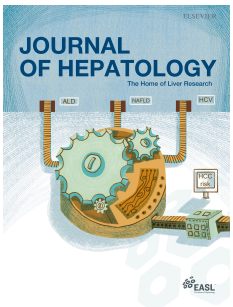
Journal Pre-proof



Phase I trial of ADP-A2AFP TCR T-cell therapy in patients with advanced hepatocellular or gastric hepatoid carcinoma

Tim Meyer, Richard S. Finn, Mitesh Borad, Amit Mahipal, Julien Edeline, Roch Houot, Petr F. Hausner, Antoine Hollebecque, Lipika Goyal, Matthew Frigault, Thomas R. Jeffry Evans, Kit Man Wong, Benjamin R. Tan, Emmanuel Mitry, Debashis Sarker, Lynn Feun, Bassel El-Rayes, Fiona Thistlethwaite, Ahmed Kaseb, Olatunji Alese, Zhaohui Jin, Chris Cirillo, Jordi Bruix, Claire Roddie, Paul Noto, Svetlana Fayngerts, Sebastiano Cristiani, Jennifer Sampson, Jane Bai, Martin Isabelle, Robyn Broad, Amy Sun, Elliot Norry, Bruno Sangro

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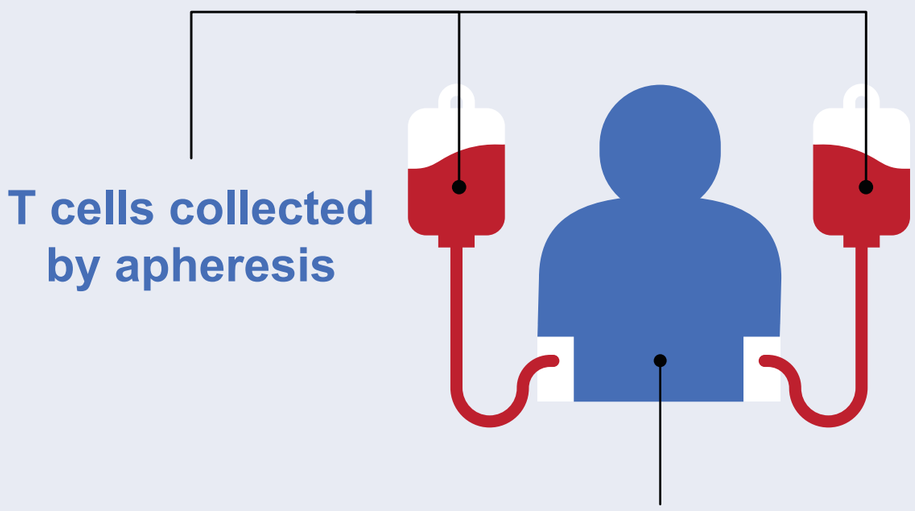
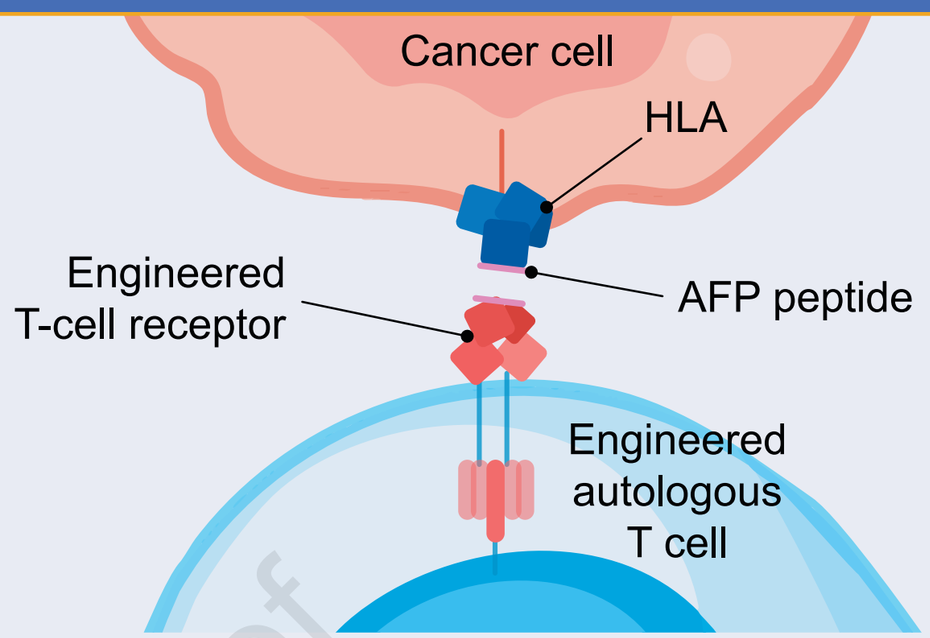
Phase 1 trial of ADP-A2AFP T-cell receptor T-cell therapy (NCT03132792)





T cells engineered to produce ADP-A2AFP

Lymphodepletion chemotherapy

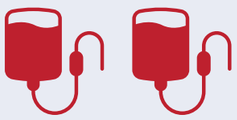
20 Hepatocellular carcinoma

1 Gastric hepatoid carcinoma

19 received

1 infusion

2 received



2 infusions

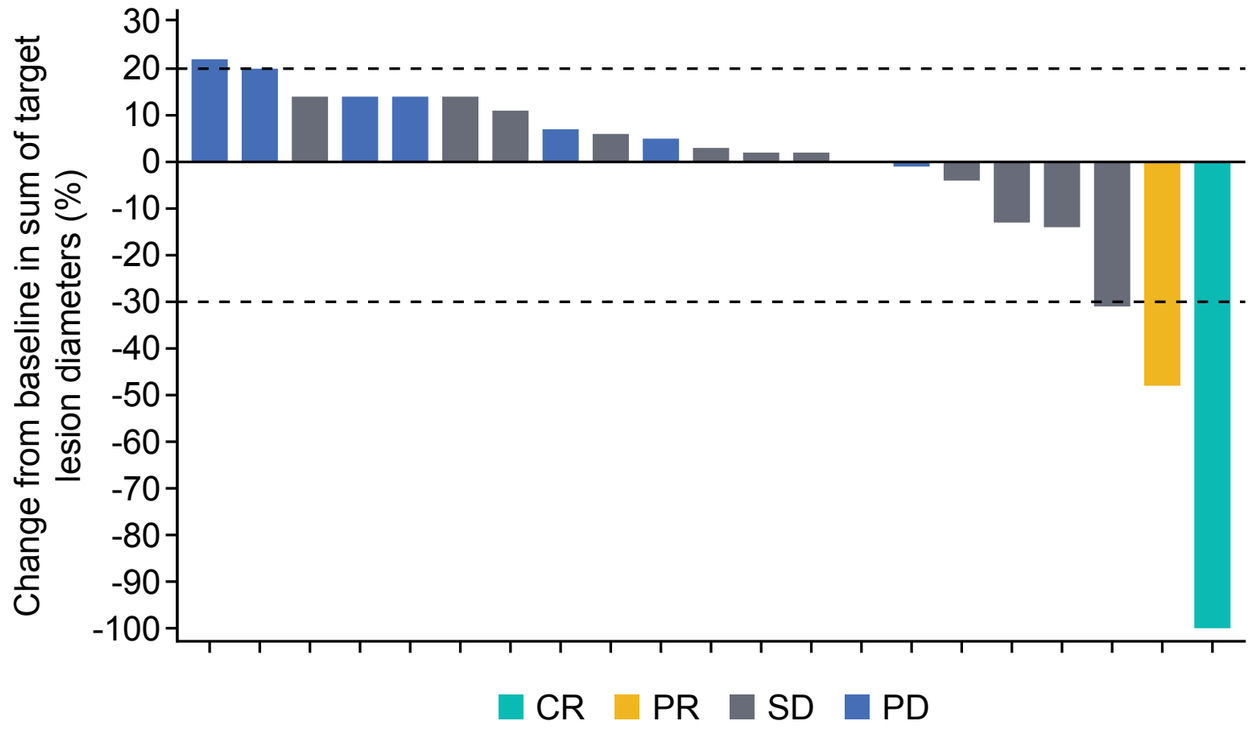
Participants experiencing AEs:

