# Izalontamab brengitecan for HR+/HER2– breast cancer in China (PANKU-Breast01): a randomised, phase 3 trial

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## Summary

**Background** Patients with heavily pretreated hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer have few treatment options. Izalontamab brengitecan (iza-bren) is a first-in-class, epidermal growth factor receptor and HER3 bispecific antibody–drug conjugate that contains a potent topoisomerase I inhibitor payload (Ed-04). The aim of PANKU-Breast01 was to compare the efficacy and safety of iza-bren versus chemotherapy in patients with pretreated HR+/HER2– breast cancer.

**Methods** In this randomised, phase 3, open-label, multicentre study in 72 hospitals in China, patients with HR+/HER2– breast cancer who had disease progression after endocrine therapy, cyclin-dependent kinase (CDK) 4/6 inhibitors, and one or two lines of chemotherapy were randomly assigned (1:1) to iza-bren (2·5 mg/kg, administered by intravenous infusion on day 1 and day 8 every 3 weeks) or physician's choice chemotherapy (eribulin, 1·4 mg/m²; vinorelbine, 25 mg/m²; or gemcitabine, 1000 mg/m², all administered by intravenous infusion on day 1 and day 8 every 3 weeks; or capecitabine, 1000–1250 mg/m², administered orally twice daily on days 1–14 of each 3-week cycle). Stratified block randomisation was performed by an independent vendor using an interactive web response system, with stratification factors of number of previous lines of chemotherapy, CNS metastasis, and HER2 expression status. Patients, investigators, and site personnel involved in patient care and performing trial procedures were not masked to treatment assignment. The primary endpoint was progression-free survival assessed by Blinded Independent Central Review per RECIST (version 1.1) in the modified intention-to-treat population, which consisted of all randomly assigned participants who had at least one dose of study drug. Median progression-free survival was estimated using the Kaplan–Meier method and hazard ratios (HRs) were calculated using a stratified Cox proportional hazards model. The trial was registered at ClinicalTrials.gov, NCT06343948, and is closed to recruitment.

**Findings** Between April 24, 2024, and June 6, 2025, 560 patients were screened, 177 were excluded, and 383 patients were randomly assigned and treated (190 were assigned to the iza-bren group and 193 were assigned to the chemotherapy group). All 383 participants in the study were female and of Chinese ethnicity. Median age was 54·0 years (IQR 47·0–60·0). At data cutoff (July 21, 2026), median follow-up for progression-free survival was 15·2 months (95% CI 13·9–16·8). Iza-bren significantly improved progression-free survival versus chemotherapy (log-rank p<0·0001), and median progression-free survival assessed by Blinded Independent Central Review was 8·2 months (95% CI 6·9–8·6) versus 4·0 months (2·9–4·3; HR 0·41 [95% CI 0·33–0·53]). Grade 3 or higher treatment-related adverse events occurred in 162 (85%) patients in the iza-bren group versus 127 (66%) patients in the chemotherapy group, and haematological adverse events were the most common in both groups. For the treatment of haematological adverse events, 138 (73%) patients in the iza-bren group received platelet-elevating agents, 28 (15%) patients in the iza-bren group received platelet transfusion, and 18 patients (10%) in the iza-bren group received a blood transfusion. Two patients in the iza-bren group died due to treatment-related adverse events.

**Interpretation** Iza-bren showed a significant improvement in progression-free survival versus chemotherapy in patients with HR+/HER2– breast cancer previously treated with endocrine therapy, CDK4/6 inhibitors, and one or two lines of chemotherapy (including taxanes). The overall survival data were immature, and an overall survival benefit has not been established. These results suggest that iza-bren could be a new treatment option for this population in China; however, further evaluation of iza-bren in global populations and in earlier lines of therapy for HER2-negative breast cancer is warranted.

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## Research in context

### Evidence before this study

We searched PubMed using the search terms "antibody-drug conjugates" and "breast neoplasm" for phase 1 to phase 3 trials published from database inception to Sept 15, 2026, with no language restrictions. Phase 3 trials DESTINY-Breast04, DESTINY-Breast06, TROPION-Breast01, and TROPiCS-02 evaluated trastuzumab deruxtecan, datopotamab deruxtecan, and sacituzumab govitecan in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor (HER2)-negative (HER2-zero and HER2-low) advanced breast cancer. In DESTINY-Breast04, trastuzumab deruxtecan demonstrated significantly longer progression-free survival (hazard ratio [HR] 0·51 [95% CI 0·40–0·64]) and overall survival versus chemotherapy (HR 0·64 [0·48–0·86]). DESTINY-Breast06 demonstrated improved progression-free survival with trastuzumab deruxtecan in patients with hormone receptor–positive, HER2-low, or HER2-ultralow metastatic breast cancer after endocrine-based therapy. TROPION-Breast01 showed that datopotamab deruxtecan significantly improved progression-free survival versus chemotherapy (HR 0·63 [95% CI 0·52–0·76]) in pretreated hormone receptor-positive/HER2-negative breast cancer. The TROPiCS-02 trial demonstrated that sacituzumab govitecan significantly improved progression-free survival (HR 0·66 [95% CI 0·53–0·83]) compared with physician's choice chemotherapy in endocrine-resistant hormone receptor-positive/HER2-negative metastatic breast cancer after two or more previous chemotherapy regimens. Evidence before this study was primarily on HER2-directed or TROP-2-directed monospecific antibody–drug conjugates and clinical studies on a bispecific antibody–drug conjugate in hormone receptor-positive/HER2-negative advanced breast cancer were not reported.

### Added value of this study

To our knowledge, PANKU-Breast01 was the first randomised phase 3 study that demonstrated a significant progression-free survival benefit with an epidermal growth factor receptor and HER3 bispecific antibody–drug conjugate compared with chemotherapy in patients with heavily pretreated HR+/HER2– breast cancer. Izalontamab brengitecan demonstrated significantly improved progression-free survival, as well as higher response rate and durable responses compared with chemotherapy.

