor therapy. Indicating on-target activity of SCG101, serum HBsAg levels dropped by 1.96 (0.16–3.84) $\log_{10}$ within 2 weeks. According to modified Response Evaluation Criteria in Solid Tumours, three of the six patients achieved tumour shrinkage with a best percentage change in target lesion size of −19.5%, −74.6% and −100%. One showed complete remission of the target lesion, remaining progression-free for 27 months and one other achieved a durable (>6 months) remission. During follow-up (median 10.9 months), three patients died, and one was lost to follow-up.

Conclusion As monotherapy for patients with HBV-HCC, SCG101 demonstrated pronounced antiviral and antitumour activities and a safety profile manageable with supportive care. SCG101's T-cell expansion, serum HBsAg drop and tumour response collectively underscore on-target activity.

Trial registration number NCT05339321.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ T-cell therapy is an interesting treatment option for hepatocellular carcinoma (HCC), but the suitable target antigen remains unclear.

WHAT THIS STUDY ADDS

⇒ This study explores hepatitis B surface antigen (HBsAg) as a target for T-cell therapy of hepatitis B virus (HBV)-induced late-stage HCC and the underlying chronic hepatitis B. T cells grafted with an HBsAg-specific T-cell receptor were able to attack HBV-infected hepatocytes and premalignant or tumour cells that carry an HBV integrate, significantly reducing HBsAg in serum in 4/6 patients and tumour lesions in 2/6 patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The study shows that the application of stably HBV-T cell receptor-expressing T cells is effective and side effects are manageable, paving the way for the treatment of larger cohorts and exploring it as a unique strategy to target HBV-induced tumours and HBV-infected cells at the same time.

INTRODUCTION

With 865 269 newly diagnosed cases and 757 948 deaths in 2022, primary liver cancer ranked sixth in incidence and third in mortality worldwide. Hepatocellular carcinoma (HCC) accounted for approximately 75–85% of cases.[1] The prevailing therapeutic strategy emphasises a comprehensive treatment regimen centred on surgical cancer removal.[2] Nevertheless, this approach is challenged by two predominant issues: the risk of early post-operative recurrence[3] and the late-stage diagnosis in most patients, rendering them ineligible for surgical intervention.[4] Non-surgical alternatives, such as tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs) and antiangiogenic therapies benefit patients with advanced-stage HCC.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

However, only a minor subset of patients experiences a substantial advantage in overall survival (OS), coupled with the looming threat of rapid resistance development, especially if tumours show high mutation rates and in the case of T-cell exhaustion.[5 6] Furthermore, severe adverse reactions to these therapies have been unpredictable so far and occur frequently.[7 8] A systematic review and meta-analysis of 30 clinical trials found that severe adverse events (AEs) occurred in 46% of patients receiving TKIs and 24% receiving ICIs.[8] Another meta-analysis found that treatment-related mortality occurred in 3.1% of patients, and treatment discontinuation occurred in 10.7% of patients receiving ICIs.[9] While an array of treatment options exists, the median OS in the Asia–Pacific region is still below 6 months in late-stage HCC,[10] underscoring the high medical need for innovative therapeutic modalities in HCC management.

Adoptive T-cell therapy is emerging as a potent modality for patients with cancer, especially in haemato-oncology, succeeding both targeted drug therapies and other immunotherapies. This approach now also sparks interest in the field of hepatology and encompasses both non-genetic and genetic modification of T cells by introducing distinct targeting receptors.[11] Cell therapies with genetic modifications predominantly comprise chimeric antigen receptor (CAR-) and T-cell receptor transduced T-cells (TCR-T) cell therapies.[11 12] CAR-T cells can identify and eliminate tumour cells that display specific antigens on their surface via antibody-mediated binding and are independent of the patient's individual human leucocyte antigen (HLA) type. While CAR-T cell products have emerged as an effective novel treatment modality in haematological cancers, their efficacy in solid tumours seems modest.[13] Engineered TCR-T cells are tailored to target intracellular and extracellular tumour-associated or tumour-specific antigens presented as peptide fragments on HLA class I and II molecules. Noteworthy, the achievements of TCR-T-cell therapies in treating melanoma, lung cancer, sarcoma and other solid malignancies are well-documented.[14 15] The treatment with high-affinity New York esophageal squamous cell carcinoma-1 -specific TCR-T cells has yielded objective response rates (ORRs) of 55% in melanoma and 61% in synovial sarcoma.[16]

HCC poses a significant challenge for the development of precision medicine because it typically lacks recurrent, targetable oncogenic driver mutations and is considered a low-immunogenic tumour with limited neoantigen load.[17] Current targets for a TCR-T cell therapy of patients with HCC include alpha-fetoprotein (AFP) and virus-derived antigens, with several clinical trials in progress.[18] Hepatitis B virus (HBV) infection is one of the most critical risk factors for HCC, accounting for around 50% of cases worldwide,[19 20] and up to 84% in China.[21] HBV-DNA integration into the host cell genome drives tumourigenesis and the expression of complete and truncated HBV antigens.[22] This makes treating HBV-HCC by targeting HBV antigens a feasible strategy. Several studies have shown that HBV-specific TCR-T cells can be redirected to recognise HBV-infected cells and HCC tumour cells expressing viral antigens from integrated HBV-DNA.[23–25] Individual clinical applications and small studies indicated that these TCR-re-directed HBV-specific T cells are safe and potentially effective for treating HBV-related (recurrent) HCC, with or without liver transplantation.[26–28] The first reported HBV-TCR T cell therapy used a low dose of retrovirally-transduced T cells in a single patient with a presumably HBV-negative liver transplant developing hepatitis B surface antigen (HBsAg)-positive metastases of the primary tumour.[29] Building on this demonstration of feasibility, Bertoletti and colleagues developed a method to generate TCR-T cells for patients with HCC through messenger RNA electroporation,[26 27] which only supports transient gene expression and, consequently, lacks persistence of TCR-T cells, requiring multiple infusions.[30]

SCG101 is composed of lentiviral vector-transduced autologous T cells that express an HBsAg-specific TCR in autologous T cells.[28] Lentiviral transduction of a TCR allows a stable expression even when T cells divide and it has a lower risk of insertional mutagenesis than retroviral vectors.[31] Our initial experiments showed that SCG101's HBV-TCR can accurately identify and bind HBV-infected hepatocytes and HCC cells expressing HBsAg from integrated or episomal HBV-DNA. Furthermore, the Good Manufacturing Practice (GMP)-compliant production, as well as the safety and feasibility of SCG101 application, were demonstrated in preclinical models and in a first patient.[28] To further prove the feasibility of HBV-specific T-cell therapy, we here analyse the safety and efficacy of SCG101 treatment in a multicentre, investigator-initiated trial of six patients with advanced, multiline pre-treated, progressive HBV-related HCC.

MATERIALS AND METHODS

Study design

In this open-label, multicentre study (NCT05339321) with a 3+3 dose escalation design, patients with HBV-related HCC, and disease progression despite multiple treatment modalities, received SCG101 TCR-T-cell therapy. Key inclusion criteria were: (1) age 18–70 years with intermediate to advanced HCC (Barcelona Clinic Liver Cancer (BCLC) stages B/C) not amenable to surgery, who showed progression or intolerance following at least one line of standard systemic therapy and had at least one measurable lesion; (2) seronegativity for hepatitis B e antigen (HBeAg) and positivity for HBsAg, HBV-DNA level $\leq 2\times10^3$ IU/mL; (3) HLA-genotype HLA-A*02 (02:01, 02:02, 02:03, 02:04, 02:07, 02:09 or 02:16)[24 25]; (4) Eastern Cooperative Oncology Group (ECOG) performance scores of 0–1, Child-Pugh scores A/B, an expected survival of more than 3 months and well-preserved organ function. Continuation of treatment with nucleos(t)ide analogues (NUCs) was mandatory.

Key exclusion criteria encompassed: (1) any other incurable malignancy either concurrently or within the previous 5 years; (2) active autoimmune diseases requiring immunosuppressive treatment; (3) a history or pending status of organ transplantation; (4) active infections with other viruses such as hepatitis C virus, hepatitis A virus, hepatitis D virus, hepatitis E virus, HIV, cytomegalovirus, Epstein-Barr virus; (5) any prior cell therapy, or antitumour treatment for the condition within 2 weeks prior to peripheral blood mononuclear cell (PBMC) collection. Informed consent was acquired from all participants, and the study was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. Patients or the public were not involved in the trial design.

Patient treatment

In this study, we report on the cohort of six HLA-A*02:01-positive patients who received SCG101 T cells from 9 October 2021 through 16 August 2022. The data cut-off date for this interim analysis was 9 March 2024. Autologous T cells were obtained via leukapheresis, transduced with a lentiviral vector encoding for one TCR that targets both versions of the HBV peptide $S_{20–28}$ (FLLTRILTI or FLLTKILTI) expressed depending on the HBV genotype and presented on HLA-A*02.[25] The TCR,[25] vector construct, cell preparation and preclinical study preparation have been described in detail previously.[28] After transduction and expansion, cells were suspended in 5% human

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

serum albumin and saline solution, filled into sterile infusion bags, stored at ≤−150°C, and transported in liquid nitrogen to the respective study site.

Before cell infusion, patients underwent lymphodepletion chemotherapy with cyclophosphamide (Cy, 500 mg/m^2/day) and fludarabine (Flu, 25 mg/m^2/day) for three consecutive days, with adjusted dose and timing, if necessary, based on the patient's clinical status (online supplemental table S1). 3 days later, SCG101 cells were thawed in a 36–38°C water bath and infused within 30 min at an infusion rate of approximately 3–5 mL/min. The trial protocol allowed an exploratory second infusion under the criteria outlined in the Online supplemental methods, which was applied in one patient. Interleukin (IL)-2 co-infusion was allowed per protocol but ultimately not applied. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) cohort reporting guidelines were applied where appropriate.[32]

Study monitoring

Demographic, laboratory and radiological data were systematically collected, along with documentation of symptoms and signs before and after SCG101 cell infusion. Symptomatic treatment, including antipyretic, antiemetic, infection prevention and liver protection therapy, was provided as needed. Patients were allowed to be discharged when their general condition was stable, vital signs were normal and the absolute neutrophil count had recovered to more than 1.5×10^9 cells/L.

During the hospitalisation period after the cell infusion, the patients were evaluated daily for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). After being discharged, the patients documented their body temperature two times a day for 1 month, and they were assessed for CRS and ICANS at each follow-up visit until all related symptoms and serum markers had resolved. Any new or worsened diseases, symptoms, signs, laboratory and auxiliary examination abnormalities after the time point of leukapheresis were recorded as AEs, whether expected or unexpected, and rated for severity according to predefined criteria. CRS and ICANS were graded using the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 standards, while other AEs were graded with the Common Terminology Criteria for Adverse Events V.5.0.