100% related to either lymphodepletion or ADP-A2AFP

87.5% related to ADP-A2AFP

19% Serious AE related to ADP-A2AFP

52.4% grade ≥3 related to ADP-A2AFP



Phase I trial of ADP-A2AFP TCR T-cell therapy in patients with advanced hepatocellular or gastric hepatoid carcinoma

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Short title: AFP-targeting TCR T-cell therapy for advanced HCC

Conflict of interest:

T.M. reports support for this study from Adaptimmune; consultancy for AstraZeneca, Geneos, GreyWolf, Guerbet, Ipsen, Roche, and Signant Health; and grants/contracts from Bayer, Boston Scientific, and MSD. R.S.F. reports grants (to institution) and consulting fees for this study from Adaptimmune; grants (to institution) from Bayer, BMS, Eisai, Genentech, Merck, and Roche; consulting

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Authors' contributions:

All authors either acquired and/or analyzed and interpreted data, and each critically reviewed the manuscript and approved the final version. A.S. supervised, contributed to design and execution of the study and drafting the manuscript. J.Bai performed statistical analyses.

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ABSTRACT

Background & Aims: Patients with advanced hepatocellular carcinoma (HCC) generally experience poor outcomes despite current therapies; alternative treatments are needed. ADP-A2AFP is an investigational autologous T-cell therapy with an affinity-enhanced T-cell receptor (TCR) targeting alpha-fetoprotein (AFP).

Methods: We describe a phase I, open-label, first-in-human clinical trial of ADP-A2AFP (NCT03132792) in human leukocyte antigen–eligible participants with AFP-expressing HCC (or other tumor) not amenable to transplant/resection that progressed on, were intolerant to, or refused prior systemic therapy. Participants received lymphodepletion chemotherapy (cyclophosphamide 500 mg/m^2/day for 3 days and fludarabine 20 mg/m^2/day for 3 days, or cyclophosphamide 600 mg/m^2/day for 3 days and fludarabine 30 mg/m^2/day for 4 days) followed by ADP-A2AFP intravenous infusion. Safety evaluation was the primary objective; response per RECIST v1.1 was the key secondary endpoint.

Results: Twenty-one participants, 20 with advanced HCC and 1 with gastric hepatoid carcinoma received ≥1 ADP-A2AFP infusion. All participants experienced ≥1 grade 3 or higher adverse event; 52.4% experienced ≥1 grade 3 or higher event considered related to ADP-A2AFP treatment. Six participants experienced cytokine release syndrome (grade 1–2: n = 5; grade 4: n = 1). Best overall responses were complete response (n = 1), partial response (n = 1), and stable disease (n = 12); overall response rate was 9.5%. Eight patients had duration of stable disease ≥16 weeks. Infiltration of ADP-A2AFP TCR and CD8+ T cells was seen in AFP-positive areas of post-treatment tumor samples. A relationship was demonstrated between increased ADP-A2AFP dose and serum AFP reduction in responders.

Conclusions: Lymphodepletion chemotherapy followed by ADP-A2AFP TCR T-cell therapy showed a manageable safety profile and preliminary indications of antitumor activity in these previously treated patients.

Impact & Implications

Adoptive T-cell therapy could be a much-needed additional treatment strategy for advanced hepatocellular carcinoma. Clinicians and researchers interested in the development of adoptive T-cell therapies for advanced solid tumors will be interested to learn that in this phase I trial, ADP-A2AFP T-cell receptor T-cell therapy was associated with an acceptable benefit-to-risk profile and encouraging antitumor activity, illustrating the treatment potential of adoptive T-cell therapy for advanced hepatocellular carcinoma.

Introduction

Liver cancer is one of the leading causes of cancer-related deaths worldwide, and its incidence and associated mortality continue to grow.[1,2] The most common type of liver cancer is HCC, accounting for approximately 90% of cases.[1] Although some patients with HCC present with early-stage disease that is amenable to potentially curative therapy, most patients eventually require systemic therapy due to vascular or extrahepatic involvement or progressive disease.[3] In the past decade, progress has been made in the development of systemic therapies, with studies reporting increases in overall survival or quality of life using single-agent or combination immune checkpoint inhibitors, targeted treatment with immunotherapy combination, or tyrosine kinase inhibitors.[1] However, HCC is a complex disease with the competing risk of the underlying liver disease, as well as the heterogenous nature of metachronous tumors that may exhibit different molecular profiles and thus different sensitivity and resistance to treatments. Therefore, due to the poor prognosis in most patients with advanced HCC, there is an unmet medical need for further innovation in treatment modalities.

HCC is an appealing candidate for adoptive T-cell therapy due to the potential for patients to develop antitumor immunity that may suppress disease progression.[4] Further, infusion of autologous lymphocytes to patients with HCC who had undergone resection reduced frequency of recurrence by 18%, significantly increased time to first recurrence, and resulted in longer recurrence-free survival compared with no adjuvant adoptive T-cell therapy; however, no significant difference in overall survival was noted over 4.4 years of follow-up.[5] These early results suggest the treatment potential of adoptive T-cell therapy for advanced HCC but imply that modifications to autologous lymphocytes, particularly to overcome the low affinity of wild-type T-cell receptors (TCRs) to their cognate tumor

antigens complexed with human leukocyte antigen (HLA) molecules, may be needed to increase antitumor activity and potency.[6]

ADP-A2AFP is an autologous mixed CD4+ and CD8+ T-cell therapy with a genetically engineered affinity-enhanced TCR targeting the tumor antigen alpha-fetoprotein (AFP). AFP is synthesized in the yolk sac and fetal liver. It is an abundant serum protein produced by the fetus, although levels considerably decrease shortly after birth.[7] AFP is aberrantly expressed in patients with HCC and other tumor types, such as cholangiocarcinoma and gastric hepatoid cancer, and is associated with poor prognosis, vascular invasion, and higher tumor grade.[8,9] Moreover, AFP levels tend to be higher in advanced HCC compared with early-stage HCC.[10] Preclinical testing of ADP-A2AFP showed antigen-driven cytokine secretion and cytotoxic activity, while extensive safety evaluations testing off-target and alloreactivity informed its use in the clinical setting.[11] Here we describe results of a phase I, open-label, first-in-human clinical trial investigating safety and antitumor activity of ADP-A2AFP (Trial registration ID: NCT03132792) in HLA-A*02:01–eligible participants with advanced HCC and other AFP-expressing tumor types.