### Implications of all the available evidence

Results of PANKU-Breast01 suggest izalontamab brengitecan could be a new treatment option for patients with heavily pretreated HR+/HER2– breast cancer and indicate the potential for future development of izalontamab brengitecan in global populations. Overall survival data are immature and a longer follow-up is needed. Health-related quality-of-life results revealed that quality of life with izalontamab brengitecan treatment was not better than chemotherapy.

## Introduction

Breast cancer is the most commonly diagnosed cancer among women and is the leading cause of cancer deaths among women globally.[1] Hormone receptor-positive and human epidermal growth factor receptor 2-negative (HR+/HER2–) breast cancer is the most common subtype defined by immunohistochemistry (IHC) and in situ hybridisation (ISH), accounting for about 70% of breast cancer cases.[2,3] Endocrine therapy with or without cyclin-dependent kinase (CDK) 4/6 inhibitors has been recommended as first-line or second-line treatment for advanced HR+/HER2– breast cancer.[4] However, intrinsic resistance and acquired resistance to endocrine therapy are common.[5] Chemotherapy remains a treatment option for most patients with disease progression following endocrine therapy, but can result in decreased survival benefit with each subsequent line of treatment.[6] Despite the approval of HER2 and trophoblast cell-surface glycoprotein antigen 2 (TROP2)-directed antibody–drug conjugate for advanced HR+/HER2- breast cancer, novel drugs with enhanced clinical efficacy and favourable safety profiles are required.[7]

Izalontamab brengitecan (iza-bren) is a first-in-class, bispecific antibody–drug conjugate, comprising an epidermal growth factor receptor (EGFR) and HER3 bispecific antibody conjugated to a potent topoisomerase I inhibitor payload (Ed-04) via a cleavable linker.[8] EGFR expression has been observed in 37–48% of breast cancer cases and was reported to be correlated with an aggressive phenotype.[9–11] HER3 expression was observed in 44–75% of breast cancer cases and expression of both EGFR and HER3 was also commonly observed.[12–14] Iza-bren binds to and is internalised by EGFR or HER3 positive cancer cells, delivering the cytotoxic payload intracellularly.[8]

In a phase 1 study, iza-bren showed an objective response rate of 34·0% in patients with advanced solid tumours.[15] In patients with HER2–, locally advanced, or metastatic breast cancer, iza-bren showed an objective response rate of 36·4% and a median progression-free survival of 6·9 months.[16] In a randomised phase 3 study, iza-bren showed significant improvement in both progression-free survival and overall survival versus chemotherapy in patients with pretreated triple-negative breast cancer.[17]

In this Article, we present results from a prespecified interim analysis of a phase 3 study, PANKU-Breast01, which was designed to compare the efficacy and safety of iza-bren versus chemotherapy in patients with locally recurrent inoperable or metastatic HR+/HER2– breast cancer.

## Methods

### Study design and participants

This phase 3, multicentre, open-label, randomised superiority trial compared iza-bren with physician's

choice of chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine) in patients with locally recurrent inoperable or metastatic HR+/HER2– breast cancer. Individual patients were enrolled from 72 hospitals in China that met Good Clinical Practice guideline qualifications, and randomly assigned to receive iza-bren or chemotherapy. A list of study investigators and participating hospitals is provided in the appendix (pp 3–5).

Eligible patients had unresectable, locally advanced, recurrent or metastatic HR+/HER2– breast cancer (HR+, oestrogen receptor ≥1% or progesterone receptor ≥1% or both; HER2–, IHC 0, IHC 1+, or IHC 2+ and ISH–) and received at least one previous endocrine therapy, one or two previous chemotherapy regimens for recurrent or metastatic disease (including a taxane), and CDK4/6 inhibitors.

Exclusion criteria included previous treatment with a topoisomerase I inhibitor-containing antibody–drug conjugate or EGFR/HER3-targeting antibody–drug conjugate or antibody; history of severe cardiovascular and cerebrovascular diseases; history of interstitial lung disease requiring corticosteroid treatment, or current interstitial lung disease, grade ≥2 radiation pneumonitis; CNS metastases (brain metastases that had been treated and stable for more than 12 weeks before the first dose of study treatment was permitted), or carcinomatous meningitis or spinal cord compression; and history of inflammatory bowel disease. The full inclusion and exclusion criteria are presented in the study protocol in the appendix (pp 33–177). Sex was self-reported by patients as being male or female. Ethnicity data were self-reported by patients as Chinese Han or others.

This trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and laws and regulations in China. The study protocol was reviewed and approved by the ethics committee at each study site before the trial started. A list of ethics committees and ethics approval numbers is provided in the appendix (pp 6–8). Patients provided written informed consent before the start of any of the study procedures. Important changes made from the study protocol when the study commenced are provided in the appendix (p 9). Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this study, and were not involved in the study design and approval. The unredacted protocol and statistical analysis plan are presented in the appendix (pp 33–270). The trial was registered at ClinicalTrials.gov, NCT06343948, and is closed to recruitment.

## Randomisation and masking

Patients were randomly assigned (1:1) to iza-bren or physician's choice of chemotherapy. Site investigators enrolled eligible participants, and an outsourced independent central randomisation service using an interactive web response system (IWRS) performed treatment allocation; randomisation personnel had no further involvement in the trial. Stratified block randomisation was performed by an independent vendor using an IWRS, with stratification factors of number of previous lines of chemotherapy (one line *vs* two lines), CNS metastasis (present *vs* absent), and HER2 expression status (IHC 0 *vs* IHC 1+ *vs* IHC 2+ and ISH–). The randomisation list was generated and maintained by the third-party vendor (Shanghai Shanhu Health Technology, China) and remained inaccessible to the sponsor and study team until database lock. Patients, investigators, and site personnel involved in patient care and performing trial procedures were unmasked to treatment assignment.