Study assessments

The first efficacy assessment occurred 1 month after SCG101 T-cell infusion, followed by an assessment every 2 months from months 2–12, and then every 3 months until the patient discontinued the study. Efficacy assessments were based on the modified response evaluation criteria in solid tumours (mRECIST) or the immune-based RECIST, using contrast-agent-enhanced CT.

Viral parameters were measured using the diagnostic assays available at each study site. HBsAg was quantified via Electrochemiluminescence Immunoassays: Site 1: Roche, LLoD 1.99 IU/mL; Site 2 and 3: Abbott, LLoD 0.05 IU/mL; Site 4 Autobio, LLoD 0.01 IU/mL. HBV-DNA was measured via quantitative real-time PCR: Site 1: XIAMEN Amplly, LLoD 1000 IU/mL; Site 2: Roche, LLoD 20 IU/mL; Site 3: Shanghai ZJ Bio-Tech, LLoD 100 IU/mL; Site 4: Sansure Biotech, LLoD 50 IU/mL.

RESULTS

Study design and patient characteristics

In this open-label, single-arm investigator-initiated study with a dose escalation design, six HLA-A*02:01 positive adult patients with HBV-related HCC, stable liver function and inactive chronic hepatitis B (CHB) were recruited (figure 1A). Patients were infused with autologous, HBV-specific SCG101 T cells as monotherapy. Before inclusion, all patients had been treated with TKIs and four patients (ST1301, ST1401, ST1105, ST1207) had received ICI treatment (table 1 and online supplemental table S1). All participants were male with a median age of 46.0 years and diagnosed with HCC 3.1 (1.2–5.7) years earlier (table 1). Four patients had liver cirrhosis, and the liver function of all patients was graded as Child-Pugh stage A. One patient had BCLC stage B, and five patients had BCLC stage C disease. Four patients had extrahepatic metastatic lesions predominantly present in the lungs, one with additional metastases in the pleura, bones and mesentery. One patient had lymph node metastases (table 1 and online supplemental table S1).

All patients had an underlying HBeAg-negative chronic HBV infection, which was treated with NUCs (table 2). Serum HBsAg was 813.4 IU/mL (median, range: 435–1582 IU/mL). Five patients had HBV-DNA levels below 100 IU/mL, while one had an HBV-DNA level of 1980 IU/mL (table 2). Biopsies were collected from four patients, all showing positive HBsAg staining in the liver, ranging from 10–50% of hepatocytes (table 2, [28]). Among these, three biopsies contained tumour cells with HBsAg positivity ranging from 0–5% (figure 1B).

Patient ST1401 also showed signs of inflammation with massive immune cell infiltration in the tumour-adjacent area (figure 1B, middle row). The patients' PBMC were collected by apheresis. T cells were stimulated with anti-CD3/anti-CD28 antibodies, transduced with a lentiviral vector for expression of the HBV-specific TCR, expanded and underwent quality controls (online supplemental table S2).[28]

Patients received a single dose of SCG101 at 5.0×10^7 or 1.0×10^8 HBV-TCR$^+$ T cells/kg intravenously (online supplemental table S1) after lymphodepletion. Patient ST1206 received a second infusion of SCG101 at month 7 without additional lymphodepletion. Patients were followed up for a median of 12.5 months (2.5–28.4 months) and monitored for SCG101 persistence, AEs, liver and viral markers, and disease progression.

SCG101 infusion and persistence

SCG101 was produced with a standardised protocol under GMP conditions with an average of 38% HBV-TCR$^+$ T cells (online supplemental table S2).[28] The HBV-specific TCR was expressed in CD8$^+$ T cells as well as CD4$^+$ T cells, which have also been shown to obtain anti-HBV effector function, although SCG101's TCR is major histocompatibility complex class I-restricted.[24] Persistence of SCG101 was detected in post-infusion blood samples via quantification of the vector copy number (VCN) of the lentiviral integrate (figure 2A). The median maximum concentrations (C_{max}) were 25.91 copies/µg for the lower dose group and 46.23 copies/µg DNA for the higher dose group. This reflected a 1.78-fold higher maximum concentration in line with the 1.78-fold increase in the actual administered dose (average 5×10^7 vs 0.89×10^8 HBV-TCR$^+$ T cells/kg; online supplemental table S1). When quantifying the SCG101 concentration over the first 4 weeks after infusion, the median area under the curve $(AUC)_{0-28d}$ values were 289 891 and 511 605 day×copies/µg genomic DNA for the lower and higher dose groups, respectively (individual values shown in figure 2B). Notably, patient ST1206

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

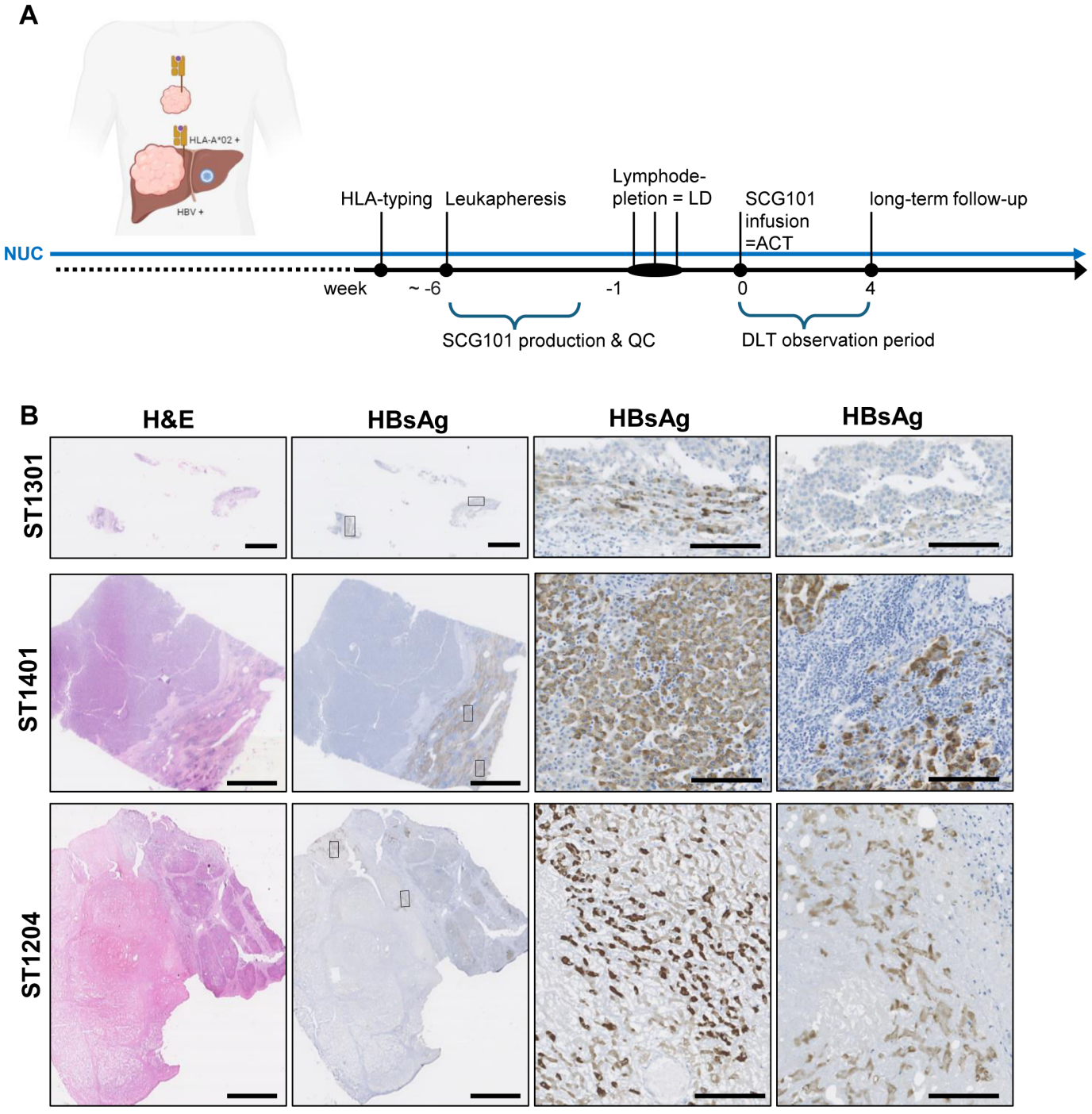

Figure 1 Inclusion of patients with HBV-associated HCC. (A) Scheme of the treatment procedure with SCG101 autologous T cells generated by lentiviral transduction to express an HBV-specific TCR, restricted towards the HBsAg-derived peptide $S_{20–28}$ and presented on HLA-A*02. Before SCG101 administration, patients received nucleos(t)ide analogue (NUC) treatment and a lymphodepleting regimen with cyclophosphamide and fludarabine (3 days). (B) Histological and immunohistochemical analyses of tumour biopsies taken 3 years (ST1301), 1 year (ST1401) and 5 years (ST1204) before SCG101 infusion. Left side: Morphological analysis using H&E staining. Right side: HBsAg staining; magnification positions are indicated with small boxes. Scale bars: 1 mm and 50 µm (inlay), respectively. Tumour biopsies of ST1105, ST1206 and ST1207 could not be obtained. A liver biopsy of ST1206 showed around 10% $HBsAg^+$ hepatocytes.[28] ACT, adoptive cell transfer; DLT, dose-limiting toxicity; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HLA, human leucocyte antigen; TCR, T-cell receptor.

exhibited an exceptionally high $AUC_{0–28d}$ and C_{max} relative to the SCG101 dose infused (figure 2A,B). The cell expansion measured by multimer staining of $HBV\text{-}TCR^+$ T cells showed similar patterns to that measured by VCN (figure 2C). Interestingly, patient ST1301's VCN fell below the limit of quantification between week 34 and 78 but became detectable and started increasing again afterward (figure 2A). In parallel, an increase in the absolute numbers of total lymphocytes and of SCG101 T cells was detected (online supplemental figure S1C, figure 2C). In patient ST1206, the $AUC_{0–28d}$ and C_{max} after the second infusion without prior lymphodepletion reached 56% of the first infusion values (figure 2A,C). Taken together, cell expansion was

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 1 Baseline characteristics of patients receiving SCG101

Patient characteristics	Number of patients (n=6)
Age (years, median, (range))	46 (30–56)
Sex (n, male)	6
ECOG performance status (n, 0/1)	3/3
Years of diagnosis with HCC, median (range)	3.1 (1.2–5.7)
BCLC stage (n, B/C)	1/5
Extrahepatic metastasis	
Lung	4
Lymph node	1
Pleural	1
Bone	1
Mesentery	1
Child-Pugh score (n, A / 5–6)	6
Serum HBsAg (IU/mL, median, (range))	813.4 (435.4–1581.6)
Serum AFP (n)	
≥400 ng/mL	2
<400 ng/mL	4
Cirrhosis (n)	
Yes	4
No	2
SLD of target lesion (mm, median, (range))	63.5 (11.0–137.3)
Prior lines of systemic therapy (n)	
1	3*
2	2
≥3	1
Prior PD-1 inhibitor treatment (n; end day before SCG101 infusion (d, range))	4 (–199 to –55)
Prior antiviral treatment (years, median, (range))	6.2 (0.4–21.4)
Nucleoside analogues (n)	6
Interferons (n)	0

*Including one patient with combination therapy.
AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; n, number in respective category; PD-1, programmed cell death protein 1; SLD, sum of the longest diameter.

dose-dependent, with a long-term persistence of >2 years in the patient with the longest follow-up.