Methods

Oversight

This trial abided by the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. Patients voluntarily agreed to participate by giving written informed consent. No compensation was provided for study participation; however, participants may have received reimbursement for any costs incurred as a result of study participation. The final study protocol and informed consent documentation were approved by the institutional review board, independent ethics committee, and any other site-level committee deemed appropriate.

Participants

Patients aged 18–75 years with histologically confirmed HCC, or another AFP-expressing tumor, not amenable to transplant or resection were eligible to enroll. Participants must have had ≥1 HLA-A*02:01 (or any A*02:01 P group) allele and tumor AFP expression. In the original version of the protocol, AFP expression was defined as immunohistochemistry (IHC) staining at ≥2+ intensity in ≥40% of tumor cells. However, given that ADP-A2AFP demonstrated strong and uniform cytotoxic activity *in vitro* toward the HepG2 HCC cell line, which showed variable staining intensities (approximately 12% of 3+, approximately 20% of 2+, and approximately 33% of 1+), it was subsequently modified to IHC staining at ≥1+ intensity in ≥20% of tumor cells. In addition, serum AFP ≥100 ng/mL was added to the definition of AFP expression due to the limitations of the IHC approach, such as tissue heterogeneity, considering that elevated serum AFP levels are often caused by tumor production and secretion of AFP. In both cases, AFP positivity must have been <5% in non-cancerous liver tissue. Other key inclusion criteria were Child-Pugh score ≤6 without ascites or encephalopathy,

Eastern Cooperative Oncology Group performance status score 0–1, and progressive disease following (or having been intolerant to) standard-of-care systemic therapy. Key exclusion criteria were positivity for any other HLA-A*02 alleles (except for null alleles and alleles in the HLA-A*02:03 P group); positivity for HLA-C*04:04 or HLA-B*51:03; previous liver transplant; history of chronic or recurrent (within the last year) severe autoimmune or immune-mediated disease; active viral hepatitis (patients with hepatitis C were allowed, provided they met all other eligibility criteria); and cytotoxic chemotherapy, immune therapy, or biological therapy within 3 weeks of leukapheresis. Exclusion of individuals with other HLA-A*02 alleles was to avoid potential alloreactivity of the AFP-specific TCR against these alleles, as indicated by preclinical observations.[11] Detailed inclusion and exclusion criteria are listed in the Supplementary Methods.

Trial design

This phase I, open-label, first-in-human clinical trial of ADP-A2AFP (Trial registration ID: NCT03132792) was conducted at 21 centers in the United States, France, Spain, and the United Kingdom. Autologous T cells were collected by leukapheresis, transduced with a lentiviral vector expressing the AFP-specific TCR, and expanded *in vitro*. Details regarding the generation and selection of the AFP-specific TCR have been reported previously.[11] Participants underwent lymphodepleting chemotherapy followed by infusion of ADP-A2AFP TCR T cells. The trial consisted of a modified 3 + 3 dose-escalation design across 3 dose groups and 2 expansion groups, one of which included participants with HCC only, whereas the other was open to participants with HCC and other tumor types expressing AFP (**Supplementary Table S1** and **Supplementary Fig. S1**).

Dose ranges (total transduced number of cells) were as follows: 0.8×10^8–1.2×10^8 in Dose Group 1; 0.5×10^9–1.2×10^9 in Dose Group 2; 1.2×10^9–6.0×10^9 in Dose Group 3; and 1.2×10^9–10.0×10^9 in Expansion Groups 4 and 5. Lymphodepleting chemotherapy regimens were as follows: cyclophosphamide 500 mg/m^2/day for 3 days and fludarabine 20 mg/m^2/day for 3 days in Dose Groups 1 and 2, and cyclophosphamide 600 mg/m^2/day for 3 days and fludarabine 30 mg/m^2/day for 4 days in Dose Group 3 and in Expansion Groups 4 and 5 (**Table S1**). Participants were monitored for dose-limiting toxicities (DLTs) from the time of lymphodepletion chemotherapy until 30 days after ADP-A2AFP infusion. If there were no DLTs in the first 2 participants enrolled in Group 1, then enrollment progressed to Group 2 after endorsement from the safety review committee. If there were no DLTs in the first 3 participants in subsequent dosing groups, then enrollment proceeded into the next higher cell dose (Group 3) in a sequential manner. If 1 out of 3 participants developed a DLT in a specific group, then an additional 3 participants were enrolled into that same dose group. After the initial safety of ADP-A2AFP from the dose-escalation portion of the study was established, participants could be considered for a second infusion with engineered T cells, receiving the highest dose level cleared in the study and the lymphodepletion regimen associated with that dose group. Participants were eligible for a second infusion if they met all of the following: (1) continued to show tumor AFP expression; (2) met the eligibility criteria; (3) at least 12 weeks had elapsed since first infusion; (4) they did not experience a grade 4 cytokine release syndrome (CRS) or other grade 4 AEs deemed at least possibly related to ADP-A2AFP; and (5) they had disease progression (Groups 1 and 2) or had a confirmed response or stable disease (SD) for at least 4 months followed by disease progression (Groups 3, 4, and 5) following first infusion.

Tumors were monitored by computed tomography or MRI scans at baseline; weeks 4, 8, 16, and 24; and then every 3 months until confirmed disease progression, death, or trial withdrawal. Long-term follow-up assessments took place every 6 months for 5 years and then yearly for up to 15 years.

Objectives and Endpoints

The primary objective was to evaluate safety of ADP-A2AFP and the primary endpoints were incidence of DLTs; determination of optimally tolerated dose range, AEs, and SAEs; and laboratory and cardiac assessments. The secondary objective was to evaluate antitumor activity of ADP-A2AFP and the key secondary endpoint was overall response rate (ORR), defined as the proportion of participants with a confirmed CR or PR per RECIST v1.1. Duration of response, duration of SD, and progression-free survival were additional secondary endpoints.

For key exploratory analyses, peripheral persistence of ADP-A2AFP, measured by quantitative PCR of the transgene from peripheral blood mononuclear cell DNA, and its relationship to dose and clinical response was examined. In addition, we investigated the spatial distribution of infiltrating immune cell phenotypes (CD4+ T cells [CD3+CD4+], cytotoxic T cells [CD3+CD8+], regulatory T cells [CD3+CD4+FoxP3+], malignant cells [PanCK/Sox10+]), along with their functional states (activated [granzyme B+], proliferating [Ki67+], PD-L1+). For this, baseline and post-infusion biopsy sections from the target tumor lesion of one participant were processed for single-plex IHC to visualize marker antigen presence using chromogenic antibody staining, and duplex IHC/*in situ* hybridization using RNAScope technology (Advanced Cell Diagnostics, Newark, CA, USA) to achieve simultaneous visualization of protein and RNA expression using both chromogenic antibody staining and *in situ* hybridization assay to detect targets' protein and RNA expression, and multiplex immunofluorescence

(Ultivue, Cambridge, MA, USA) was also utilized as described previously,[12] which uses a panel of fluorescence antibody staining against a number of antigen markers. Stained slides were scanned using the AxioScan.Z1 microscope slide scanner and analyzed using HALO image analysis software (Indica Labs, Albuquerque, NM, USA). Finally, serum AFP was measured by the ELISA method, employing assays locally established by participating clinical sites, to explore the change from baseline in serum AFP and its association with treatment response.