## Procedures

In the experimental group, patients received iza-bren via intravenous infusion at a dose of 2·5 mg/kg (dose compensated per study protocol, administration volume of iza-bren = bodyweight × 2·5 mg/kg × 1·1 ÷ [120 mg/10 mL]) on day 1 and day 8 every 3 weeks. In the control group, patients received one of the following chemotherapies selected by the investigator: eribulin (1·4 mg/m², day 1 and day 8 every 3 weeks), vinorelbine (25 mg/m², day 1 and day 8 every 3 weeks), or gemcitabine (1000 mg/m², day 1 and day 8 every 3 weeks) via intravenous infusion; or oral capecitabine (1000–1250 mg/m², twice daily on days 1–14 of each 3-week cycle). Concomitant medications permitted included supportive care, such as antiemetics, analgesics, leukopoietic agents, erythropoietic agents, and bone-protective agents. Prophylactic agents such as granulocyte colony-stimulating factor (G-CSF), antiemetic, and gastroprotective medications were recommended for use, and the specific use was determined by the investigator. The intervention and control were administered by nurses who had received Good Clinical Practice training and had a practising certificate at each participating hospital.

Study treatment continued until disease progression, initiation of new anticancer therapy, occurrence of intolerable toxicity, or discontinuation criteria were met. Details of dose adjustments for iza-bren or chemotherapy are presented in the appendix (pp 10–12).

Tumour imaging (CT or MRI) was performed during the screening period, and every 6 weeks (plus or minus 7 days; plus 7 days for the first tumour imaging) after first dose of study treatment, until disease progression, initiation of new anticancer treatment, death, loss to follow-up, or withdrawal of informed consent, whichever occurred first. Imaging assessments were performed by Blinded Independent Central Review and investigators according to RECIST (version 1.1) criteria.

Safety assessments included adverse events, vital signs, and laboratory tests (blood routine tests, blood biochemistry, and coagulation function). Blood routine tests included white blood cell count, neutrophil count,

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See Online for appendix

red blood cell count, and platelet count. Blood biochemistry tests included alanine aminotransferase and aspartate aminotransferase. Details of laboratory tests are provided in the study protocol in the appendix (pp 33–177). Data on adverse events were collected if they occurred after the first dose of study treatment until 28 days after the last dose of study treatment, informed consent withdrawal, initiation of new anticancer treatment, loss to follow-up, or death, whichever occurred first. Adverse events were coded by using the Medical Dictionary for Regulatory Activities (version 27.1) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). The relationship between the adverse events and study treatment was determined by the investigator. Incidences of adverse events between the two groups were compared numerically and no formal statistical test was prespecified. A summary of major protocol deviations is presented in the appendix (p 19).

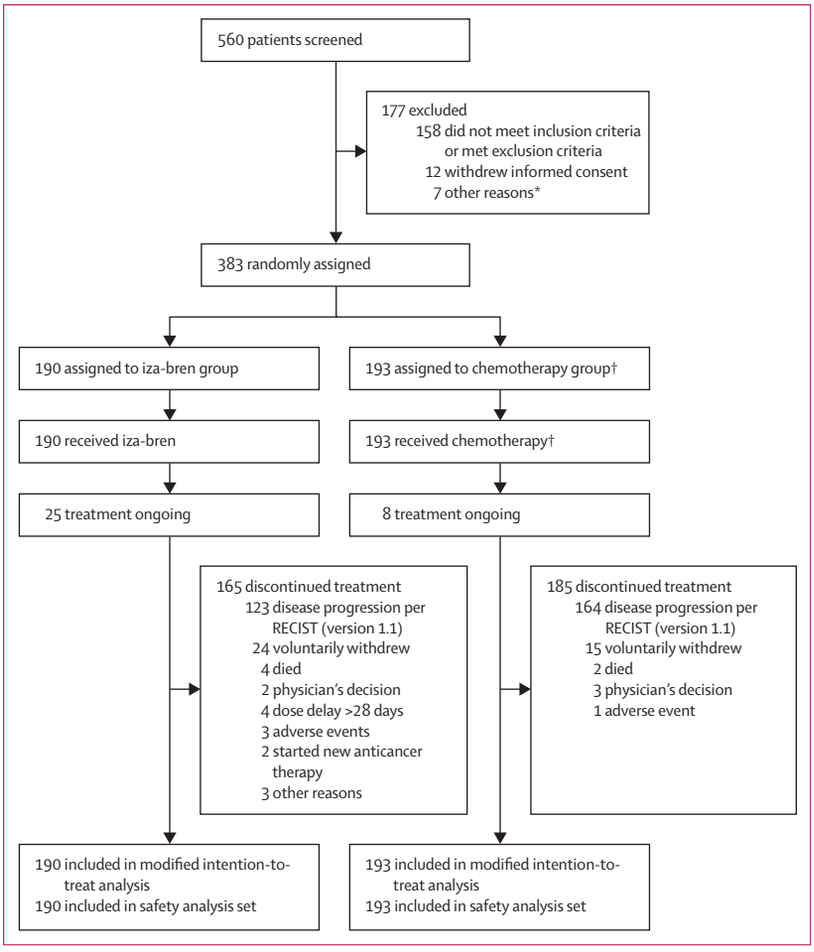



***Figure 1:*** **Trial profile**
Iza-bren=izalontamab brengitecan. *Seven patients were not randomly assigned after screening due to other reasons (six patients withdrew voluntarily and one patient was deemed ineligible by the investigator). †141 patients received eribulin, 13 received vinorelbine, 18 received gemcitabine, and 21 received capecitabine.