Safety of HBV-specific T-cell transfer

The most frequently reported treatment-related AEs (TRAEs) of grade 3 (5~20× upper limit of normal (ULN)) or grade 4 (>20× ULN) were an alanine and aspartate aminotransferase (ALT/AST) increase in all patients (6/6, 100%), a decreased platelet count in five patients (5/6, 83.8%), a CRS in four patients (4/6, 66.7%), hypotension, decreased neutrophil, white blood cell and lymphocyte count in three patients (3/6, 50.0%) (online supplemental figure S1), as well as gamma-glutamyl transferase increase and anaemia in one patient (1/6, 16.7%) (table 3 and online supplemental table S3). None of the patients experienced neurotoxicity or serious AEs related to SCG101 treatment. The haematological toxicities were consistent with the known AE profile of cyclophosphamide and fludarabine as lymphodepletion chemotherapy agents (online supplemental figure S1). Patient ST1206 did not experience any AE after the second SCG101 infusion. A transient creatinine increase on day 7 in this patient (data not shown) was not considered an off-target activity of SCG101 but a consequence of the CRS.[28]

Per the definition of the ASTCT, all patients developed a CRS.[33] A body temperature >38°C was reported in all patients (6/6, 100%) (figure 3A). Other symptoms included hypotension in four patients (blood pressure systolic <90 mm Hg, diastolic <60 mm Hg; 4/6, 66.7%) (figure 3B), sinus tachycardia in four patients (heart rate >100 beats per minute; 4/6, 66.7%), headache in three patients (3/6, 50.0%), hypoxia (blood oxygen <90%), nausea and vomiting in two patients each (2/6, 33.3%) (table 3 and online supplemental table S3). A CRS was observed on the day of infusion, accompanied by a rapid increase of CRP (figure 3C) and IL-6 (figure 3D), with IL-6 levels most likely being dose-dependent. All four patients dosed with 1×10^8 cell/kg experienced a CRS of grade 3 (online supplemental table S3) within 24 hours to 4 days and lasting for 2–4 days. Treatment included glucocorticosteroids (GCs) in all six patients (figure 3E), tocilizumab (figure 3F) and vasopressors (norepinephrine bitartrate in ST1204, ST1206 and ST1207; dopamine in ST1105) in the four patients receiving the higher dose of SCG101, and oxygen therapy in three patients (ST1401, ST1204 and ST1105). In total, the CRS could clinically be handled well and all patients recovered with no remaining symptoms. The patients could be discharged after a mean observation time of 16 days (range 7–29 days).

All patients showed a transient increase in AST and ALT (grade 3–4) activity within 1–3 days after SCG101 infusion, which lasted for 2–14 days (figure 4A,B). ALT levels correlated with the number of infused cells (figure 4C). Patients who had received the 5×10^7 TCR-T$^+$ cells/kg dose experienced up to grade 3 elevations (5~20× ULN), while those receiving the 1×10^8 TCR-T$^+$ cells/kg dose experienced grade 4 elevations (>20×ULN). Among the higher dose group, three patients experienced grade 1 (1~1.5×ULN) or grade 2 (1.5~3× ULN) increases in total serum bilirubin at day 1 (patients ST1206 and ST1207) or 10

Table 2 Pretreatment HBV markers

Patient ID	Age/sex	Antiviral treatment	Serum HBeAg	HBV-DNA (IU/mL)	Serum HBsAg (IU/mL)	HBsAg$^+$ cells in liver area	HBsAg$^+$ cells in HCC area	Dose (TCR$^+$ cells/kg)
ST1301	56/M	ETV	neg*	<100	1004	50%	1%	5×10^7
ST1401	34/M	ETV	neg	<50	1582	20%	0%	5×10^7
ST1105	42/M	ETV	neg	1980	1000	n/a	n/a	1×10^8
ST1204	30/M	ETV/TDF	neg	59	435	20%	5%	1×10^8
ST1206	54/M	ETV	neg	29	557	10%	n/a	1×10^8
ST1207	50/M	ETV	neg	66	626	n/a	n/a	1×10^8

*ST1301 tested positive (index value 25.1, normal range 0–1) for HBeAg on 20 October 2021, but tested negative (0.48 S/CO, normal range 0–1) the following day at a different hospital. Time point of biopsy: ST1301 3 years, ST1204 5 years, ST1401 1 year before SCG101 infusion.
ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; neg, negative; S/CO, Signal-to-Cut-Off Ratio; TCR, T-cell receptor; TDF, tenofovir disoproxil fumarate.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

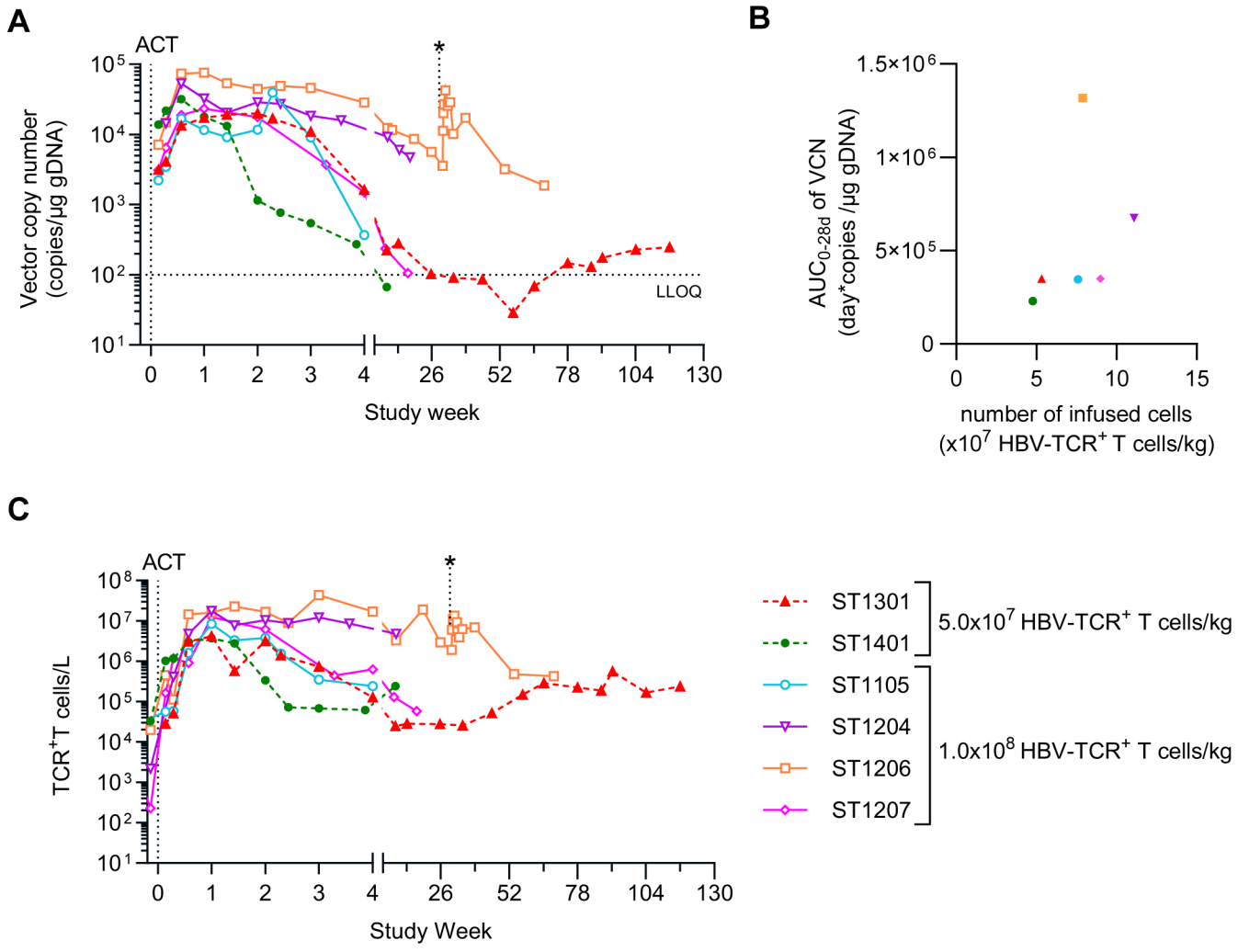

Figure 2 Long-term monitoring of SCG101 in blood. Six HLA-A*02:01 patients were enrolled; two received a targeted dose of 5×10^7 HBV-TCR$^+$ T cells/kg (dashed lines), and four received 1×10^8 HBV-TCR$^+$ T cells/kg (solid lines). Reddish lines indicate responders with ≥1 $\log_{10}$ HBsAg reduction (ST1301, ST1204, ST1206, ST1207); green and blue lines indicate <1 $\log_{10}$ HBsAg reduction (ST1401, ST1105). (A) Genomic DNA was extracted from whole blood samples. The viral copy number (VCN) of a fragment of the lentiviral vector integrated into the T cells was quantified via qPCR. (B) Correlation analysis of the area under the curve (AUC) for 28 days and the number of infused SCG101 T cells. (C) The number of TCR$^+$ T cells in peripheral blood was determined by multimer staining of the TCR and quantified via flow cytometry. *Indicates a second infusion of 1.11×10^8 HBV-TCR$^+$ T cells/kg into patient ST1206 without additional lymphodepletion. ACT, adoptive cell transfer; gDNA, genomic DNA; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HLA, human leucocyte antigen; LLOQ, lower limit of quantification; qPCR, quantitative PCR; TCR, T-cell receptor.

days (ST1204) post SCG101 infusion and recovered without sequelae (figure 4D). All patients showed significant increases in serum lactate dehydrogenase (LDH), following the same trend as the liver enzymes (figure 4E). Five patients had a transient and significant increase in serum ferritin levels (figure 4F), two patients (ST1301 and ST1105), who did not show increased bilirubin levels, demonstrated a transient increase in the International Normalised Ratio (INR) of up to 32% (figure 4G). A mild and transient decrease in serum albumin levels was observed in all patients (figure 4H). These markers for liver function remained unremarkable during the long-term follow-up monitoring (online supplemental figure S2), and all TRAEs were manageable and reversible. Thus, no dose-limiting toxicity (DLT) was observed during the DLT monitoring period (within 28 days after the first infusion).