Statistical Analysis

Trial sample size was determined by the rate and extent of dose escalation and based on clinical judgment, no power calculations were performed. Descriptive statistics are reported, and no formal hypothesis testing was planned.

Results

Participants

The first participant was enrolled and started screening on June 12, 2017, and met eligibility criteria on March 27, 2018, and the last participant ended the interventional phase on April 4, 2022. The data reported here are as of a data cut-off date of November 8, 2022, unless otherwise stated. Of 477 participants screened, 39 were eligible for treatment and 38 underwent leukapheresis. Of the 17 participants who underwent leukapheresis but did not receive lymphodepletion, the most common reason was not meeting eligibility criteria before lymphodepletion (n = 9; **Fig. S2**). There were 21 participants who received lymphodepletion chemotherapy and ADP-A2AFP infusion, forming the modified intent-to-treat (mITT) population. All 21 participants in the mITT population ended the

interventional phase of the study, primarily due to disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (**Fig. S2**).

Demographics and baseline characteristics are reported in **Table 1**. All participants had HCC, except for one participant in Expansion Group 5 with gastric hepatoid carcinoma. All participants had screening/baseline serum AFP values of >100 ng/mL, and median tumor AFP H score was 45 (minimum, maximum: 0, 280). Median dose of ADP-A2AFP was 5.04×10^9 transduced T cells (range: 0.10×10^9–9.98×10^9); 2 participants received a second ADP-A2AFP infusion of 9.87×10^9 and 2.74×10^9 transduced T cells administered approximately 3 years and 1 year after the initial infusion, respectively.

Endpoints

Primary: Safety

All participants in the mITT population experienced ≥1 adverse event (AE), 18 (85.7%) experienced an AE that was considered by the investigator to be related to ADP-A2AFP (**Table 2**), and all participants experienced an AE that was considered by the investigator to be related to any study treatment (either lymphodepletion or ADP-A2AFP; **Table S2**). Likewise, all participants experienced ≥1 grade 3 or higher AE, 11 (52.4%) experienced a grade 3 or higher AE considered to be related to ADP-A2AFP, and all participants experienced a grade 3 or higher AE considered to be related to lymphodepletion or ADP-A2AFP. Of the 7 participants (33.3%) who experienced ≥1 serious AE (SAE), 4 (19.0%) had an SAE that was considered to be related to ADP-A2AFP (**Table 3**).

The only grade 5 event occurred in a participant in Group 3. This patient was also the only one to experience DLT during the trial (a grade 4 SAE of atrial fibrillation, which was considered by the investigator to be related to ADP-A2AFP and resolved the next day). This participant experienced 5

additional grade 4 SAEs that were considered by the investigator to be related or possibly related to ADP-A2AFP and not related to cyclophosphamide or fludarabine; these were CRS, which resolved within a day; sepsis; angioedema; bradycardia; and hyperbilirubinemia. No other grade 4 SAEs that were deemed related to study treatment occurred. This participant passed away 61 days post infusion due to a grade 5 event of cholangitis, which, although assessed by the investigator as not related to ADP-A2AFP, cyclophosphamide, or fludarabine, occurred secondary to sepsis and possible drug (*i.e.*, TCR T-cell therapy)-induced liver injury. Analysis of liver tissue revealed inflamed biliary duct epithelium, but a lack of AFP expression and absence of ADP-A2AFP TCR T cells. Therefore, no direct causality between the grade 5 AE and cell therapy could be established. The participant had received previous systemic treatment of atezolizumab and bevacizumab and had early-stage disease (single or ≤3 nodules, 3 cm) at screening.

AEs of special interest are detailed in **Table S3**. Six participants experienced CRS (5 with grade 1–2 CRS and 1 with grade 4 CRS) after the first infusion; 2 received tocilizumab to manage CRS symptoms. Overall, median time to first CRS event was 4 days (range: 1–17 days), median duration of CRS was 2.5 days (range: 1–7 days), and all CRS events resolved. Both participants who received a second infusion reported grade 1 CRS events occurring 3 and 5 days after the second infusion; both participants received tocilizumab and the events resolved. Anemia was the most frequently reported prolonged cytopenia, defined as grade 3 or higher neutropenia, anemia, or thrombocytopenia persisting for ≥4 weeks after receiving ADP-A2AFP. One participant had a grade 3 SAE of febrile neutropenia possibly related to ADP-A2AFP TCR T-cell therapy that resolved after treatment with antibiotics. There were no cases of immune effector cell–associated neurotoxicity syndrome (ICANS).

There was no graft-versus-host-disease reported in this trial. One participant who entered the long-term follow-up phase had a grade 3 SAE of cellulitis that was not considered related to ADP-A2AFP. At the time of data cut-off, all tested samples were negative for replication-competent lentivirus.

Secondary and Exploratory

Best overall responses (BORs) among the 21 participants evaluated were complete response (CR; n = 1), partial response (PR; n = 1), stable disease (SD; n = 12), and progressive disease (n = 7), illustrated in **Fig. 1**. ORR was 9.5% and disease control rate (CR + PR + SD) was 66.7%. All responders had HCC. The participant with a CR had 2 target lesions in the liver at baseline with a sum of diameters of 37 mm. The participant with a PR had 4 target lesions at baseline, including 2 liver lesions and 2 lymph node lesions; the sum of diameters of these lesions decreased from 236.9 mm at baseline to 143.3 mm (-39.5%) at week 4 post infusion and 123.6 mm (-47.8%) at week 8 post infusion. The participants' responses over time are shown in **Fig. 1**. Duration of SD after first infusion in 14 participants ranged between 6.7 to 73.0 weeks. Eight participants had duration of SD >16 weeks. Both participants who received a second infusion of ADP-A2AFP TCR T cells had BORs of SD following both the first and second infusions. Three male participants aged 17, 48, and 73 years were censored without progressive disease (**Fig. 1B**). These participants had a maximum percentage change in target lesion sum of lesion diameters from baseline of 4.1%, -13.8%, and -12.7%, respectively. An updated survival analysis was conducted on February 3, 2025, and these 3 participants had died of the disease under study, approximately 4.2, 2.0, and 1.6 years after first infusion. Of the other 3 participants whose survival was censored in **Fig. 1B**, 2 died of the disease under study or tumor progression approximately 1.7 and 3.4 years after first infusion, and the other was alive at date of last contact ~5.0 years after first infusion.