## Outcomes

The primary endpoint was progression-free survival (the time from the date of randomisation to the first documented radiological disease progression or death, whichever occurred first) as assessed by Blinded Independent Central Review per RECIST criteria (version 1.1). Secondary endpoints were overall survival (time from randomisation to documented death), investigator-assessed progression-free survival, objective response rate, disease control rate, and duration of response, assessed both by Blinded Independent Central Review and investigators, together with safety, pharmacokinetic profile, and immunogenicity. Prespecified exploratory endpoints included quality-of-life assessment based on European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30), EORTC Quality of Life Questionnaire Breast 45 (EORTC QLQ-BR45), and EuroQol Group 5-Dimension 5-Level questionnaire (EQ-5D-5L) visual analogue scale (VAS). The QLQ-C30 global health and quality-of-life scale provides an overall measure of health-related quality of life, and subscales of functioning and symptoms assess the effect of disease on daily patient life. The QLQ-BR45 questionnaire assesses the effect of disease on daily life specifically for breast cancer, such as breast and arm symptoms. The EQ-5D-5L VAS measures the overall self-rated health status ranging from 0 (representing the worst health) to 100 (representing the best health). For QLQ-C30 and QLQ-BR45 questionnaires, all scales and single item scores ranged from 0 to 100. A higher score for the global health and quality-of-life scale and functioning scale represents a better quality of life and a better level of functioning and a higher score for the symptom scale represents worse symptoms. Pharmacokinetic and biomarker data will be reported separately.

## Statistical analysis

Efficacy analyses were conducted in the modified intention-to-treat population, which included all patients who were randomly assigned and received at least one dose of the study treatment. Safety analyses were conducted in the safety analysis set, which also included all patients who were randomly assigned and received at least one dose of the study treatment.

All quantitative data are reported as means with SDs for normally distributed continuous variables and medians with IQRs for non-normally distributed continuous variables. Time-to-event endpoints are summarised with medians and 95% CIs. Hazard ratios (HRs) are presented with corresponding 95% CIs. Categorical data are reported as absolute values and percentages.

Progression-free survival and overall survival between the iza-bren and control groups were compared by using a stratified log-rank test. HRs were calculated using a

stratified Cox proportional hazards model. Median progression-free survival and overall survival were estimated using the Kaplan–Meier method. All subgroup analyses were prespecified exploratory analyses and not powered to detect subgroup-by-treatment interactions.

To control the overall type I error at 0·025 one-sided level, a prespecified fixed-sequence procedure was used for the Blinded Independent Central Review assessments of progression-free survival and overall survival. At study initiation, the one-sided type I error allocated to the assessment of progression-free survival was 0·025. If statistical significance was shown in the analysis of progression-free survival, then overall survival would be tested. An interim analysis was planned to be conducted when 276 progression-free survival events were observed; this was the final analysis for the primary endpoint and the interim analysis for overall survival. An Independent Data Monitoring Committee (IDMC) conducted the interim analysis. Additionally, a final analysis was planned for overall survival when about 250 overall survival events were observed. The efficacy boundaries at the interim and final analyses of overall survival were to be determined using the Lan–DeMets alpha spending function to approximate O'Brien–Fleming boundaries. Based on the overall one-sided alpha of 0·025, the planned one-sided efficacy boundary was $\alpha$=0·0074 at the interim analysis and $\alpha$=0·0228 at the final analysis of overall survival. The efficacy boundaries will be updated based on the actual number of overall survival events. Predefined stopping guidelines were established for the IDMC to consider early trial termination in the event of overwhelming efficacy, unacceptable safety signals, or futility, in accordance with the IDMC charter. As of data cutoff (July 21, 2026), 289 progression-free survival events were observed.

Assuming the target HR for progression-free survival was 0·714 (median progression-free survival, 6·3 months with iza-bren *vs* 4·5 months with chemotherapy), a total of 312 patients with 276 progression-free survival events (disease progression or death) were required to achieve a statistical power of 80% with an overall one-sided alpha of 0·025, an enrolment period of 12 months, and a follow-up period of 12 months. Considering a dropout rate of 8% and a censoring rate of 10% for Blinded Independent Central Review assessment, a sample size of 382 patients was planned. Censored progression-free survival events were defined as participants without confirmed disease progression or death, under predefined scenarios including absent baseline or post-baseline tumour assessments, initiation of new anti-tumour therapy, events after two or more consecutive missed tumour assessments, and participants free of events at data cutoff or study end. Details of censoring rules per condition are listed in the appendix (pp 14–15).

Missing data for efficacy, safety, and other analytical endpoints were not imputed unless otherwise specified. When fully or partially missing electronic case report form measurement or assessment dates were required to derive variables (eg, duration calculations, treatment-period indicators), prespecified rules in the statistical analysis plan were applied. For time-to-event endpoints, patients with missing progression or survival information were censored at the last known date of adequate tumour assessment or last contact date.