HBsAg reduction after T-cell infusion

HBsAg reduction was observed in all six patients (figure 5A–F, upper panels) concurrently with the peak expansion time of SCG101 T cells 4–16 days post-infusion (figure 2). Median baseline serum HBsAg was 813.4 IU/mL (435.4–1581.6 IU/mL). Four patients showed a reduction of ≥1 $\log_{10}$ and were defined as antiviral responders (figure 5A,D–F). The reduction remained stable throughout the follow-up period, which extended to 26.9 months until the data cut-off (figure 5A,E). The transient ALT flares occurred simultaneously with the HBsAg reduction, indicating cytolytic clearance of target cells with HBV integration or infection (figure 5A–F, lower panels). Interestingly, patient ST1301 had stable HBsAg levels of around 8 IU/mL throughout 1 year following SCG101 infusion, and it further reduced to 4.3 IU/mL at month 27 after more T cells became detectable in blood again (figures 2A,C and 5A). However, in patient ST1206 the second infusion without lymphodepletion at month 7 did neither lead to further reduction of serum HBsAg (0.35 IU/mL before the second infusion) nor an ALT increase (figure 5E). The overall median relative decrease of HBsAg was 1.96 $\log_{10}$ (range, 0.16–3.84 $\log_{10}$) (online supplemental figure S3A) and there was

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Table 3 Treatment-related adverse events after SCG101 infusion and lymphodepletion

Preferred term	All, n (%)	Grade 3 or 4, n (%)
Alanine aminotransferase increased	6 (100)	6 (100)
Aspartate aminotransferase increased	6 (100)	6 (100)
Cytokine release syndrome	6 (100)	4 (66.7)
Fever	6 (100)	0
Platelet count decreased	5 (83.3)	5 (83.3)
Hypoalbuminaemia	5 (83.3)	0
Neutrophil count decreased	4 (66.7)	3 (50.0)
Hypotension	4 (66.7)	3 (50.0)
Gamma-glutamyl transferase increased	4 (66.7)	1 (16.7)
Alkaline phosphatase increased	4 (66.7)	0
Sinus tachycardia	4 (66.7)	0
White blood cell count decreased	3 (50.0)	3 (50.0)
Lymphocyte count decreased	3 (50.0)	3 (50.0)
Monocyte count decreased	3 (50.0)	0
Bilirubin in the blood increased	3 (50.0)	0
Chills	3 (50.0)	0
Abdominal distension	3 (50.0)	0
Headache	3 (50.0)	0
Anaemia	2 (33.3)	1 (16.7)
Procalcitonin increased	2 (33.3)	0
Eosinophil count decreased	2 (33.3)	0
Nausea	2 (33.3)	0
Vomiting	2 (33.3)	0
Hypoxia	2 (33.3)	0

Any grade TRAEs occurring in ≥2 patients and all grade 3 or 4 TRAEs are listed.
TRAEs, treatment-related adverse events.

a general trend of high numbers of cell expansion and the intensity of simultaneous HBsAg reduction (figure 5G).

During screening, all six patients had HBV-DNA levels below the quantification limit of the individual assay applied at each study site (online supplemental figure S3B). HBV-DNA levels had slightly increased in four patients the day before T-cell infusion (figure 5H, online supplemental figure S3B). In two of those, the HBV-DNA rose slightly above 100 IU/mL after T-cell transfer and then returned to normal. In patient ST1105, the HBV-DNA level of 1980 IU/mL detected before infusion remained at a comparable level after infusion and during follow-up (figure 5H). As an exception, patient ST1401, who did not show a significant drop in HBsAg, experienced a significant increase of HBV-DNA one to 2 days after SCG101 infusion, peaking at 1410 IU/mL and returning to below 50 IU/mL on day 7 (figure 5H, online supplemental figure S3B).

Overall, the antiviral activity of SCG101, as determined by the decrease of HBsAg, was rapid, strong and sustained in most patients.

HCC monitoring after T-cell infusion

All six patients with their far-advanced HCC were analysed for the antitumour efficacy of the SCG101 T-cell therapy. Target lesions were measured 1 and 2 months after infusion and bimonthly thereafter. According to mRECIST criteria, 3/6 patients achieved tumour shrinkage with a best percentage change in target lesion size of −19.5%, −74.6% and −100% (figure 6A,B). This constituted two partial responses (PR) with a duration of 8.0 and ≥9.5 months, respectively (figure 6A–C). The two patients who showed a PR, ST1301 and ST1206, had low baseline AFP levels (online supplemental figure S3D) and the least tumour progression between screening and SCG101 infusion (figure 6A). ST1206 first experienced a decrease in AFP, followed by an increase in month 5 and hence underwent a reinfusion approximately 7 months after the first infusion. Nevertheless, the patient experienced disease progression in non-target lesions, subsequently transitioning to long-term survival follow-up and receiving additional anticancer therapies. The median follow-up time was 10.9 months. In total, three patients died, one was lost to follow-up and two patients are known to remain alive more than 2 years after SCG101 infusion.

Two of the patients with tumour shrinkage had 1–5% $HBsAg^+$ tumour cells within the HCC area of the biopsy (figure 1B and table 2). The target lesion of patient ST1301 was detected in the lung with an unknown presence of the target peptide. Following an initial minor reduction, a pronounced size reduction of this lung lesion was observed 18 months after SCG101 infusion (figure 6A, online supplemental figure S3C), concurrently with the re-emergence of SCG101 T cells (figure 2). Two patients were evaluated as stable disease (figure 6B), resulting in an ORR of 33.3% and a disease control rate of 66.7%. The median progression-free survival (PFS) was 12.8 weeks, with one patient remaining progression-free, including non-target lesions, for over 2 years until data cut-off (figure 6D).

DISCUSSION

New therapies for both HCC and its leading cause, CHB, are urgently needed. As a new immunotherapeutic modality addressing both challenges, we developed lentiviral vector-transduced autologous HBsAg-specific TCR-T cells (SCG101). SCG101 exploits a high-avidity TCR that is expressed on $CD4^+$ and $CD8^+$ T cells. Viral vector transduction of the TCR allows TCR-T cells to persist in both animal models[24 28 34] and in a patient with HCC.[28] In this study, we present a larger population of six HLA-A*02:01 positive patients with an advanced HBV-associated HCC treated with SCG101 after up to three prior systemic therapies. In this study population, we confirmed SCG101's safety and efficacy. All TRAEs, including CRS and increased liver enzymes, were reversible. A substantial HBsAg reduction was observed in 5/6 participants, and a tumour response per mRECIST was observed in 2/6 after SCG101 infusion.

CRS is one of the most common adverse reactions in T-cell immunotherapy, most likely induced by macrophage activation.[35] In our study, all six participants experienced varying levels of CRS up to grade 3, primarily presenting with symptoms of high fever, hypotension and elevation of CRP and IL-6 in serum. A comparable CRS was also observed in other studies using glypican 3 (GPC3)-specific CAR-T cells in patients with HCC[36 37] or CAR-T cells against haematological cancers in chronically HBV-infected patients.[38 39] In those studies, no correlation between the development of CRS and liver function was observed. SCG101-induced CRS was manageable using tocilizumab and GC pulse therapy to mitigate the macrophage activation and typical CRS symptoms, although the four patients receiving the higher dose of SCG101 still required vasopressor treatment.

The CRS treatment may, however, also alter T-cell functionality and thus the efficacy of SCG101. While the anti-IL6 receptor antibody does not seem to affect the efficacy of transferred T cells in CAR-T studies, the data on the effect of GCs remains less clear. Studies have reported either a reduced or unaltered efficacy of CAR-T cells after GC treatment.[35 40] In patient ST1401, who was the only patient without sustained HBsAg reduction,