The presence of circulating ADP-A2AFP TCR T cells was observed in all participants after ADP-A2AFP infusion. Peak persistence was higher in participants from the dose-expansion groups than in those from Groups 1, 2, and 3, with a broad range within each group (**Fig. 2A**). In the 2 participants who received second infusions, one had a -15% change in serum AFP from baseline at month 9 after the first infusion with persistence of ADP-A2AFP TCR T cells observed at 8 months after the first infusion, and at a low level (483 vector copies/μg genomic DNA) before the second infusion, peaking to 108,489 vector copies/μg genomic DNA at week 2 and remaining >70,000 vector copies/μg genomic DNA until week 12 following second infusion. The second, who received 0.1×10^9 ADP-A2AFP TCR T cells for the first infusion, did not have T-cell persistence observed at week 4 post infusion or after and had a 64% change in serum AFP from baseline 12 weeks after the first infusion, and had peak persistence of 402,093 vector copies/μg genomic DNA at week 2 following second infusion with persistence remaining >175,000 vector copies/μg genomic DNA until the completion visit ~week 6.

Between 4–8 weeks after infusion, infiltration of ADP-A2AFP TCR T cells, along with the presence of activated CD8+ T cells, was seen in AFP-positive areas of target tumor lesion samples from one patient who went on to achieve a BOR of SD (**Fig. 2B**, upper panel). This region of interest (AFP-positive areas) also showed decreases in regulatory T cells and programmed death-ligand 1 (PD-L1)+ immune cells after infusion, with an increase in activated CD4+ and CD8+ T cells (**Fig. 2B**, lower panel). Across whole samples (including AFP-positive and AFP-negative areas), average distance of activated CD8+ T cells from the tumor interface was 8.58 μm at baseline and 7.5 μm post infusion. Within the region of interest described above, average distance of activated CD8+ T cells from the tumor interface post infusion was 0.77 μm, highlighting increased infiltration into tumor tissue.

Finally, a relationship was demonstrated between dose of ADP-A2AFP and extent of serum AFP reduction after infusion (**Fig. 3**). Doses >5×10^9 transduced T cells were associated with a robust decrease in levels of serum AFP, with peak reductions observed at around week 4. There was an association observed between duration of serum AFP reduction and duration of SD (>16 weeks; **Fig. 3**), although duration of serum AFP reduction varied significantly.

Discussion

Here we report safety, antitumor activity, and translational effects of ADP-A2AFP, the first TCR T-cell therapy to be evaluated in advanced refractory HCC. Our results suggest that ADP-A2AFP TCR T-cell therapy and the associated lymphodepleting therapy has an acceptable benefit-to-risk profile, especially considering that most participants were heavily pretreated and had cirrhosis. Hematological toxicities were the most frequently reported AEs considered to be related to ADP-A2AFP, and incidence of these events was also more frequently reported as related to ADP-A2AFP or lymphodepletion, which is consistent with those reported in trials of other TCR T-cell therapies.[12,13] There was one occurrence of grade 3 or higher CRS (4.8%), no occurrences of ICANS, and no fatal events related to ADP-A2AFP treatment. Our findings suggest that the higher lymphodepletion chemotherapy regimen tested here would be appropriate for future potential TCR T-cell therapy trials. The association between cell dose and AFP serum reduction also suggests that cell doses ≥1 billion could be tested. There was no evidence of on-target, off-tumor effects observed in this trial. This study also demonstrated the ability to target an overexpressed tumor antigen that is also expressed at lower levels in normal liver without inducing significant hepatotoxicity.

The CR, PR, and prolonged SD indicating antitumor activity, combined with the observed relationship between ADP-A2AFP dose and serum AFP reduction, offers proof of concept of TCR T-cell therapies in HCC. Independent of tumor regression, there may be a component of immune control imposed on the tumor by ADP-A2AFP T cells that requires further characterization but is supported by the evidence of these cells having trafficked to the tumor. Both patients with RECIST v1.1 responses had marked reductions in serum AFP. However, we do note that AFP reductions did not correlate as closely with prolonged stable disease. Also, despite requiring evidence of AFP expression for eligibility,

there were patients that did not experience meaningful antitumor activity. A potential factor contributing to non-response despite this AFP positivity may be associated with heterogeneity of AFP expression on the target tumor lesions. Some participants in this trial did not have tumor AFP expression as detected by IHC (an H score of 0) but still had serum AFP above the threshold, and intratumoral heterogeneity of AFP expression has been reported previously.[14,15] It is also worth noting that AFP is a secreted protein, and therefore may not be concentrated in tumor cells despite being overproduced.[16] This may contribute to some discordance between AFP protein as measured by IHC in the tumor, serum AFP levels, and AFP peptide presented on the tumor cell surface by HLA. The variability between tumor response and AFP level could indicate epitope spreading (although no data on this are available from this trial). Our experience of modifying the AFP enrollment criteria in favor of serum measurements over IHC could be important for future designs of trials with cell therapies targeting AFP-expressing tumors. Advanced molecular techniques such as the most sensitive and specific RNAscope, which already contributes to TCR T-cell therapy research,[17] could also be considered to enhance patient selection and more clearly identify the presence of the specific target on tumor cells.

It is often observed in cancer therapeutics that molecularly targeted therapies do not always induce a response despite the presence of the target. A range of additional factors are likely to influence response rates, including the patient's immune status, tumour heterogeneity and evolution, microbiome, prior treatments, and the tumor mutation burden. The immunosuppressive tumor microenvironment may also play a role; therefore, there may be an added benefit of combining TCR T-cell therapies with immune checkpoint inhibitors, such as those that target the PD-L1 axis. ADP-A2AFP T-cells are a first-generation product; further development of affinity-enhanced TCRs either targeting AFP, targeting alternative AFP peptides, or targeting other tumor antigens could be used to further enhance antitumor

activity. Extensive research on next-generation T-cell therapies that include various enhancements intended to improve responses is currently ongoing.[6,17]

TCR T-cell therapies are just one type of adoptive cell therapy, related to, but distinct from, chimeric antigen receptor (CAR) T-cell therapies which typically target cell surface antigens, with both thought to have potential to treat HCC.[18] Multiple CAR T-cell therapies are under preclinical and clinical investigation for HCC, including those with next-generation modifications to target intracellular antigens such as AFP.[6] In preclinical studies, AFP-CAR T-cell therapy led to tumor regression in xenograft models of AFP-positive liver cancer.[16] However, a phase I clinical trial of AFP-CAR T cells in AFP-positive HCC was terminated and no results are available.[6] The proteoglycan glypican-3, which is overexpressed in HCC, is a more common target for investigational CAR T-cell therapies for HCC.[6] Recent preclinical work suggests CAR T cells targeting both glypican-3 and AFP are more effective than single-targeted cells, indicating another potential avenue for T-cell therapy optimization.[19]

There were several limitations to this study. First, this was an early-phase trial in participants with refractory disease. The heterogeneity of tumors may be especially relevant at advanced stages when several previous treatments may have induced tumor plasticity. Based on data from other immunotherapies, a larger trial designed to assess efficacy of ADP-A2AFP as an earlier-line therapy may reveal more robust antitumor activity. Enrolling patients for such a trial would be challenging due to the availability of several treatment options with established benefits. However, the current trial did include some patients with early-stage disease, indicating that there could be candidates for enrollment in a trial of TCR T-cell therapy at an earlier line. Recently, combination therapies including immune checkpoint inhibitors have been approved to treat unresectable HCC in the first-line setting.[20,21] Second, sequential biopsies were only available from a few patients, limiting translational analyses of the effect