All statistical analyses were performed using SAS (version 9.4). Additional details of statistical analysis methods are presented in the statistical analysis plan in the appendix (pp 178–270).

| | Iza-bren group (n=190) | Chemotherapy group (n=193) |
|---|---|---|
| Age, years | | |
| Median age | 54 (47–61) | 54 (47–59) |
| <65 | 166 (87%) | 172 (89%) |
| ≥65 | 24 (13%) | 21 (11%) |
| Female sex | 190 (100%) | 193 (100%) |
| Ethnicity | | |
| Chinese | 190 (100%) | 193 (100%) |
| ECOG performance status score | | |
| 0 | 68 (36%) | 69 (36%) |
| 1 | 122 (64%) | 124 (64%) |
| CNS metastases | 4 (2%) | 3 (2%) |
| Liver metastases | 136 (72%) | 137 (71%) |
| Lung metastases | 80 (42%) | 76 (39%) |
| Oestrogen receptor expression status | | |
| Positive | 188 (99%) | 188 (97%) |
| Negative | 2 (1%) | 5 (3%) |
| Progesterone receptor expression status | | |
| Positive | 121 (64%) | 124 (64%) |
| Negative | 68 (36%) | 68 (35%) |
| Unknown | 1 (1%) | 1 (1%) |
| HER2 expression status | | |
| IHC 0 | 64 (34%) | 66 (34%) |
| IHC 1+ | 73 (38%) | 74 (38%) |
| IHC 2+/ISH– | 53 (28%) | 53 (27%) |
| Median number of previous anticancer therapies | 3 (2–3) | 3 (2–4) |
| Number of previous chemotherapy regimens | | |
| 1 | 135 (71%) | 139 (72%) |
| 2 | 55 (29%) | 54 (28%) |
| Duration of previous endocrine therapy | | |
| ≥6 months | 162 (85%) | 164 (85%) |
| <6 months | 28 (15%) | 29 (15%) |
| Duration of previous CDK4/6 inhibitor use | | |
| ≥12 months | 93 (49%) | 103 (53%) |
| <12 months | 96 (51%) | 90 (47%) |
| Unknown | 1 (1%) | 0 |

Data are n (%) or median (IQR). CDK=cyclin-dependent kinase. ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2. IHC=immunohistochemistry. ISH=in situ hybridisation. Iza-bren=izalontamab brengitecan.

***Table 1:*** **Baseline characteristics**

**Role of the funding source**
This trial was designed by the academic authors in collaboration with Baili-Bio (Chengdu) Pharmaceutical. The authors and Baili-Bio (Chengdu) Pharmaceutical were involved in data collection, data analysis, and data interpretation, guaranteed the accuracy and completeness of the data, were involved in writing of the report, and were involved in the decision to submit the manuscript for publication. CAMS Innovation Fund for Medical Sciences, Noncommunicable Chronic Diseases-National Science and Technology Major Project, National High Level Hospital Clinical Research Funding, and the National Natural Science Foundation of China had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

## Results

Between April 24, 2024, and June 6, 2025, a total of 560 patients were screened, 177 were excluded (158 did not meet inclusion criteria or met exclusion criteria, 12 withdrew informed consent, and seven for other reasons [six patients withdrew voluntarily, and one patient was deemed ineligible by the investigator]) and 383 were enrolled from 72 hospitals in China. Patients were randomly assigned to the iza-bren group (190 patients) and the chemotherapy group (193 patients; 141 received eribulin, 13 received vinorelbine, 18 received gemcitabine, and 21 received capecitabine). 190 patients in the iza-bren group and 193 patients in the chemotherapy group were included in the modified intention-to-treat analysis (figure 1).

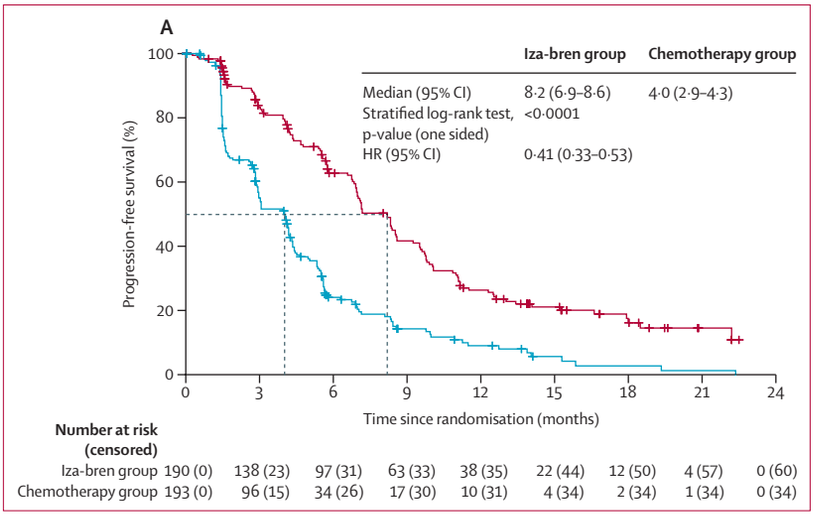
The characteristics of the patients at baseline were balanced between the two groups and are summarised in table 1. All 383 participants in the study were female and of Chinese ethnicity. Median age was 54·0 years (IQR 47·0–60·0). All participants had received previous CDK4/6 inhibitor, endocrine therapy, and taxane-based chemotherapy. The majority of patients in the iza-bren and chemotherapy groups previously received endocrine therapy for at least 6 months (162 [85%] *vs* 164 [85%]). 93 (49%) patients in the iza-bren group and 103 (53%) patients in the chemotherapy group previously received CDK4/6 inhibitor for at least 12 months. At the data cutoff date (July 21, 2026), 25 patients (13%) treated with iza-bren and eight patients (4%) treated with chemotherapy remained on study treatment. In both groups, the most common reason for discontinuing study treatment was disease progression per RECIST version 1.1 (iza-bren group, 123 [65%] patients; chemotherapy group, 164 [85%] patients). Anticancer therapy post study treatment discontinuation is presented in the appendix (p 20).

As of the data cutoff date, median follow-up was 15·2 months (95% CI 13·9–16·8) for progression-free survival. Iza-bren significantly improved progression-free survival compared with chemotherapy (log-rank p<0·0001; figure 2A). The median progression-free survival was 8·2 months (95% CI 6·9–8·6) with iza-bren and 4·0 months (2·9–4·3) with chemotherapy (HR for disease progression or death 0·41 [95% CI 0·33–0·53]).

