Human Chimeric Antigen Receptor Macrophages Targeting C-MET for C-MET-positive Advanced Stage of Pancreatic Cancer Patients:

A single-arm, single-center, IIT study

Protocol

Version: 7.0

DATE: 2026-01-22

1. Study Objectives and Expected Outcomes

1.1 Primary Objective

To preliminarily observe the safety and tolerability of intraperitoneal injection of CAR-M-C-MET cells in patients with advanced pancreatic cancer, and to explore the recommended dose for subsequent clinical studies.

1.2 Secondary Objectives

To preliminarily observe the potential efficacy (ORR, DCR, PFS, OS, etc.) of intraperitoneal injection of CAR-M-C-MET cells in patients with advanced pancreatic cancer.

1.3 Expected Outcomes

Intraperitoneal injection of autologous CAR-M-C-MET cells (maximum single dose of 1.0 x 10^9 cells) is safe and may have certain efficacy against pancreatic cancer.

2. Study Methods

2.1 Study Nature

Single-arm, single-center, IIT study (autologous genetically modified adoptive cell therapy)

2.2 Indication

Patients with advanced pancreatic cancer who have failed or are intolerant to second-line or later therapy.

2.3 Cell Product

- **Cell Source:** Apheresis-derived autologous peripheral blood mononuclear cells, followed by magnetic bead sorting of CD14-positive monocytes.
- **Induction Conditions:** Addition of GM-CSF to the culture medium to induce differentiation of CD14-positive monocytes into macrophages.
- **CAR Molecule Sequence:** CD8 signal peptide + scFV (anti-C-MET) + (GGGGS)3 linker + CD8 hinge region + CD8 transmembrane domain + CD3 zeta sequence.
- **Viral Vector:** The CAR molecule is inserted into an Ad5f35 adenoviral backbone vector driven by an EF1α promoter.
- **Long-term Storage Conditions:** Liquid nitrogen.
- **Shelf Life:** 3 months.
- **Transport Conditions:** Liquid nitrogen.

2.4 Administration Route and Regimen

- Intraperitoneal injection.
- Single cell injection.

2.5 Primary Endpoints

- **Safety:** Occurrence and severity of Dose-Limiting Toxicity (DLT) events and Adverse Events (AEs), including but not limited to acute peritonitis, moderate-to-severe pancreatitis, severe liver function injury, abdominal infection, intestinal obstruction, intestinal perforation, cytokine release syndrome (CRS), as well as clinically significant abnormal laboratory test results, vital signs, and electrocardiogram (ECG) findings.
- **Efficacy:** Objective Response Rate (ORR) assessed based on RECIST v1.1.

2.6 Secondary Endpoints

- **Safety:** Recommended Phase 2 Dose (RP2D).
- **Efficacy:** Progression-Free Survival (PFS), Disease Control Rate (DCR), Duration of Response (DoR), Time to Response (TTR), Time to Progression (TTP), and Overall Survival (OS) assessed by the investigator based on RECIST v1.1.

2.7 Cellular Pharmacokinetic Analysis

- Detection of CAR copy number in peripheral blood cells using q-PCR.

3. Statistical Methods and Sample Size

3.1 Study Duration and Sample Size Calculation

- **Study Dates:** October 2025 – December 2029
- **Study End:** 52 weeks after the last patient receives the last cell treatment.
- **Expected Enrollment:** 3-18 patients.
- Dose escalation exploration across 3 dose levels (2x10^8, 4.0x10^8, 1.0 x 10^9 cells) using a "3+3" design.
- Reference: Kunshi Bio's previous experience with intraperitoneal CAR-M-HER2 injection for advanced solid tumors and literature review. The dose escalation principles for this study are as follows:
    - Enroll 3 subjects initially in the 2x10^8 (Dose-1) cohort, then proceed to enroll the 4.0x10^8 (Dose-2) cohort. If 1 DLT occurs in the Dose-1 cohort during the DLT observation period (4 weeks), enroll an additional 3 subjects. If ≥ 2 subjects in the initial 3 subjects of the Dose-1 cohort experience DLT after cell infusion, the trial will be paused, and dose de-escalation or an

adjusted dosing regimen will be discussed by the investigators and the Data Monitoring Committee (DMC).