462 of ADP-A2AFP on tumors, including HLA/AFP expression, over time. Thirdly, there is the limited
463 potential of RECIST v1.1 to capture antitumor responses that are not associated with a tumor size
464 reduction, illustrated in this trial by the extended duration of SD in a number of patients. Finally, only 2
465 patients received a second infusion of ADP-A2AFP, precluding us from drawing conclusions about
466 repeated dosing. Early evidence evaluating multiple infusions of CAR T cells for refractory B-cell
467 malignancies suggests that a second infusion may be well tolerated and associated with more durable
468 responses compared with a single infusion.[22]

469 In conclusion, lymphodepleting chemotherapy followed by ADP-A2AFP TCR T-cell therapy up
470 to doses of 10 billion transduced T cells was associated with an acceptable benefit-to-risk profile and
471 preliminary antitumor activity, given the advanced stage of disease and poor prognosis of participants
472 enrolled in this trial. These results suggest there is a therapeutic window that could potentially be
473 exploited to develop cell therapies to treat HCC. However, the threshold for continued ADP-A2AFP
474 development was not met. These results, along with ongoing translational and *post hoc* analyses will
475 inform future T-cell therapy investigational product development to treat HCC.

Data Availability Statement

The clinical datasets generated and analyzed during the current study are available upon reasonable request for research only, non-commercial purposes. Such datasets include the study protocol, statistical analysis plan, individual participant data that underlie the results reported in this article after de-identification (text, tables, figures, and appendices), and supporting documentation, as required. Restrictions relating to patient confidentiality and consent will be maintained by aggregating and anonymizing identifiable patient data. The clinical data will be available beginning immediately after article publication and thereafter with no time limit. Requests should be sent in writing describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement that describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests should be directed to Elliot.Norry @adaptimmune.com and will be reviewed by the first and last authors, and by Adaptimmune. Responses will typically be provided within 60 days of the initial request.

Abbreviations:

AE, adverse event; AFP, alpha-fetoprotein; BORs, best overall responses; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; HCC, hepatocellular carcinoma; ICANS, immune effector cell–associated neurotoxicity syndrome; IHC, immunohistochemistry; mITT, modified intent-to-treat; ORR, overall response rate; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious AE; SD, stable disease; TCR, T-cell receptor.

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Author names in bold designate shared co-first authorship.

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554 **Table 1. Baseline participant and disease characteristics.**

Characteristic	**N = 21**
Female, n (%)	6 (28.6)
Male, n (%)	15 (71.4)
Age (years), median (min, max)	59 (17, 75)
ECOG PS, n (%)	
0	8 (38.1)
1	13 (61.9)
Extra hepatic spread, n (%)	13 (61.9)
Number of lesions,[a] median (min, max)	6 (1, 10)
Baseline sum diameter of target lesions, mm, median (min, max)	98 (28, 364)
Etiology and underlying liver disease/history,[b] n (%)	
HBV	4 (19.0)
HCV	6 (28.6)
NAFLD[c]	2 (9.5)
Alcoholic liver disease	3 (14.3)
Not available	4 (19.0)
Prior lines of systemic therapy, median (range)	2 (1–10)
Received prior liver-directed radiotherapy, n (%)	2 (9.5)
AFP expression	
Participants enrolled under serum AFP inclusion criterion, n (%)	21 (100)
Serum AFP at screening, ng/mL, median (min, max)	3,779 (185, 155,840)
<10, n (%)	0
10–40, n (%)	0
40–400, n (%)	3 (14.3)

>400, n (%)	18 (85.7)
Tumor AFP H score,[d] median (min, max)	45 (0, 280)

AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; max, maximum; min, minimum; NAFLD, nonalcoholic fatty liver disease.

[a]Includes target and non-target lesions.

[b]Categories are not mutually exclusive.

[c]Now described as metabolically associated steatotic liver disease.

[d]H score was calculated as (3 × percentage of strongly staining nuclei) + (2 × percentage of moderately staining nuclei) + percentage of weakly staining nuclei.

564 **Table 2. AEs related to ADP-A2AFP TCR T-cell therapy in ≥2 participants, and those of grade 3**

565 **or 4 (first infusion).**

Preferred term, n (%)	Any grade (N = 21)	Grade 3 (N = 21)	Grade 4 (N = 21)
Participants with any AE	18 (85.7)	9 (42.9)	9 (42.9)
Neutropenia/neutrophil count decreased	11 (52.4)	3 (14.3)	7 (33.3)
Leukopenia/WBC decreased	8 (38.1)	2 (9.5)	6 (28.6)
Anemia/RBC decreased	6 (28.6)	2 (9.5)	0
Aspartate aminotransferase increased	6 (28.6)	0	0
CRS	6 (28.6)	0	1 (4.8)
Pyrexia	6 (28.6)	0	0
Alanine aminotransferase increased	5 (23.8)	2 (9.5)	0
Lymphopenia/lymphocyte count decreased	5 (23.8)	3 (14.3)	1 (4.8)
Thrombocytopenia/platelet count decreased	4 (19.0)	0	2 (9.5)
Hypotension	3 (14.3)	2 (9.5)	0
Blood alkaline phosphatase increased	2 (9.5)	0	0
Chills	2 (9.5)	0	0
Fatigue	2 (9.5)	0	0
Rash	2 (9.5)	0	0
Vomiting	2 (9.5)	0	0
Hyperbilirubinemia	1 (4.8)	0	1 (4.8)
Angioedema	1 (4.8)	0	1 (4.8)
Atrial fibrillation	1 (4.8)	0	1 (4.8)
Bradycardia	1 (4.8)	0	1 (4.8)
Cardiac arrest	1 (4.8)	0	1 (4.8)
Cytomegalovirus infection reactivation	1 (4.8)	1 (4.8)	0
Face edema	1 (4.8)	1 (4.8)	0
Oral pain	1 (4.8)	1 (4.8)	0

Preferred term, n (%)	Any grade (N = 21)	Grade 3 (N = 21)	Grade 4 (N = 21)
Sepsis	1 (4.8)	0	1 (4.8)
Stomatitis	1 (4.8)	1 (4.8)	0

566 AE, adverse event; CRS, cytokine release syndrome; RBC, red blood cell; WBC, white blood cell.

567 Participants were counted once for each preferred term under the most severe grade.

568

Table 3. Overall SAEs and those related to ADP-A2AFP TCR T-cell therapy (first infusion).

SAE, n (%); grade	Overall (N = 21)	Related (N = 21)
Participants with any SAEs	7 (33.3)	4[a] (19.0)
CRS	2 (9.5); grades 1, 4	2 (9.5); grades 1, 4
Febrile neutropenia/neutrophil count decreased	2 (9.5); grade 3	1 (4.8); grade 3
Bile duct obstruction	2 (9.5); grade 3	0
Angioedema	1 (4.8); grade 4	1 (4.8); grade 4
Atrial fibrillation	1 (4.8); grade 4	1 (4.8); grade 4
Bradycardia	1 (4.8); grade 4	1 (4.8); grade 4
Cytomegalovirus infection reactivation	1 (4.8); grade 3	1 (4.8); grade 3
Face edema	1 (4.8); grade 3	1 (4.8); grade 3
Hyperbilirubinemia	1 (4.8); grade 4	1 (4.8); grade 4
Infusion-related reaction	1 (4.8); grade 2	1 (4.8); grade 2
Sepsis	1 (4.8); grade 4	1 (4.8); grade 4
Abdominal pain	1 (4.8); grade 3	0
Atrial ventricular block	1 (4.8); grade 4	0
Back pain	1 (4.8); grade 3	0
Cholangitis	1 (4.8); grade 5	0
Confusional state	1 (4.8); grade 3	0
Respiratory distress	1 (4.8); grade 4	0

CRS, cytokine release syndrome; SAE, serious adverse event; TCR, T-cell receptor.