Per Blinded Independent Central Review assessment, the progression-free survival rate (iza-bren *vs* chemotherapy) at 6 months was 62·8% versus 24·2%, at 9 months was 41·8% versus 14·4%, and at 12 months was 26·5% versus 9·2%. Progression-free survival benefit with iza-bren was observed across most subgroups (figure 2B). In the subgroup of HER2 IHC2+/ISH– the median progression-free survival in the iza-bren and chemotherapy groups was 8·3 versus 3·1 months, for IHC1+ was 8·2 versus 4·1 months, and for IHC0 was 7·1 versus 3·1 months, respectively. Sensitivity and supportive analyses of progression-free survival are provided in the appendix (p 21).

With a median follow-up of 17·8 months (95% CI 16·9–18·3) for overall survival, 157 of the 250 planned overall survival events had occurred (information rate, 62·8%). The primary overall survival analysis in the modified intention-to-treat population yielded an HR of 1·02 (95% CI 0·75–1·40). Exploratory post-hoc inverse probability of censoring weighting analyses adjusting for any subsequent anticancer therapy and subsequent antibody–drug conjugate therapy yielded HRs of 0·48 (95% CI 0·24–0·95) and 0·81 (0·54–1·21), respectively (appendix p 22).

The median progression-free survival per investigator assessment was 7·3 months (95% CI 6·9–8·8) with iza-bren and 4·3 months (4·0–5·5) with chemotherapy (HR for disease progression or death, 0·42 [95% CI 0·33–0·54]; appendix p 16). Per Blinded Independent Central Review assessment, confirmed partial responses occurred in 77 patients (41%; 95% CI 33–48) with iza-bren and in 39 patients (20%; 15–27) with chemotherapy




(Figure 2 continues on next page)

**B**

| | Number of events/cases | | HR (95% CI) | $p_{interaction}$ |
|---|---|---|---|---|
| | Iza-bren group | Chemotherapy group | | |
| **All patients** | **130/190** | **159/193** | 0·42 (0·33–0·54) | |
| **Age (years)** | | | | 0·21 |
| <65 | 113/166 | 146/172 | 0·40 (0·31–0·52) | |
| ≥65 | 17/24 | 13/21 | 0·65 (0·30–1·41) | |
| **Number of previous chemotherapy lines** | | | | 0·24 |
| One line | 90/135 | 113/139 | 0·45 (0·34–0·60) | |
| Two lines | 40/55 | 46/54 | 0·31 (0·20–0·50) | |
| **CNS metastasis** | | | | 0·13 |
| Yes | 3/4 | 3/3 | .. | |
| No | 127/186 | 156/190 | 0·43 (0·34–0·55) | |
| **HER2 expression** | | | | 0·22 |
| IHC 0 | 47/64 | 58/66 | 0·41 (0·28–0·62) | |
| IHC 1+ | 54/73 | 61/74 | 0·53 (0·36–0·76) | |
| IHC 2+/ISH– | 29/53 | 40/53 | 0·32 (0·19–0·53) | |
| **Previous CDK inhibitor use ≥12 months** | | | | 0·71 |
| Yes | 62/93 | 88/103 | 0·44 (0·31–0·61) | |
| No | 67/96 | 71/90 | 0·37 (0·26–0·53) | |
| **Previous anthracycline use** | | | | 0·49 |
| Yes | 104/152 | 133/160 | 0·41 (0·32–0·54) | |
| No | 26/38 | 26/33 | 0·48 (0·27–0·86) | |
| **Endocrine therapy use in advanced disease ≥6 months** | | | | 0·80 |
| Yes | 109/162 | 134/164 | 0·41 (0·32–0·54) | |
| No | 21/28 | 25/29 | 0·45 (0·24–0·85) | |
| **Progression within 6 months after neoadjuvant chemotherapy** | | | | 0·014 |
| Yes | 9/16 | 16/18 | 0·11 (0·04–0·33) | |
| No | 121/174 | 143/175 | 0·45 (0·35–0·58) | |
| **Baseline diagnosis liver metastasis** | | | | 0·88 |
| Yes | 97/136 | 115/137 | 0·40 (0·30–0·54) | |
| No | 33/54 | 44/56 | 0·43 (0·27–0·69) | |
| **ECOG performance status** | | | | 0·56 |
| 0 | 47/68 | 57/69 | 0·48 (0·33–0·72) | |
| 1 | 83/122 | 102/124 | 0·39 (0·29–0·52) | |
| **Stage IV at initial diagnosis** | | | | 0·74 |
| Yes | 21/33 | 36/42 | 0·41 (0·24–0·72) | |
| No | 109/157 | 123/151 | 0·43 (0·33–0·56) | |
| **Previous radiotherapy** | | | | 0·24 |
| Yes | 78/106 | 82/103 | 0·50 (0·36–0·68) | |
| No | 52/84 | 77/90 | 0·36 (0·25–0·51) | |
| **Previous neoadjuvant therapy** | | | | 0·87 |
| Yes | 105/152 | 122/149 | 0·42 (0·32–0·55) | |
| No | 25/38 | 37/44 | 0·45 (0·27–0·77) | |
| **Chemotherapy drugs** | | | | NA |
| Eribulin | 130/190 | 117/141 | 0·43 (0·33–0·56) | |
| Vinorelbine | 130/190 | 12/13 | 0·26 (0·14–0·48) | |
| Gemcitabine | 130/190 | 17/18 | 0·21 (0·13–0·35) | |
| Capecitabine | 130/190 | 13/21 | 0·53 (0·21–0·95) | |

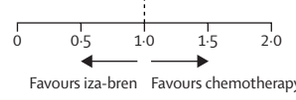



***Figure 2:*** **Progression-free survival by Blinded Independent Central Review in the modified intention-to-treat population**
(A) Kaplan–Meier estimates of progression-free survival. Dashed lines indicate the timepoints when 50% of patients in the iza-bren and control groups had a progression-free survival event. (B) Subgroup analysis of progression-free survival. CDK=cyclin-dependent kinase. ECOG=Eastern Cooperative Oncology Group. HER2=human epidermal growth factor receptor 2. HR=hazard ratio. IHC-immunohistochemistry. ISH=in situ hybridisation. Iza-bren=izalontamab brengitecan. NA=not applicable.