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

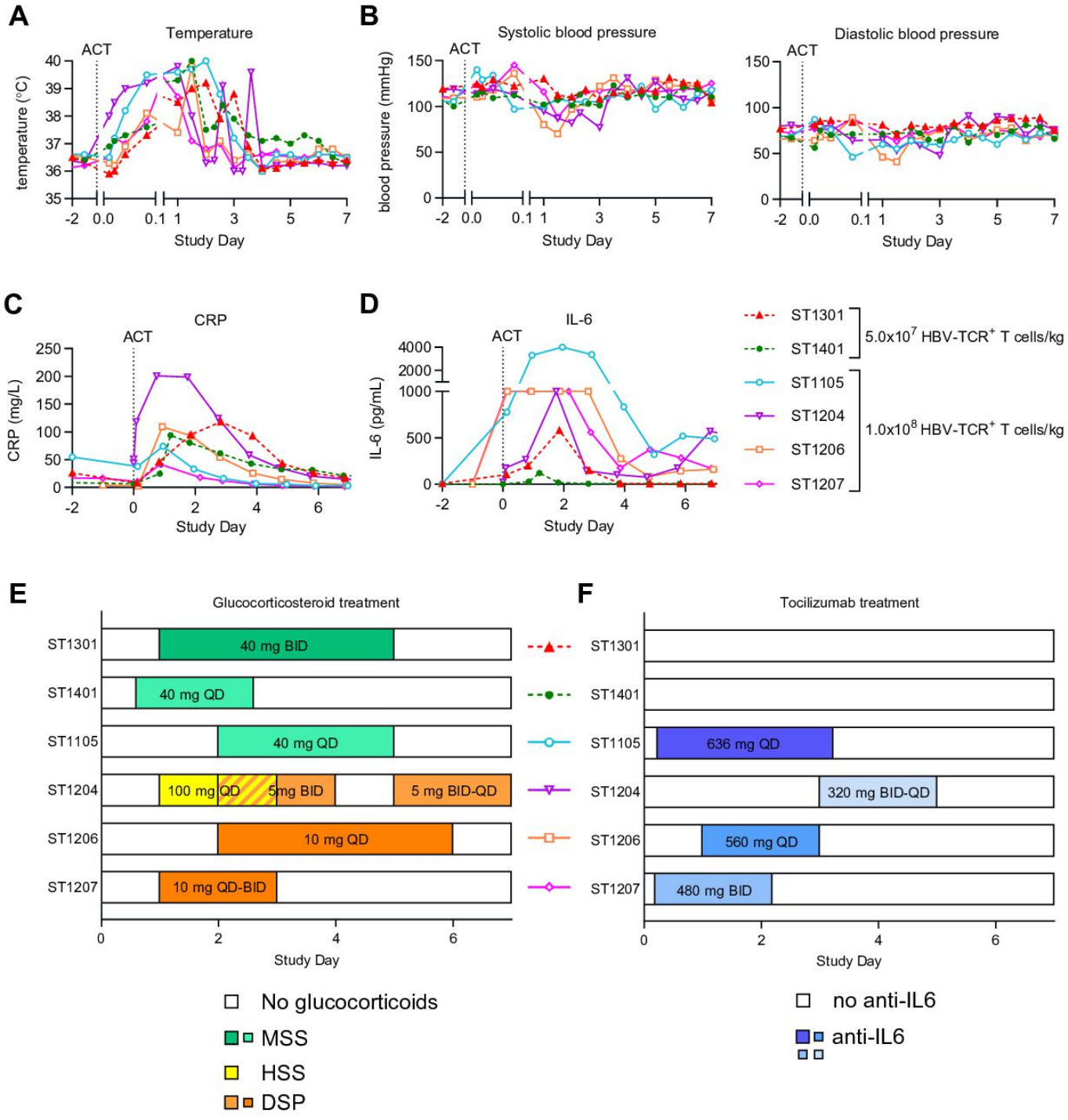

Figure 3 Transient cytokine release syndrome after infusion of HBV-specific T cells. (A, B) Body temperature and blood pressure were measured at 15 min (±5 min), 30 min (±5 min), 1 hour (±15 min), and 2 hour (±15 min) after infusion on D0, and twice a day until D14. A sudden decrease in body temperature indicates treatment with antipyretics. (C) C-reactive protein (CRP) (D) and IL-6 serum levels indicate ongoing inflammation. The upper detection limit of the diagnostic IL-6 assay was 4000 for site 1 (ST1105) and 1000 pg/mL for site 2 (ST1204, ST1206, ST1207). (E, F) Systemic treatment of CRS with glucocorticosteroids and the anti-IL-6 receptor antibody tocilizumab during the first week after infusion of SCG101 is indicated by the coloured blocks. ACT, adoptive cell transfer; BID, two times a day; CRS, cytokine release syndrome; D0, day 0; DSP, dexamethasone sodium phosphate; HBV, hepatitis B virus; HSS, hydrocortisone sodium succinate; IL, interleukin; MSS, methylprednisolone sodium succinate; QD, once a day; TCR, T-cell receptor.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

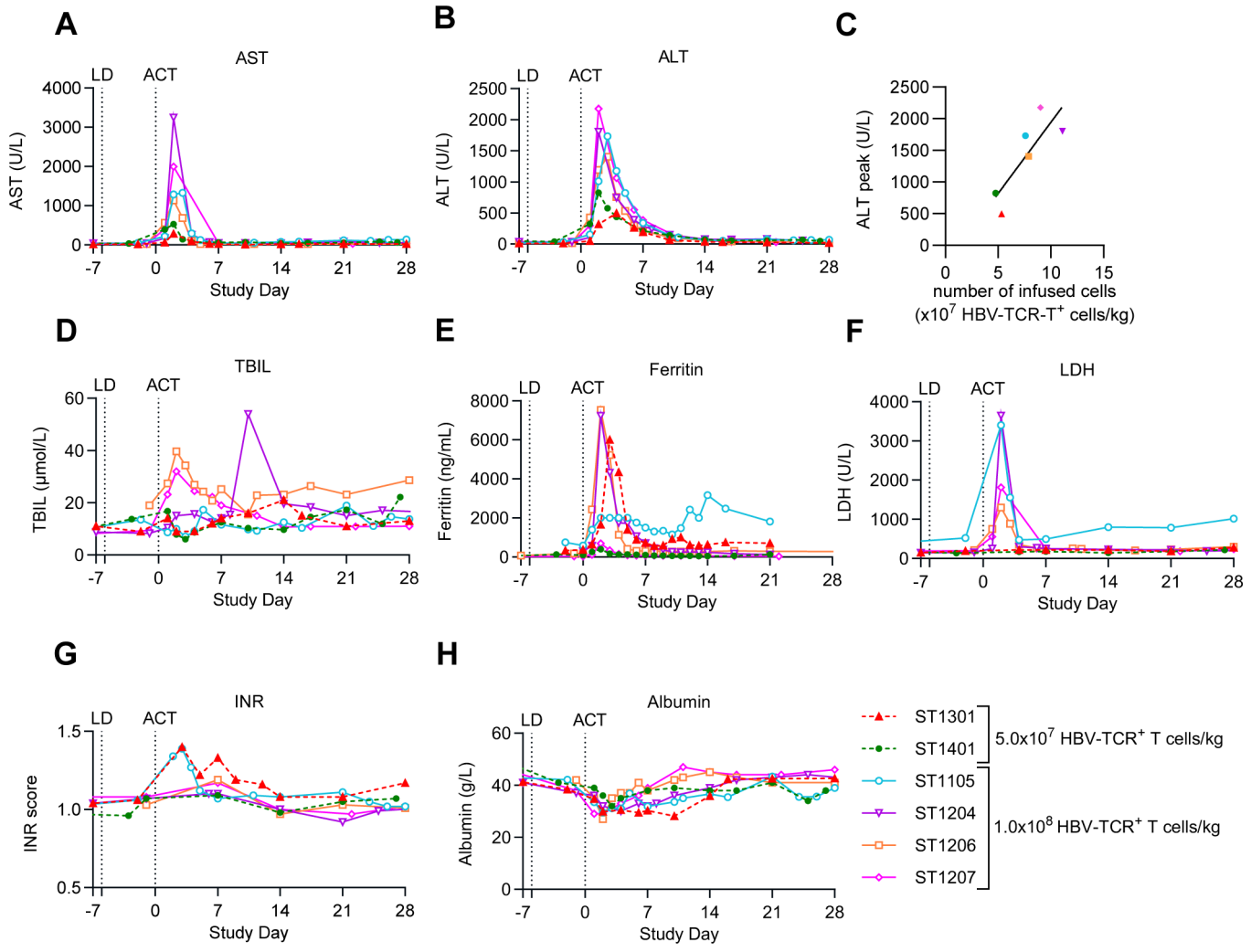

Figure 4 Liver function after transfer of SCG101 HBV-specific T cells. (A–B, D–H) Serum levels of liver function biomarkers monitored for 28 days after T-cell transfer: aspartate transaminase (AST), alanine transaminase (ALT), TBIL (total bilirubin), ferritin, lactate dehydrogenase (LDH), the International Normalised Ratio (INR) for blood-clotting and albumin were measured on indicated days. (C) Correlation analysis of the maximum ALT elevation and the infused dose of SCG101, R^2=0.6881, p value=0.0411 by simple linear regression analysis. ACT, adoptive cell transfer; HBV, hepatitis B virus; LD, lymphodepletion; TCR, T-cell receptor.

markedly lower IL-6 levels in serum and a lower expansion rate of SCG101 T cells were detected. This could suggest that induction of inflammation and a certain level of cytokine release could also be beneficial or an indicator of a good response. In this regard, real-world data of commercial CD19 CAR-T cell products have shown that the product with the highest percentage of CRS induction also has the highest efficacy.[41]

After the infusion of SCG101 T cells, a significant increase in serum ALT, AST, LDH and ferritin was observed, in some patients accompanied by mild alterations in bilirubin, INR and albumin levels. All this, however, was reversible and rapidly normalised in parallel with the anti-inflammatory treatment given for CRS management. The liver injury and the simultaneous decrease of serum HBsAg were related to the on-target activity of SCG101, with its known cytolytic activity clearing hepatocytes and HCC cells expressing HBsAg.[24] In acute, self-limiting HBV infection, these transient ALT flares are considered a sign of antiviral efficacy and ultimately lead to a functional HBV cure.[42] During acute, self-resolving hepatitis B or benign flares in CHB, ALT elevations last for one to 3 months.[43 44] In our observation, ALT peaks occurred 2–3 days after SCG101 T-cell transfer and lasted for less than 2 weeks. Although the overall ALT peaks reached similar levels as in acute hepatitis B, the faster kinetics might be attributed to more HBV-specific cells being directly effective after infusion instead of T-cell responses building up over several weeks.[43] Also, the inflammatory environment associated with the CRS itself can lead to an elevation of liver enzymes.[45] Furthermore, the shorter duration of the ALT flare was possibly associated with much lower numbers of infected cells in these long-term CHB patients.[46]

Surprisingly, in the six patients presented here, the levels of ALT did not correlate with baseline HBsAg levels in serum. One possible explanation is that serum HBsAg does not fully reflect the overall number of HBsAg-expressing cells in the liver[47] or that some patients contain shorter fragments of HBsAg that are not detected by the diagnostic assays but still express the peptide S_{20-28},[48] which the SCG101 TCR recognises. Instead, in this small cohort, we observed a trend that both the degree of liver enzyme elevations and the grade of CRS were related to the quantity of TCR-T cells infused, in line with an increased killing velocity *in vitro* when the number of effector cells is increased.[24] However, the success, as measured by the relative decrease of