Participants were counted once for each preferred term under the most severe grade.

[a]Of the SAEs that were related to ADP-A2AFP, 1 patient had cytomegalovirus infection reactivation, one patient had CRS, one patient had an infusion-related reaction and febrile neutropenia, and one

patient had atrial fibrillation, face edema, CRS, sepsis, angioedema, bradycardia, and hyperbilirubinemia.

FIGURE LEGENDS

Fig. 1. Best overall response over time. (A) Maximum percentage change in target lesion sum of lesion diameters from baseline per patient, colored by RECIST v1.1 BOR (first infusion). **(B)** Participants' responses over time (first infusion, data cut-off April 5, 2022). *Participant in Group 5 (non-HCC expansion). BOR, best overall response; CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease; PR, partial response; SD, stable disease.

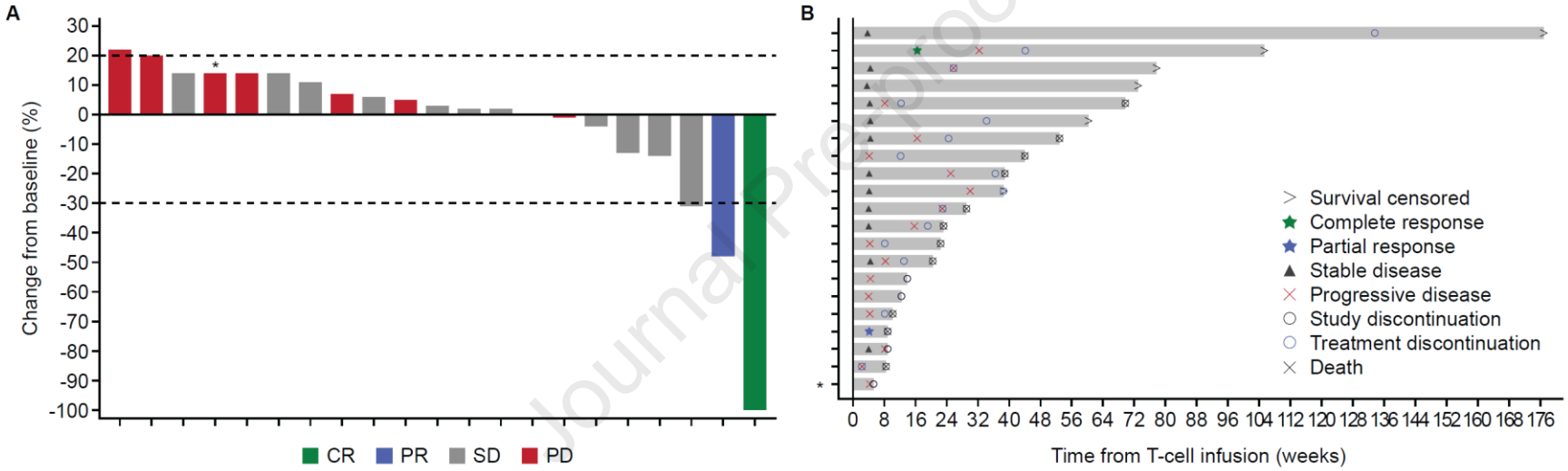
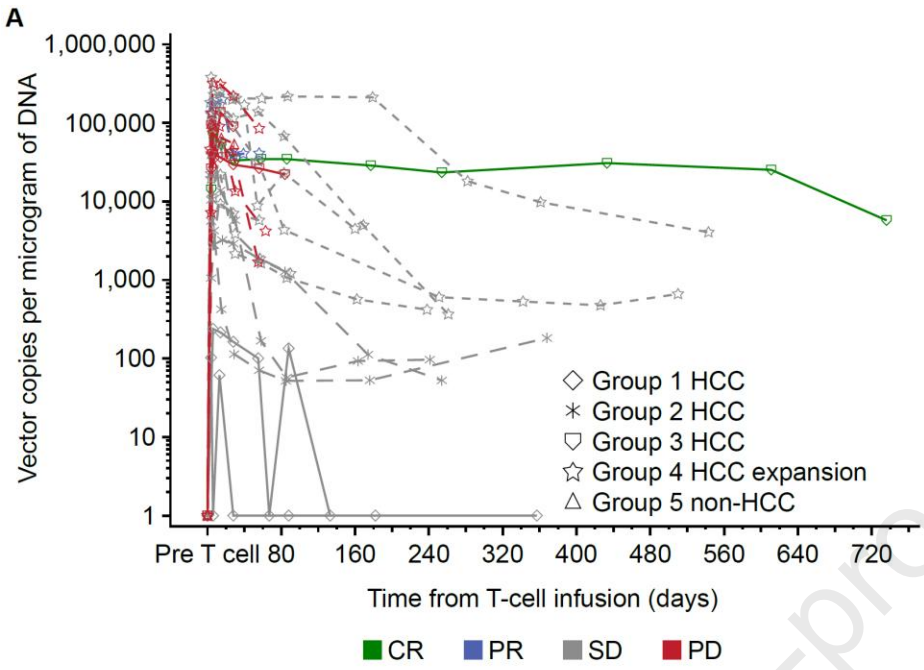