(table 2). The median duration of response per Blinded Independent Central Review assessment was 6·9 months (95% CI 5·7–8·6) with iza-bren and 4·2 months (3·5–6·8) with chemotherapy (table 2; appendix p 18).

| | Iza-bren group (n=190) | Chemotherapy group (n=193) |
|---|---|---|
| Best overall response | | |
| Partial response | 77 (41%) | 39 (20%) |
| Non-complete response or non-progressive disease | 3 (2%) | 3 (2%) |
| Stable disease | 84 (44%) | 81 (42%) |
| Progressive disease | 16 (8%) | 61 (32%) |
| Not evaluable | 10 (5%) | 9 (5%) |
| Confirmed objective response rate (95% CI) | 41% (33–48) | 20% (15–27) |
| Odds ratio (95% CI) | 2·71 (1·71–4·29) | .. |
| Rate difference (95% CI) (*vs* chemotherapy) | 20·21% (11·19–29·03) | .. |
| Median duration of response, months | 6·9 (5·7–8·6) | 4·2 (3·5–6·8) |
| Disease control rate (95% CI) | 86% (81–91) | 64% (57–71) |
| Rate difference *vs* chemotherapy (95% CI) | 22·5% (14·0–30·7) | .. |

Data are n (%) or median (95% CI), unless otherwise specified.
Iza-bren=izalontamab brengitecan.

***Table 2:*** **Anti-tumour activity as assessed by Blinded Independent Central Review in the modified intention-to-treat population**

The best percentage change from baseline in target-lesion size per Blinded Independent Central Review assessment and tumour responses per investigator assessment are presented in the appendix (pp 17, 23).

Median duration of treatment was 7·3 months (IQR 3·2–11·5) in the iza-bren group and 4·3 months (1·6–6·1) in the chemotherapy group. Treatment-related adverse events were reported in 189 (99%) patients in the iza-bren group and in 188 (97%) patients in the chemotherapy group; grade 3 or worse treatment-related adverse events occurred in 162 (85%) patients in the iza-bren group and 127 patients (66%) in the chemotherapy group (table 3). The most common treatment-related adverse events of any grade in the iza-bren and chemotherapy groups were haematological, including anaemia (181 [95%] *vs* 121 [63%]), white blood cell count decreased (165 [87%] *vs* 164 [85%]), platelet count decreased (161 [85%] *vs* 71 [37%]), and neutrophil count decreased (151 [79%] *vs* 168 [87%]; appendix pp 25–26). Febrile neutropenia (grade 3 or 4) occurred in 15 (8%) patients in the iza-bren group and six (3%) patients in the chemotherapy group. The most common non-haematological treatment-related adverse event in both groups was alopecia (101 [53%] with iza-bren and 83 [43%] with chemotherapy). The most common grade 3 or worse treatment-related adverse event in the iza-bren and chemotherapy groups was neutrophil count decrease (102 [54%] *vs* 106 [55%]). Grade 3 or worse treatment-related

| | Iza-bren group (n=190) | | | | | | Chemotherapy group (n=193) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 | Any grade | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
| Any treatment-related adverse event | 189 (99%) | 1 (1%) | 26 (14%) | 88 (46%) | 72 (38%) | 2 (1%) | 188 (97%) | 11 (6%) | 50 (26%) | 82 (42) | 44 (23%) | 1 (1%) |
| Any serious treatment-related adverse event | 79 (42%) | NA | NA | NA | NA | NA | 22 (11%) | NA | NA | NA | NA | NA |
| Investigations | 184 (97%) | 11 (6%) | 37 (19%) | 64 (34%) | 72 (38%) | 0 | 184 (95%) | 16 (8%) | 49 (25%) | 77 (40%) | 42 (22%) | 0 |
| Blood and lymphatic system disorders | 181 (95%) | 19 (10%) | 63 (33%) | 88 (46%) | 11 (6%) | 0 | 121 (63%) | 62 (32%) | 39 (20%) | 17 (9%) | 3 (2%) | 0 |
| Metabolism and nutrition disorders | 158 (83%) | 87 (46%) | 50 (26%) | 18 (9%) | 3 (2%) | 0 | 103 (53%) | 72 (37%) | 25 (13%) | 5 (3%) | 1 (1%) | 0 |
| Gastrointestinal disorders | 151 (79%) | 39 (21%) | 93 (49%) | 19 (10%) | 0 | 0 | 99 (51%) | 62 (32%) | 33 (17%) | 3 (2%) | 1 (1%) | 0 |
| General disorders and administration site conditions | 113 (59%) | 48 (25%) | 38 (20%) | 26 (14%) | 0 | 1 (1%) | 71 (37%) | 51 (26%) | 15 (8%) | 5 (3%) | 0 | 0 |
| Skin and subcutaneous tissue disorders | 106 (56%) | 55 (29%) | 50 (26%) | 1 (1%) | 0 | 0 | 88 (46%) | 51 (26%) | 35 (18%) | 2 (1%) | 0 | 0 |
| Infections and infestations | 56 (29%) | 24 (13%) | 23 (12%) | 7 (4%) | 1 (1%) | 1 (1%) | 34 (18%) | 14 (7%) | 15 (8%) | 4 (2%) | 0 | 1 (1%) |
| Nervous system disorders | 49 (26%) | 36 (19%) | 13 (7%) | 0 | 0 | 0 | 50 (26%) | 28 (15%) | 15 (8%) | 7 (4%) | 0 | 0 |
| Cardiac disorders | 45 (24%) | 32 (17%) | 13 (7%) | 0 | 0 | 0 | 28 (15%) | 24 (12%) | 4 (2%) | 0 | 0 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 35 (18%) | 18 (9%) | 14 (7%) | 3 (2%) | 0 | 0 | 15 (8%) | 12 (6%) | 3 (2%) | 0 | 0 | 0 |
| Eye disorders | 22 (12%) | 16 (8%) | 6 (3%) | 0 | 0 | 0 | 11 (6%) | 6 (3%) | 5 (3%) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 20 (11%) | 16 (8%) | 4 (2%) | 0 | 0 | 0 | 16 (8%) | 13 (7%) | 3 (2%) | 0 | 0 | 0 |