- For the Dose-2 cohort, first enroll 3 subjects. If 1 DLT occurs, enroll an additional 3 subjects. If DLT ≤ 1, escalate to 1.0 x 10^9 (Dose-3).
- If the DLT proportion is ≥ 2/6 for Dose-n (n=1,2,3), then Dose-(n-1) is the RP2D. If no more than 1 DLT event occurs in the Dose-3 cohort, then Dose-3 is the RP2D.
- For the first three patients in each dose cohort, subsequent patient cell infusion can only proceed after the previous patient has completed the DLT observation period safely.

- Reference: Riess KA et al. CAR-macrophage therapy for HER2-overexpressing advanced solid tumors: a phase 1 trial. Nat Med. 2025 Apr;31(4):1171-1182.

3.2 DLT Definition

I. Any clinically significant Grade 3 or higher toxicity involving major organ systems, as per NCI CTCAE v.5 criteria, occurring within 28 days post-infusion and lasting more than 72 hours.

II. Any Grade 4 Cytokine Release Syndrome (CRS) occurring during treatment that does not resolve to Grade ≤ 2 within 72 hours, or any death attributed to CRS.

III. Any Grade 3 CRS occurring during treatment that does not resolve to Grade ≤ 2 within 7 days.

IV. Any Grade 3 or higher autoimmune toxicity occurring during treatment.

V. Grade 3 or higher allergic reaction related to the investigational cell infusion.

VI. Grade 4 hematological toxicity per CTCAE not resolving within 7 days.

VII. Any Grade 2 or higher neurotoxicity not resolving to Grade 1 within 72 hours.

Reference: Riess KA et al. CAR-macrophage therapy for HER2-overexpressing advanced solid tumors: a phase 1 trial. Nat Med. 2025 Apr;31(4):1171-1182.

3.3 Allocation Method

Single-center, single-arm, non-controlled, interventional study.

3.4 Data Collection, Management, Statistics, and Analysis of Results

- **General Principles:** Analysis will be performed based on the number of enrolled subjects, the Full Analysis Set (FAS), the Per-Protocol Set (PPS), and the Safety Analysis Set (SS). Unless otherwise specified, all statistical tests will be two-sided, with statistical significance determined using a Type I error rate of 0.05 (α value).

- **Quantitative Data:** Described using number of cases, median, mean, standard deviation, and range.
- **Qualitative Data:** Described using frequencies, constituent ratios, or percentages.
- **Statistical Tests:** Parametric statistical methods will be considered first. If the data distribution deviates significantly from the assumptions of the test, non-parametric methods will be used.
- **Statistical Analysis Tools:** Statistical analysis will be performed using the SAS statistical software package or the SPSS software package.
- **Patient Characteristics:**
    - **Enrollment and Disposition:** Summarize the number of cases and list the drop-out cases.
    - **Baseline Characteristics:** Baseline is defined as data obtained during the screening period. Describe patients' demographic characteristics, symptoms/signs, comorbidities, allergy history, medical history, etc.

3.4.1 Efficacy Evaluation

- Assess changes in tumor number and size according to RECIST 1.1.
- Analyze time-to-event endpoints (DoR, TTP, PFS, OS) using the Kaplan-Meier method.

- Graphical analysis will include spider plots showing the percentage change in target lesion tumor burden over time from baseline, waterfall plots showing the best percentage change in target lesion tumor burden from baseline, and Kaplan-Meier curves for DoR, TTP, PFS, and OS.

3.4.2 Safety Evaluation

Describe in detail the types and severity of AEs and SAEs occurring during the study, including time of onset, end date, severity, relationship to study treatment, actions taken, and outcome, and analyze the related factors for their occurrence.

3.4.3 Analysis Sets

- **Efficacy Baseline Data:** Defined as data obtained before cell treatment. Analysis of efficacy endpoints will be based on the Full Analysis Set (FAS). This set includes all subjects who received at least one cell treatment and had measurable lesions at baseline (as per RECIST v1.1).
- **Safety Analysis:** Will be performed based on the Safety Analysis Set (SS). This set includes all enrolled subjects who received at least one cell treatment.