Fig. 2. Persistence of ADP-A2AFP T cells over time and infiltration into tumors. (A) T-cell persistence over time per patient, colored by RECIST v1.1 BOR (first infusion). (**B)** Multiplex immunofluorescence of the region of interest of target lesion biopsies at baseline and 4–8 weeks post infusion in one participant who achieved a BOR per RECIST v1.1 of SD. Upper panel: Infiltration of ADP-A2AFP TCR T cells (highlighted by purple arrows) and other T-cell subtypes into AFP-positive regions. Lower panel: Single-cell resolution of T cells infiltrating AFP-positive regions. AFP, alpha-fetoprotein; BOR, best overall responses; CR, complete response; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TCR, T-cell receptor.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Time from T-cell infusion (days)
CR
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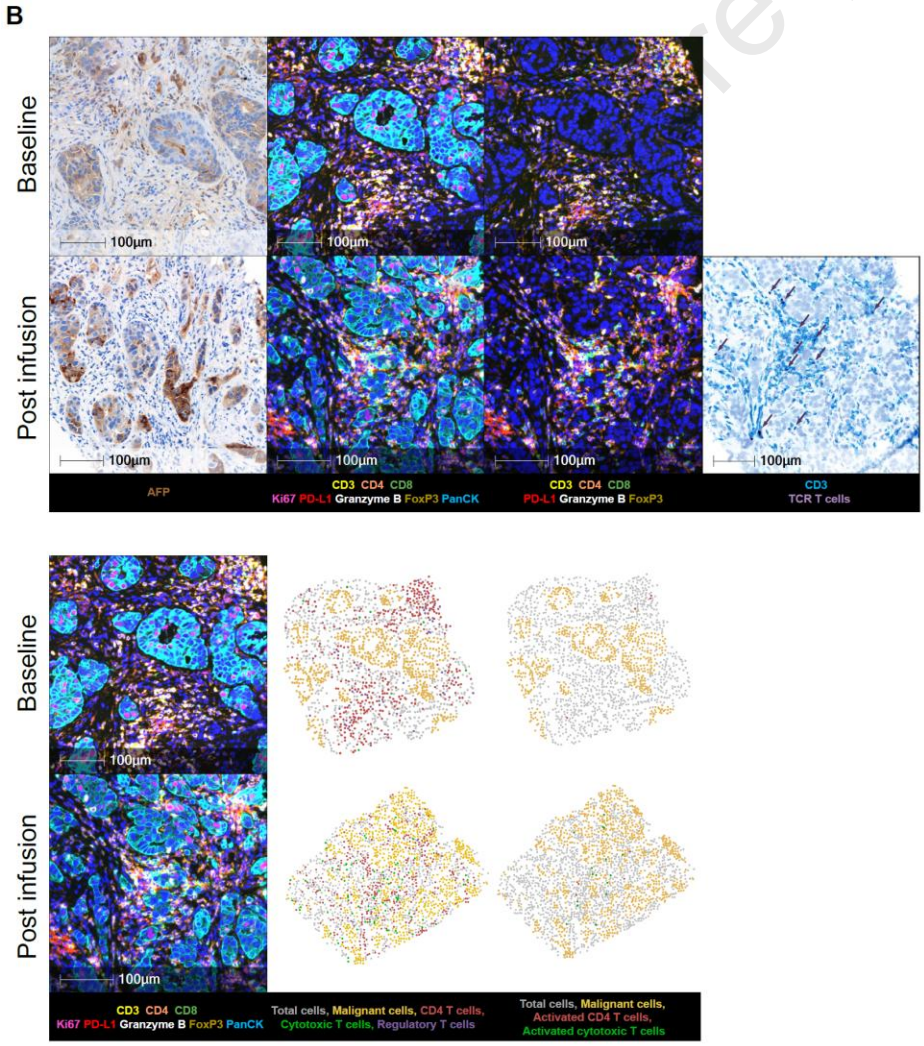
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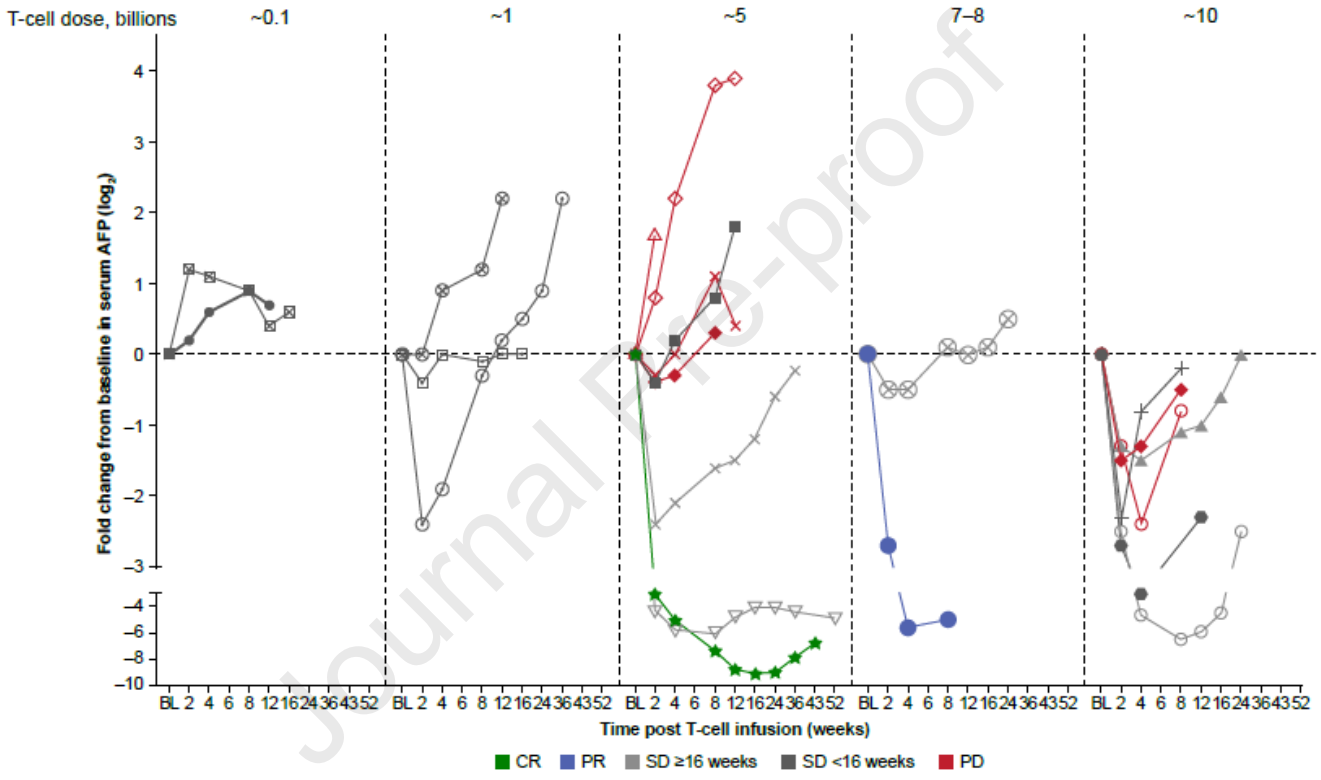
Baseline
Post infusion
100μm
AFP
CD3 CD4 CD8
Ki67 PD-L1 Granzyme B FoxP3 PanCK
CD3 CD4 CD8
PD-L1 Granzyme B FoxP3
CD3
TCR T cells
Total cells, Malignant cells, CD4 T cells,
Cytotoxic T cells, Regulatory T cells
Total cells, Malignant cells,
Activated CD4 T cells,
Activated cytotoxic T cells

590

Fig. 3. Relationship between dose of ADP-A2AFP and extent of serum AFP reduction after infusion. Change from baseline to week 52 in serum AFP per patient by T-cell dose and colored by RECIST v1.1 BOR. Data cut-off April 5, 2022; data were unavailable as of the November 8, 2022, cut-off. AFP, alpha-fetoprotein; BL, baseline; BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.



Highlights:

- ADP-A2AFP is an autologous engineered T cell therapy targeting AFP
- This phase 1 trial tested lymphodepletion chemotherapy and ADP-A2AFP infusion
- All 21 patients with advanced AFP-positive tumors experienced ≥1 grade ≥3 AE
- ORR was 9.5%, with 1 CR, 1 PR, and 12 SD (8 of which had a duration ≥16 weeks)
- T cell dose of $>5 \times 10^9$ cells was associated with a decrease in serum AFP