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

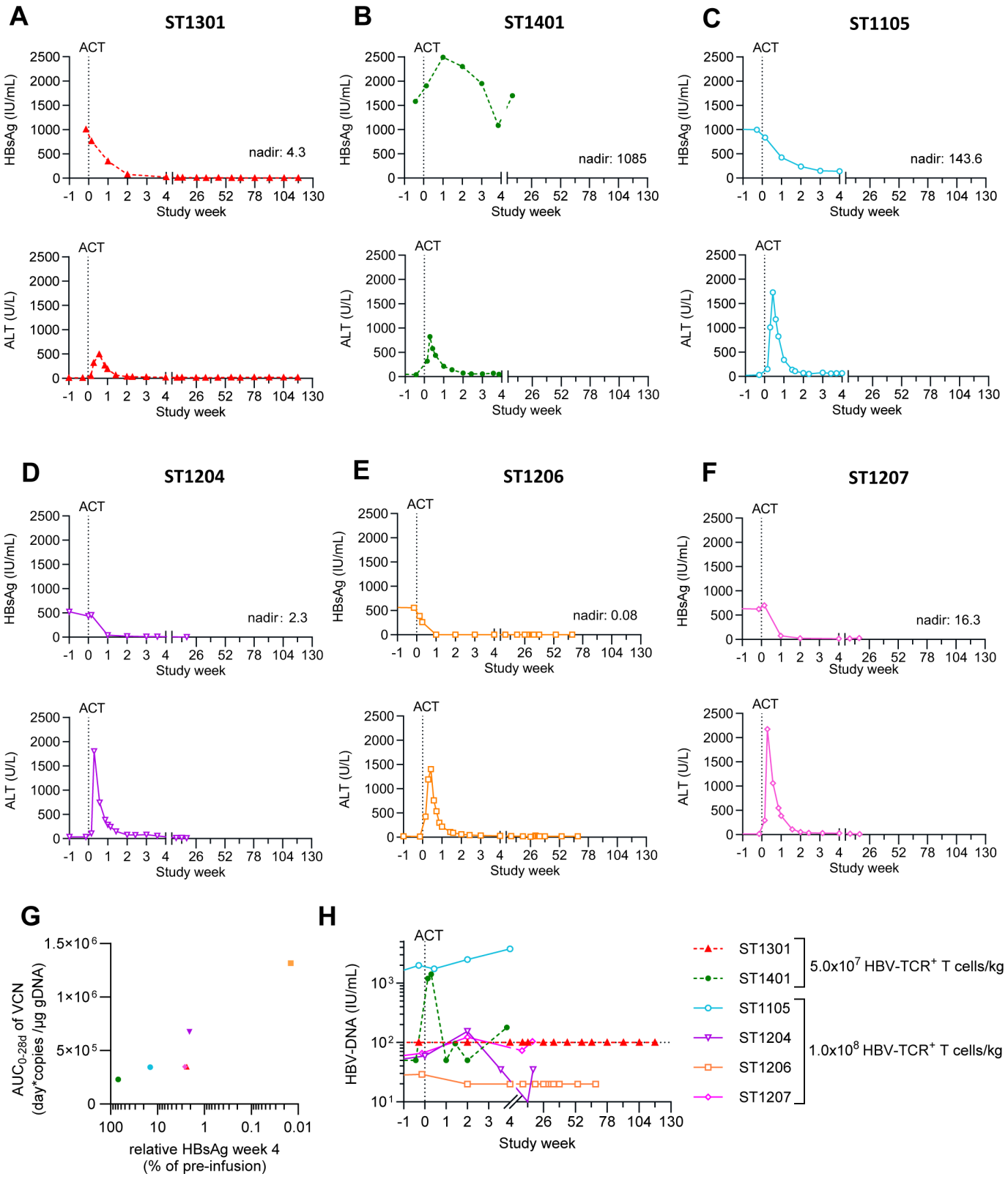

Figure 5 Viral markers and liver flares following infusion of HBV-specific SCG101 T cells. (A–F) Serum HBsAg (upper panels) and ALT (lower panels) levels of individual patients. (G) Correlation analysis of the accumulated amount of SCG101 over 4 weeks as determined by AUC calculation of the VCN and the relative HBsAg reduction during that timeframe. (H) HBV-DNA levels determined by qPCR at individual study sites (lower levels of quantification: site 01: <1000, site 02: <20, site 03: <100, site 04: <50). ACT, adoptive cell transfer; ALT, alanine aminotransferase; AUC, area under the curve; gDNA, genomic DNA; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; qPCR, quantitative PCR; TCR, T-cell receptor; VCN, vector copy number.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

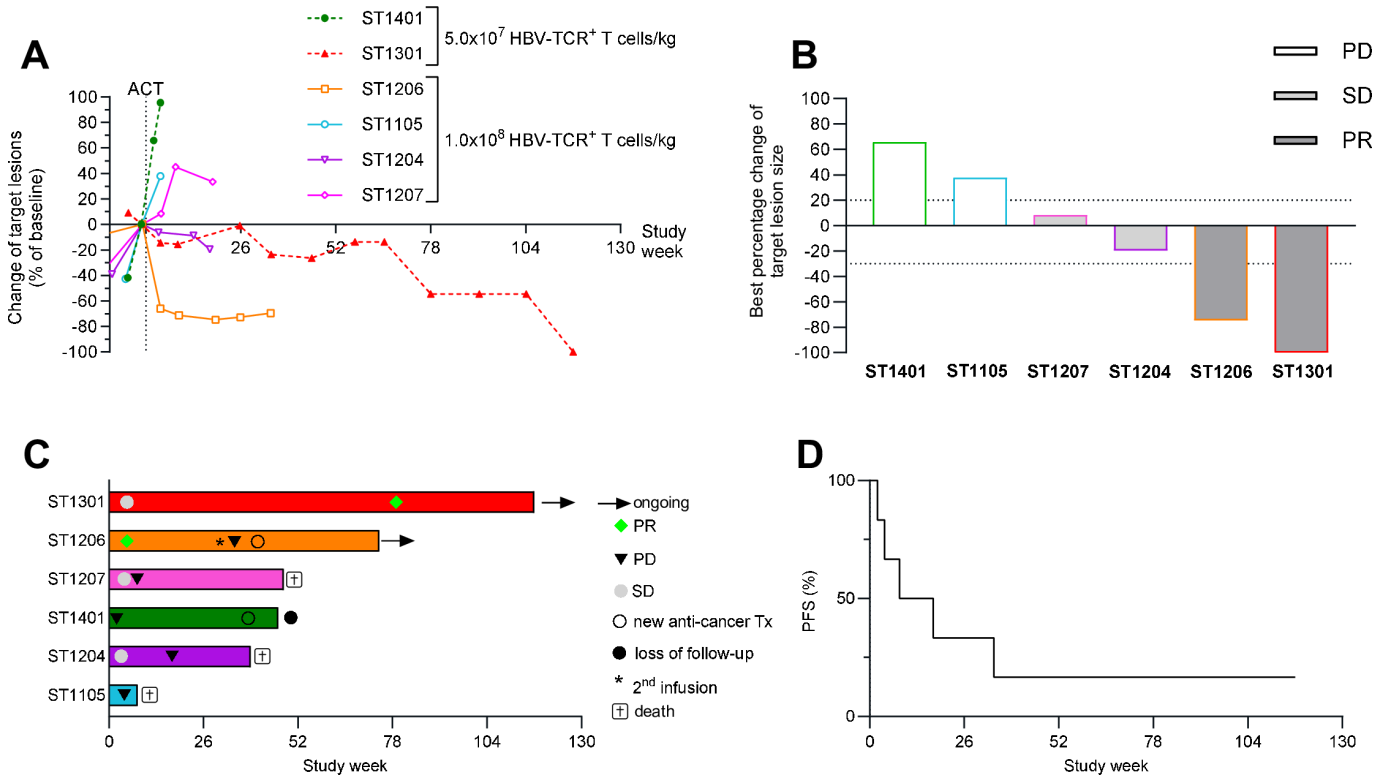

Figure 6 Tumour responses after infusion of SCG101. (A) Percentage change in the sum of diameters of target lesion(s) over time, assessed by multiphasic CT scan at indicated time points, until a PD was documented. For patients ST1401 and ST1207, PD was confirmed by an additional scan per iRECIST criteria. (B) Best percent change from baseline in the sum of diameters of target lesion(s) at any time point for each patient. The dashed lines at –30% and +20% represent thresholds for PR and PD, respectively, per mRECIST criteria. (C,D) Tumour responses and PFS as per mRECIST criteria. Although patient ST1204 experienced a tumour size reduction at month 4, the overall response was regarded as PD due to the development of a new lesion. ACT, adoptive cell transfer; HBV, hepatitis B virus; iRECIST, immune response evaluation criteria in solid tumours; mRECIST, modified response evaluation criteria in solid tumours; PD, progressive disease; PFS, Progression-free survival; PR, partial response; SD, stable disease; TCR, T-cell receptor.

HBsAg, highlighted the importance of cell persistence rather than the infusion dose. The only patient without sustained HBsAg decrease, ST1401, had a very poor T-cell engraftment, and cell numbers quickly dropped. Similarly, in a prior study, long-term serum HBsAg levels were barely affected when HBV-specific T cells transiently expressed a TCR after RNA electroporation.[27] Patient ST1401, in which T-cell expansion was low, had not only lower IL-6 levels but also stood out because of much higher numbers of blood lymphocytes, eosinophils and monocytes before treatment, continuously high monocytes during treatment and high numbers of liver-infiltrating immune cells. Among those, anti-inflammatory immune cells might have contributed to the dysfunction of HBV-specific T cells.[49]

By contrast, patient ST1206 had exceptionally good cell persistence and a 99.99% reduction of HBsAg.[28] A few clinical studies in solid tumours have analysed cell persistence and found positive correlations with the response to T cell therapy. Already in a trial in the early days of T-cell therapy, it was found that patients with cell persistence for more than 6 weeks had less neuroblastoma progression.[50] More recently, it was shown that clinical responses to treatment with CLDN6-specific CAR-T cells only occurred in patients with sustained T-cell persistence over 6 weeks.[51] Similarly, the recent clinical data from Adaptimmune's TCR-T cell product, the world's first approved TCR-T cell therapy (afamitresgene autoleucel), demonstrated a correlation between long T-cell persistence and treatment efficacy in its Phase II pivotal trial.[52] Our findings align with this perspective, suggesting that the durable persistence of TCR-T cells, as achievable with lentiviral transduction, can be associated with better clinical outcomes in solid tumours such as HBV-HCC.

Another observation also supports the idea that not only the infused cell dose but also the setting plays an important role in engraftment. When patient ST1206 had an increase in AFP, and it was unclear whether the remaining SCG101 T cells were potentially exhausted, he received a second injection of SCG101 at the highest dose level. We refrained from a second lymphodepletion to avoid depleting any anti-HBV or antitumour immune cells that had potentially built up after the first infusion of SCG101. This time, cells expanded less than after the previous lower dose injection, no symptomatic CRS or ALT elevations occurred, and serum HBsAg, which had remained below 1 IU/mL, was not further decreased. This indicates that either the remaining antigen stimulus was insufficient or that the lymphodepletion preconditioning is indispensable. Lymphodepletion is a chemotherapeutic treatment regimen that is standard practice to facilitate T-cell engraftment and persistence and has been shown to consequently improve treatment outcomes.[53] However, lymphodepletion bears the theoretical risk of a hepatitis flare. Encouragingly, we only observed minor increases in HBV-DNA after the lymphodepletion and before T-cell transfer. HBV reactivations have indeed been observed after CAR-T cell treatment of B cell lymphomas but have been attributed to the subsequent B cell aplasia and not to the lymphodepletion.[54] A sudden increase and decrease of HBV-DNA just after SCG101

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

T-cell transfer might have resulted from HBV$^+$ hepatocyte killing and a sudden release of HBV-DNA-containing capsids or integrated HBV-DNA. We have already observed this phenomenon *in vitro* in the co-culture of HBV-specific T cells and HBV-infected HepG2-NTCP cells,[24] and it warrants further studies into SCG101's mode of action with more narrow screening and different virological assays.