3.4.4 Protocol Deviation (PD)

Protocol deviation refers to non-compliance with the study protocol during the trial. PDs are classified by severity as **minor** or **major**.

- **Minor PD:** A deviation that does not affect subject safety or data integrity and can be appropriately managed.
- **Major PD:** A significant deviation that may affect the subject's rights, safety, willingness to continue participation, and/or the integrity, accuracy, and reliability of the study data. In case of a major PD, the subject may be excluded from the Per-Protocol Set (PPS). Major PDs requiring exclusion from the PPS will be discussed and decided upon at the data review meeting before database lock.

Examples of major PDs that may lead to exclusion from the PPS:

(1) Failure to meet inclusion/exclusion criteria.

(2) Non-compliance with study treatment, e.g., receiving the wrong study drug/treatment.

(3) Use of any prohibited concomitant medications or treatments.

3.4.5 Statistical Analysis Methods

- Differences between two groups for categorical variables will be compared using the Chi-square test or Fisher's exact test.

- Differences between two groups for continuous variables will be compared using the independent samples t-test or Wilcoxon rank-sum test.
- Changes within a group at different follow-up time points compared to baseline will be analyzed using the Signed Rank test.

3.4.6 Data Collection

Data collected during the study will be recorded in subject-specific Case Report Forms (CRFs). Designated personnel will provide EDC training and login accounts, along with instructions for completing the CRFs. Each subject will be assigned a unique subject ID in the EDC for identification. All data outside the EDC will be integrated with the subject's CRF data according to the data transfer agreement or analysis plan. The subject ID and study participation dates should be recorded by the investigator in the subject's medical/research records along with the study code. The investigator should also record the following in the medical/research records: confirmation of written and verbal informed consent, the subject's clinical status, dates of each study visit, dates of investigational product administration, concomitant medications, copies of all relevant reports and laboratory test results, opinions on results, and any mentioned AEs. Investigators will provide electronic signatures via the EDC system, indicating they have checked or reviewed the data, data queries, and site communications within the CRF and agree with the

content. All information and other materials used for subjects and research personnel must use clear and understandable vocabulary and language. Data managers will verify and review data during the trial to ensure timeliness, accuracy, reliability, and consistency. Data managers will perform electronic and manual checks of CRF data, generate queries for resolution by the investigator or designee, and close or re-open queries based on responses until issues are resolved. Data managers will also perform consistency checks between external data (e.g., from a central lab) and corresponding clinical database data, and between SAEs in the clinical database and corresponding data points in the safety database to ensure consistency.

3.4.7 Database Design, Testing, Data Entry, and Modification

- **Database Design:** The data manager designs the database and tests it using simulated data or real eCRF data to ensure it meets protocol requirements and is configured correctly.
- **Data Entry:** The Sponsor/CRO is responsible for training the site investigators or their authorized research staff on the "eCRF Completion Guidelines" to ensure understanding of eCRF content, familiarity with the database structure and functions, and awareness of potential issues during entry. During data entry, investigators or their

staff can contact the data department at any time to discuss and resolve questions encountered.

- **Data Verification:** Data verification methods during data management include logical data checks, manual checks, medical review, and pre-statistical analysis review phases. Data queries will be generated within the EDC system for site resolution. If the response meets requirements, the query is closed. If the query remains unresolved or the previous response leads to new queries upon database update, the investigator or their staff needs to respond again. This process repeats until all data in the database is confirmed accurate.

3.4.8 Database Lock

Based on statistical analysis needs, if discussion is required to determine analysis populations, a data review meeting will be held before database lock, convened by the Project Manager with attendance from the Sponsor Funder, Principal Investigator, Statistician, and Data Manager. Data will be reviewed to determine analysis populations, and a data review 决议 (decision/confirmation) will be signed by representatives from all participating parties. After database lock, the Data Manager (DM) will submit the locked data to the Statistician for statistical analysis.

3.4.9 Data Review and Site Monitoring

The investigator must maintain source documents for each patient participating in the trial, including study medical records and visit records (inpatient or outpatient medical records), containing demographic and medical information, laboratory data, ECGs, and results of any other examinations or evaluations. All information in the EDC must be derived from source documents in the patient's file. The investigator must also retain signed informed consent forms from patients.