As a preventive measure against HBV reactivation, all patients continued oral nucleoside analogue therapy throughout enrolment in the study. Long-term antiviral therapy has been recommended as an important component of a comprehensive treatment of HCC to suppress viral replication or reactivation, reducing the risk of further liver deterioration and improving long-term prognoses.[55] Nevertheless, these drugs rarely achieve meaningful HBsAg reductions or even seroconversion because of their inability to eliminate the HBV covalently closed circular DNA or integrated HBV-DNA from hepatocytes.[56] For the six patients discussed here, serum HBsAg had remained high despite long antiviral treatment but was reduced rapidly after infusion. Liver biopsies for ST1206 taken before and after SCG101 infusion confirmed the clearance of HBsAg-positive cells.[28] The only other therapeutic approaches that have been shown to trigger sustainable HBsAg reductions in some patients are pegylated interferon (IFN) and nucleic acid polymers. Both require long-term treatment. IFN therapy is accompanied by unpleasant side effects, and nucleic acid polymers by constantly elevated liver enzymes over months.[57] With this in mind, it would be interesting to also test SCG101 T-cell infusion as a therapy in CHB patients at high risk of developing an HCC, and to potentially combine it with HBV vaccination to achieve a full seroconversion.

Although SCG101 showed very promising antiviral activity, the primary goal of the clinical trial was to assess its safety and efficacy against HBV-associated HCC. Regarding the antitumour efficacy, the ORR was 33.3%, and the disease control rate was 4/6, with one PR occurring at each dose level. Since T-cell therapy trials lack control arms, a categorical evaluation or a comparison to compatible historical cohorts remains tricky.

One patient achieved an initial PR with about 70% tumour reduction but progressed with new lesions emerging 8 months afterward, while the original target lesions remained well suppressed. The development of these new lesions was accompanied by a marked increase in AFP with no significant change in serum HBsAg. The new lesions were not affected by the second infusion of SCG101, indicating that they might have lost HBsAg expression and could not efficiently be targeted by the TCR-T cells. Considering that HCC may lose HBsAg expression, dual-targeted TCR-T cell therapy against both AFP and HBsAg could be an interesting approach. AFP has been suggested to promote the formation of cancer stem cells and to attenuate T-cell responses by shaping the immune suppressive tumour microenvironment.[58] This may have inhibited dendritic cells from presenting viral or tumour antigens and prevented the activation of endogenous T cells. The other PR in a patient with a lung metastasis was noted after 18 months. A complete loss of the target lesion coincided with SCG101's reappearance in the blood circulation along with a general increase in lymphocyte count. This observation underlines SCG101's capability of forming memory cells with the potential for giving rise to new TCR-T cells even a long time after infusion.

HBsAg could not be stained in all the HCCs we treated. This may have several reasons. In general, HBsAg is hard to stain if it is secreted and not retained in hepatocytes, and a biopsy taken from one area of the liver does not represent the average of HBsAg$^+$ target cells in other areas, as a histology study from Gilead Sciences revealed.[47] In addition, not all HCC cells are expected to contain the complete HBV S-gene due to the late tumour stage. Some cells may only contain HBV-DNA fragments that do not express the entire HBsAg detectable by immunological assays, but still can express polypeptide sequences that can be targeted by S_{20-28}-specific TCR-T cells.[48] Therefore, HBsAg expression in the tumour was not an inclusion criterion in our study.

In addition, a phenomenon referred to as epitope spreading may occur. Tan *et al* hypothesised that immunological alterations could follow the transfer of RNA-electroporated, HBV-specific TCR-T cells, leading to the induction of additional antitumour T-cell responses.[59 60] This may be fostered by the elimination of non-cancerous HBV-infected hepatocytes. However, whether HBV-specific T-cell therapy results in epitope spreading remains to be further investigated in upcoming studies. Furthermore, PFS and OS data need to be analysed in bigger cohorts to assess whether there is a benefit of reducing the viral antigen and eliminating the infected hepatocytes will provide additional advantages, such as improved long-term survival and other clinical benefits, even when the tumour is not ultimately controlled. This will pave the way for also treating patients with CHB and patients with HCC at high risk of tumour occurrence or recurrence, for example, after surgical removal of the primary tumour, and for enabling HBV functional cure in patients with preserved liver function, who have a lower risk of complications during T-cell therapy than the patients with end-stage HCC in this study.

Taken together, SCG101 T-cell therapy, applied as a monotherapy for patients with HBV-related HCC, demonstrated both antiviral activity with significant reduction of HBsAg and antitumour activities with a delayed progression in responders. The expansion of SCG101 T cells, reduction in serum HBsAg and observed tumour responses collectively underscore its on-target activity. However, a CRS up to grade 3 was observed that required therapeutic intervention and could be managed with steroid and anti-IL-6 receptor treatment. The proof-of-concept data accumulated to date support the continued development of HBV-specific T cell therapy as a novel therapeutic option for both CHB and HBV-associated HCC. Larger and systematic, controlled trials are required for a proper risk-benefit analysis. Optimising the dosing regimen and exploring combinations with other agents with potentially complementary mechanisms could further improve the efficacy–safety balance of T cells with a stable expression of an HBV-specific TCR.

Author affiliations
[1]Department of Liver Surgery, Peking Union Medical College Hospital, Beijing, Beijing, China
[2]Department of General Surgery, The Sixth People's Hospital of Shenyang, Shenyang, China
[3]Department of Medical Oncology, Zhongshan Hospital Fudan University, Shanghai, Shanghai, China
[4]SCG Cell Therapy GmbH, Munich, Germany
[5]Department of Medical Oncology, The First Hospital of China Medical University, Shenyang, China
[6]SCG Cell Therapy Pte Ltd, Singapore
[7]SCG (Shanghai) Cell Therapy Co Ltd, Shanghai, China
[8]Institute of Virology, Technical University of Munich / Helmholtz Munich, Munich, Germany
[9]German Center for Infection Research, Munich, Germany

X Mengyao Zheng @Mengyao Zheng and Ulrike Protzer @ProtzerUlrike

Contributors X'aW, DQ, YZ, WW, Y-PL, WL, XuW, SD and XQ performed T-cell transfer and follow-up treatment. LY and MZ acquired, validated and analyzed the data. KW and XiW analyzed the data. KW and XiW wrote the manuscript. KZ, XZ and UP designed the clinical study. KW, SD and UP revised the manuscript. KZ is the guarantor.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

Funding Scientific background work was supported by the Deutsche Forschungsgemeinschaft (German Research Foundation) via project SFB-TRR 338/1 2021–452881907. SCG Cell Therapy Pte. Ltd. provided resources for cell product manufacturing, logistics and sample testing.

Competing interests KW, XiW, XZ, LY, MZ and KZ are employees of SCG Cell Therapy. KW, KZ, and UP are board members and shareholders of SCG Cell Therapy Pte. Ltd. The other authors declare that there is no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval for the study was obtained from the principal investigator's site at the 'Institutional Review Board and Ethics Committee of Peking Union Medical College Hospital' under the approval number HS-2780. Additional ethical approvals were obtained from each local institutional review board at The sixth People's Hospital of Shenyang (#2020-X003-01), The First Affiliated Hospital of China Medical University (#2021-266-2) and Zhongshan Hospital, Fudan University (#B2021-342R).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Xiang'an Wu http://orcid.org/0009-0009-8729-8113
Dongmei Quan http://orcid.org/0000-0002-5361-1484
Karin Wisskirchen http://orcid.org/0000-0002-7447-4044
Wei Wu http://orcid.org/0009-0007-4250-5559
Yuhong Zhou http://orcid.org/0000-0001-6333-8226
Yun-Peng Liu http://orcid.org/0000-0002-9645-7990
Xueshuai Wan http://orcid.org/0000-0003-2140-5384
Xiaorui Wang http://orcid.org/0009-0003-6675-5094
Xuxu Zhang http://orcid.org/0009-0005-2930-2322
Lu Yang http://orcid.org/0009-0005-1280-0413
Mengyao Zheng http://orcid.org/0009-0000-3396-3434
Ke Zhang http://orcid.org/0000-0002-4595-7098
Ulrike Protzer http://orcid.org/0000-0002-9421-1911
Shunda Du http://orcid.org/0000-0002-9357-3259
Xiujuan Qu http://orcid.org/0009-0005-9366-2314

REFERENCES

1 Bray F, Laversanne M, Sung H, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA A Cancer J Clinicians* 2024;74:229–63.
2 Wen N, Cai Y, Li F, *et al*. The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines: 2022 update. *Biosci Trends* 2022;16:20–30.
3 Inchingolo R, Posa A, Mariappan M, *et al*. Locoregional treatments for hepatocellular carcinoma: Current evidence and future directions. *World J Gastroenterol* 2019;25:4614–28.
4 Wu Q, Qin S-K. Features and treatment options of Chinese hepatocellular carcinoma. *Chin Clin Oncol* 2013;2:38.
5 Yang C, Zhang H, Zhang L, *et al*. Evolving therapeutic landscape of advanced hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2023;20:203–22.
6 Manfredi GF, Celsa C, John C, *et al*. Mechanisms of Resistance to Immunotherapy in Hepatocellular Carcinoma. *J Hepatocell Carcinoma* 2023;10:1955–71.
7 Rizzo A, Carloni R, Ricci AD, *et al*. Treatment-related adverse events of first-line immunotherapy versus sorafenib for advanced hepatocellular carcinoma: a meta-analysis. *Expert Opin Drug Saf* 2023;22:323–9.
8 Griffiths CD, Zhang B, Tywonek K, *et al*. Toxicity Profiles of Systemic Therapies for Advanced Hepatocellular Carcinoma. *JAMA Netw Open* 2022;5:e2222721.
9 Wang B, Hao X, Yan J, *et al*. A bibliometric analysis of immune-related adverse events in cancer patients and a meta-analysis of immune-related adverse events in patients with hepatocellular carcinoma. *J Transl Intern Med* 2024;12:225–43.
10 Sim YK, Chong MC, Gandhi M, *et al*. Real-World Data on the Diagnosis, Treatment, and Management of Hepatocellular Carcinoma in the Asia-Pacific: The INSIGHT Study. *Liver Cancer* 2024;13:298–313.
11 Roddy H, Meyer T, Roddie C. Novel Cellular Therapies for Hepatocellular Carcinoma. *Cancers (Basel)* 2022;14:504.
12 Zhao L, Cao YJ. Engineered T Cell Therapy for Cancer in the Clinic. *Front Immunol* 2019;10:2250.
13 Tian Y, Li Y, Shao Y, *et al*. Gene modification strategies for next-generation CAR T cells against solid cancers. *J Hematol Oncol* 2020;13:54.
14 Tan E, Gakhar N, Kirtane K. TCR gene-engineered cell therapy for solid tumors. *Best Pract Res Clin Haematol* 2021;34:101285.
15 Tsimberidou A-M, Van Morris K, Vo HH, *et al*. T-cell receptor-based therapy: an innovative therapeutic approach for solid tumors. *J Hematol Oncol* 2021;14:102.
16 Robbins PF, Kassim SH, Tran TLN, *et al*. A pilot trial using lymphocytes genetically engineered with an NY-ESO-1-reactive T-cell receptor: long-term follow-up and correlates with response. *Clin Cancer Res* 2015;21:1019–27.
17 Löffler MW, Mohr C, Bichmann L, *et al*. Multi-omics discovery of exome-derived neoantigens in hepatocellular carcinoma. *Genome Med* 2019;11:28.
18 Ozer M, Goksu SY, Akagunduz B, *et al*. Adoptive Cell Therapy in Hepatocellular Carcinoma: A Review of Clinical Trials. *Cancers (Basel)* 2023;15:1808.
19 McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. *Hepatology* 2021;73 Suppl 1:4–13.
20 Wang S-H, Yeh S-H, Chen P-J. Unique Features of Hepatitis B Virus-Related Hepatocellular Carcinoma in Pathogenesis and Clinical Significance. *Cancers (Basel)* 2021;13:2454.
21 Liu X, Xia F, Chen Y, *et al*. Chinese expert consensus on refined diagnosis, treatment, and management of advanced primary liver cancer (2023 edition). *Liver Res* 2024;8:61–71.
22 Mason WS, Jilbert AR, Litwin S. Hepatitis B Virus DNA Integration and Clonal Expansion of Hepatocytes in the Chronically Infected Liver. *Viruses* 2021;13:210.
23 Gehring AJ, Xue S-A, Ho ZZ, *et al*. Engineering virus-specific T cells that target HBV infected hepatocytes and hepatocellular carcinoma cell lines. *J Hepatol* 2011;55:103–10.
24 Wisskirchen K, Kah J, Malo A, *et al*. T cell receptor grafting allows virological control of Hepatitis B virus infection. *J Clin Invest* 2019;129:2932–45.
25 Wisskirchen K, Metzger K, Schreiber S, *et al*. Isolation and functional characterization of hepatitis B virus-specific T-cell receptors as new tools for experimental and clinical use. *PLoS One* 2017;12:e0182936.
26 Yang F, Zheng X, Koh S, *et al*. Messenger RNA electroporated hepatitis B virus (HBV) antigen-specific T cell receptor (TCR) redirected T cell therapy is well-tolerated in patients with recurrent HBV-related hepatocellular carcinoma post-liver transplantation: results from a phase I trial. *Hepatol Int* 2023;17:850–9.
27 Meng F, Zhao J, Tan AT, *et al*. Immunotherapy of HBV-related advanced hepatocellular carcinoma with short-term HBV-specific TCR expressed T cells: results of dose escalation, phase I trial. *Hepatol Int* 2021;15:1402–12.
28 Wan X, Wisskirchen K, Jin T, *et al*. Genetically redirected HBV-specific T cells target HBsAg-positive hepatocytes and primary lesions in HBV-associated HCC. *Clin Mol Hepatol* 2024.
29 Qasim W, Brunetto M, Gehring AJ, *et al*. Immunotherapy of HCC metastases with autologous T cell receptor redirected T cells, targeting HBsAg in a liver transplant patient. *J Hepatol* 2015;62:486–91.
30 Foster JB, Barrett DM, Karikó K. The Emerging Role of In Vitro-Transcribed mRNA in Adoptive T Cell Immunotherapy. *Mol Ther* 2019;27:747–56.
31 Morgan RA, Boyerinas B. Genetic Modification of T Cells. *Biomedicines* 2016;4:9.
32 von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.
33 Lee DW, Santomasso BD, Locke FL, *et al*. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant* 2019;25:625–38.
34 Festag J, Festag MM, Asen T, *et al*. Vector-Mediated Delivery of Human Major Histocompatibility Complex-I into Hepatocytes Enables Investigation of T Cell Receptor-Redirected Hepatitis B Virus-Specific T Cells in Mice, and in Macaque Cell Cultures. *Hum Gene Ther* 2023;34:1204–18.
35 Morris EC, Neelapu SS, Giavridis T, *et al*. Cytokine release syndrome and associated neurotoxicity in cancer immunotherapy. *Nat Rev Immunol* 2022;22:85–96.
36 Fu Q, Zheng Y, Fang W, *et al*. RUNX-3-expressing CAR T cells targeting glypican-3 in patients with heavily pretreated advanced hepatocellular carcinoma: a phase I trial. *eClinicalMedicine* 2023;63:102175.
37 Shi D, Shi Y, Kaseb AO, *et al*. Chimeric Antigen Receptor-Glypican-3 T-Cell Therapy for Advanced Hepatocellular Carcinoma: Results of Phase I Trials. *Clin Cancer Res* 2020;26:3979–89.
38 Wang Y, Liu Y, Tan X, *et al*. Safety and efficacy of chimeric antigen receptor (CAR)-T-cell therapy in persons with advanced B-cell cancers and hepatitis B virus-infection. *Leukemia* 2020;34:2704–7.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

39 Fu S, Zhang Q, Jing R, *et al*. HBV reactivation in patients with chronic or resolved HBV infection following BCMA-targeted CAR-T cell therapy. *Bone Marrow Transplant* 2023;58:701–9.
40 Canadian Agency for Drugs and Technologies in Health. Anticytokine Therapy and Corticosteroids for Cytokine Release Syndrome and for Neurotoxicity Following T-Cell Engager or CAR T-Cell Therapy. *Can J Heal Technol* 2024;4.
41 Bastos-Oreiro M, Gutierrez A, Reguera JL, *et al*. Best Treatment Option for Patients With Refractory Aggressive B-Cell Lymphoma in the CAR-T Cell Era: Real-World Evidence From GELTAMO/GETH Spanish Groups. *Front Immunol* 2022;13:855730.
42 Ghany MG, Feld JJ, Chang K-M, *et al*. Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad. *Lancet Gastroenterol Hepatol* 2020;5:406–17.
43 Webster GJM, Reignat S, Maini MK, *et al*. Incubation Phase of Acute Hepatitis B in Man: Dynamic of Cellular Immune Mechanisms. *Hepatology* 2000;32:1117–24.
44 Chang M-L, Liaw Y-F. Hepatitis B flares in chronic hepatitis B: pathogenesis, natural course, and management. *J Hepatol* 2014;61:1407–17.
45 Sun Q, Qi YK, Qi KM, *et al*. Observation of liver indexes in patients with relapsed/refractory multiple myeloma treated with CAR-T-cells based on BCMA. *Chin J Hematol* 2023;44:832–7.
46 Montanari NR, Ramírez R, Aggarwal A, *et al*. Multi-parametric analysis of human livers reveals variation in intrahepatic inflammation across phases of chronic hepatitis B infection. *J Hepatol* 2022;77:332–43.
47 Aggarwal A, Odorizzi PM, Brodbeck J, *et al*. Intrahepatic quantification of HBV antigens in chronic hepatitis B reveals heterogeneity and treatment-mediated reductions in HBV core-positive cells. *JHEP Rep* 2023;5:100664.
48 Tan AT, Yang N, Lee Krishnamoorthy T, *et al*. Use of Expression Profiles of HBV-DNA Integrated Into Genomes of Hepatocellular Carcinoma Cells to Select T Cells for Immunotherapy. *Gastroenterology* 2019;156:1862–76.
49 Baudi I, Kawashima K, Isogawa M. HBV-Specific CD8+ T-Cell Tolerance in the Liver. *Front Immunol* 2021;12:721975.
50 Louis CU, Savoldo B, Dotti G, *et al*. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma. *Blood* 2011;118:6050–6.
51 Mackensen A, Haanen JBAG, Koenecke C, *et al*. CLDN6-specific CAR-T cells plus amplifying RNA vaccine in relapsed or refractory solid tumors: the phase 1 BNT211-01 trial. *Nat Med* 2023;29:2844–53.
52 D'Angelo SP, Araujo DM, Abdul Razak AR, *et al*. Afamitresgene autoleucel for advanced synovial sarcoma and myxoid round cell liposarcoma (SPEARHEAD-1): an international, open-label, phase 2 trial. *Lancet* 2024;403:1460–71.
53 Lickefett B, Chu L, Ortiz-Maldonado V, *et al*. Lymphodepletion - an essential but undervalued part of the chimeric antigen receptor T-cell therapy cycle. *Front Immunol* 2023;14:1303935.
54 Lin H, Dai Z, Huang L, *et al*. Hepatitis B virus reactivation associated with CAR T-cell therapy. *Holist Integ Oncol* 2024;3.
55 Kubo S, Takemura S, Tanaka S, *et al*. Management of hepatitis B virus infection during treatment for hepatitis B virus-related hepatocellular carcinoma. *World J Gastroenterol* 2015;21:8249–55.
56 Fanning GC, Zoulim F, Hou J, *et al*. Therapeutic strategies for hepatitis B virus infection: towards a cure. *Nat Rev Drug Discov* 2019;18:827–44.
57 Bazinet M, Pântea V, Placinta G, *et al*. Safety and Efficacy of 48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a in Patients With Chronic HBV Infection Naïve to Nucleos(t)ide Therapy. *Gastroenterology* 2020;158:2180–94.
58 Lu Y, Lin B, Li M. The role of alpha-fetoprotein in the tumor microenvironment of hepatocellular carcinoma. *Front Oncol* 2024;14:1363695.
59 Tan AT, Meng F, Jin J, *et al*. Immunological alterations after immunotherapy with short lived HBV-TCR T cells associates with long-term treatment response in HBV-HCC. *Hepatol Commun* 2022;6:841–54.
60 Tan A, Hang S, Chia A, *et al*. THU-081 Association of Tcell epitope spreading with the clinical efficacy of HBV-TCR T cell therapy for HBV-related HCC. *J Hepatol* 2025;82:S433.

Gut: first published as 10.1136/gutjnl-2025-335456 on 12 August 2025. Downloaded from http://gut.bmj.com/ on November 5, 2025 at Helmholtz Zentrum Muenchen Zentralbibliothek . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.