3.4.10 Retention of Trial Records

To meet regulatory authority audit and/or inspection requirements, the investigator/institution must agree to retain relevant records, including identification codes for all participating subjects, all originally signed informed consent forms, copies of all CRFs, safety reports, source documents, details of treatment administration, and relevant correspondence (e.g., letters, meeting minutes, phone reports). The investigator/institution must retain records according to relevant regulatory requirements.

Trial materials should be retained by the research institution for 30 years after the end of the clinical trial.

3.4.11 Publication of Study Results

Ownership of the study results belongs jointly to the Principal Investigator and Kunshi No.1 Biotechnology Co., Ltd. Kunshi No.1 Biotechnology Co., Ltd. does

not restrict the investigator from publishing any information generated or collected, regardless of whether the results are favorable to the study drug. Any content related to the study and/or the study results may be published in journals, presented at academic or commercial conferences, only after mutual discussion and agreement between the Principal Investigator and Kunshi Company.

4. Subject Inclusion and Exclusion Criteria

Study Population:

Patients with advanced (unresectable or abdominopelvic metastatic) pancreatic ductal adenocarcinoma who have failed or are intolerant to second-line or later therapy (regimens must include at least one of the following: gemcitabine, paclitaxel, fluorouracil, oxaliplatin, or irinotecan).

4.1 Inclusion Criteria (Donor/Recipient)

1. Able to understand and voluntarily sign a written informed consent form.
2. Must be willing and able to comply with scheduled visits, treatment plans, laboratory tests, and other study requirements.
3. Age ≥ 18 years and ≤ 75 years on the day of signing informed consent, male or female.

4. ECOG performance status 0-1.
5. Histologically or cytologically confirmed locally unresectable or abdominopelvic metastatic pancreatic ductal adenocarcinoma.
6. Pancreatic cancer patients who have failed or are intolerant to at least first-line therapy.
7. Medium or high expression of C-MET in pancreatic cancer tissue (≥ 2+, with >25% positive cells).
8. At least one measurable lesion according to RECIST v1.1.
9. Life expectancy ≥ 4 months.
10. Adequate organ function as required by laboratory tests:
    - **Hematology** (subjects must not receive transfusions or growth factor support within 7 days prior to first dose):
        - Absolute Neutrophil Count (ANC) ≥ 1.5 × 10^9/L.
        - Platelet Count ≥ 100 × 10^9/L.
        - Hemoglobin ≥ 90 g/L or ≥ 5.6 mmol/L.
    - **Liver and Kidney Function**:
        - Creatinine (Cr) ≤ 1.5 × ULN.
        - Albumin ≥ 30 g/L (no albumin infusion allowed within 14 days prior to first dose).
        - Total Bilirubin (TBIL) ≤ 1.5 × ULN (≤ 3 × ULN for subjects with liver metastases).

- Alanine Aminotransferase (ALT) ≤ 2.5 × ULN.
- Aspartate Aminotransferase (AST) ≤ 2.5 × ULN (≤ 5 × ULN for subjects with liver metastases).

- **Urinalysis**:
  - Urine protein ≤ 1+, without edema or serum albumin below the lower limit of normal (LLN).
- **Coagulation**:
  - International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT) ≤ 1.5 × ULN (unless subject is receiving anticoagulant therapy, and PT/APTT are within the expected therapeutic range of the anticoagulant).
  - Prothrombin Time (PT) within normal range.

11. Females of childbearing potential must have a negative serum pregnancy test result within 7 days prior to the first dose and must be non-lactating.

4.2 Exclusion Criteria

1. Received the following anti-tumor therapies prior to apheresis: Immunomodulators within 7 days; Cytotoxic therapy within 14 days; Investigational drugs, targeted therapy, or anti-tumor traditional Chinese medicine within 28 days.

2. Prior treatment with CAR-T cells or other cell therapies targeting any antigen.
3. Liver metastases occupying > 30% of liver volume.
4. History of other concurrent malignancies, except for the following: completely resected or cured basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, micropapillary thyroid carcinoma, or micro-breast cancer, or other malignancies with extremely low risk of recurrence or metastasis.
5. Patients with a history of autoimmune diseases requiring immunosuppressive drugs or hormone therapy (except physiological replacement doses).
6. History of significant Central Nervous System (CNS) disease, such as epilepsy (generalized seizures), paralysis, aphasia, stroke, severe brain injury, dementia, Parkinson's disease, psychosis.
7. Left Ventricular Ejection Fraction (LVEF) < 50%, or severe cardiac structural abnormalities or arrhythmias requiring medication.
8. History of medical treatment for intestinal obstruction, or imaging findings during screening indicating intestinal obstruction requiring treatment.
9. Moderate-to-severe fatty liver.
10. Moderate-to-severe liver cirrhosis (above Child-Pugh Class A) and significant portal hypertension.

11. History of gastrointestinal bleeding within the past 6 months requiring transfusion, emergency room observation, or hospitalization.
12. Patients with active peptic ulcers.
13. Patients with a history of severe intra-abdominal infection.
14. History of abdominal surgery within the past 3 months.
15. Any uncontrolled active infection.
16. Infectious diseases, including but not limited to:
    - Known history of Human Immunodeficiency Virus (HIV) infection or AIDS-related illness.
    - Hepatitis B (HBsAg positive) or Hepatitis C (HCV RNA positive).
    - Active tuberculosis infection, currently receiving anti-TB treatment, or having received anti-TB treatment within 1 year prior to first dose of study drug.
    - Positive Treponema pallidum antibody test.
    - Other infectious diseases deemed unsuitable for participation by the investigator.
17. Previous anti-tumor treatment-related AEs not resolved to Grade ≤ 1.
18. Patients with deep vein thrombosis or other conditions requiring anticoagulation therapy (e.g., heparin, warfarin).
19. Patients with a history of any arterial embolism.
20. Presence of other severe diseases prior to apheresis that might limit participation in this trial, for example: poorly controlled diabetes

(HbA1c > 8% despite treatment), poorly controlled hypertension (BP > 160/100 mmHg) on medication, myocardial infarction within the last 6 months, severe arrhythmia or unstable angina not well controlled with medication, pulmonary embolism, Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), etc.

21. Pregnant or breastfeeding women; women planning to become pregnant during the study period, or men planning to father children during the study period.
22. Substance abuse (drugs or alcohol), clinical or psychological or social factors that would compromise informed consent or study behavior.
23. Subjects with an allergic predisposition (allergy to three or more types of food, drugs, or other substances).
24. Presence of moderate or greater ascites.
25. Currently participating in another interventional clinical trial.
26. Any uncertainty that may affect the patient's safety or compliance.
27. Any other condition deemed unsuitable for enrollment by the investigator.

4.3 Early Discontinuation Criteria

Subjects who do not complete the protocol are considered early discontinuations. The reason for early discontinuation (e.g., voluntary withdrawal, toxicity, death) must be documented in the CRF. Study

assessments will be completed at the time of final discontinuation. Potential reasons for early discontinuation include, but are not limited to:

1. Subject lost to follow-up.
2. Principal Investigator deems the patient too ill to continue.
3. Subject non-compliance with study treatment and/or clinical schedule.
4. Pregnancy.
5. Voluntary withdrawal. Subjects may change their mind and withdraw from the study at any time.
6. Significant and rapid tumor progression requiring alternative therapy, including but not limited to radiotherapy or surgery.
7. Technical difficulties or uncontrollable factors encountered during the CAR-M production and transportation process that prevent the generation of a clinical cell dose meeting quality control standards.

4.4 Study Termination Criteria

Clinical study termination refers to the premature cessation of the entire study before its planned completion. The purpose of study termination is primarily to protect subject rights and interests, ensure study quality, and avoid unnecessary economic losses.

- Discovery of major flaws in the clinical study protocol design that make it difficult to objectively evaluate the investigational product.

- Request for termination by the Sponsor, provided subject rights, safety, and welfare are fully protected.
- Termination ordered by the National Medical Products Administration (NMPA) or the Ethics Committee for any reason.