Data are n (%). Treatment-related adverse events by system organ class that occurred in 10% or more of patients in any group are presented. Iza-bren=izalontamab brengitecan. NA=not applicable.

***Table 3:*** **Treatment-related adverse events in the safety analysis population**

white blood cell count decrease occurred in 92 (48%) patients in the iza-bren group and 78 (40%) patients in the chemotherapy group. Grade 3 or worse treatment-related anaemia (94 [49%] *vs* 12 [6%]) and platelet count decrease (88 [46%] *vs* 11 [6%]) occurred more frequently in the iza-bren group than in the chemotherapy group. Two patients in the iza-bren group died due to treatment-related adverse events: one case of pneumonia and one case of death of unknown cause. One patient in the chemotherapy group died due to sepsis.

Treatment-related interstitial lung disease occurred in two (1%) patients treated with iza-bren (grade 2). A Central Independent Adjudication Committee adjudicated the interstitial lung disease cases retrospectively and adjudicated interstitial lung disease occurred in two (1%) with iza-bren (one case of grade 1 and one case of grade 2). No cases of interstitial lung disease were observed in the chemotherapy group.

Serious treatment-related adverse events occurred in 79 (42%) patients in the iza-bren group and in 22 (11%) in the chemotherapy group. Treatment-related adverse events leading to the discontinuation of study treatment were reported in three (2%) patients in the iza-bren group and in two (1%) patients in the chemotherapy group. Dose interruptions of study treatment due to treatment-related adverse events occurred in 107 (56%) patients in the iza-bren group and in 73 (38%) patients in the chemotherapy group, and dose reductions of study treatment occurred in 123 (65%) patients in the iza-bren group and in 55 (29%) patients in the chemotherapy group (appendix p 24). Treatment-emergent adverse events are presented in the appendix (pp 27–28).

129 (68%) and 49 (26%) patients in the iza-bren group received primary or secondary prophylactic G-CSF, respectively. 141 (74%) patients in the iza-bren group received therapeutic G-CSF.

Prophylactic platelet-stimulating agents were received by 54 (28%) patients in the iza-bren group, including thrombopoietin receptor agonist or recombinant human thrombopoietin, and all were administered as secondary prophylaxis. Platelet-elevating agents were used in 138 (73%) patients in the iza-bren group for treating thrombocytopenia. Platelet transfusion was used in 28 (15%) patients in the iza-bren group for treating thrombocytopenia, of whom the majority (20 [11%] patients) required only a single platelet transfusion. Blood transfusion was used in 18 (9%) patients in the iza-bren group for treating anaemia.

Health-related quality of life was assessed using EORTC QLQ-C30, EORTC QLQ-BR45, and EQ-5D-5L VAS and results are presented in the appendix (pp 29–32). For QLQ-C30 scales, across treatment cycles, global health status and quality-of-life scores with iza-bren were not observed to be better than those observed with chemotherapy. The change from baseline in mean global health status or quality-of-life scores in the iza-bren and chemotherapy groups was –3·2 (SD 18·8) *vs* 0·8 (17·4) at week 12, 1·1 (17·6) *vs* 0·6 (17·8) at week 24, and –0·9 (18·5) *vs* 5·0 (14·8) at week 36, respectively (appendix p 29).

In the iza-bren group, 172 (91%) patients had evaluable immunogenicity data, of whom four (2%) had a positive anti-drug antibody result post-baseline.

## Discussion

In this prespecified interim analysis of PANKU-Breast01, the primary endpoint of progression-free survival assessed by Blinded Independent Central Review was met. Iza-bren demonstrated a significant improvement in progression-free survival compared with chemotherapy among patients with HR+/HER2– breast cancer who were previously treated with endocrine therapy, one or two previous chemotherapy regimens, and CDK4/6 inhibitors. The safety profile was consistent with previous studies and no new safety signals were observed. The health-related quality-of-life data with iza-bren treatment were not better than with chemotherapy.

To our knowledge, PANKU-Breast01 was the first randomised, phase 3 study that showed a significant progression-free survival benefit with an EGFR and HER3 bispecific antibody–drug conjugate compared with chemotherapy in patients with HR+/HER2– breast cancer who had received standard of care and one or two chemotherapy regimens. The study population was heavily pretreated (median three previous lines of therapy). All patients had received previous endocrine therapy and CDK4/6 inhibitor therapy. In this population, iza-bren prolonged median progression-free survival by 4·2 months compared with chemotherapy. Consistent progression-free survival benefit was observed regardless of HER2 expression status. The overall survival data are immature in this preplanned analysis and additional follow-up is ongoing for observation of the overall survival benefit with iza-bren. Objective response rate was higher with iza-bren compared with chemotherapy and responses were durable, supporting the clinical benefit with iza-bren.

Regarding the safety profile, the incidence of grade 3 or higher treatment-related adverse events was higher with iza-bren compared with chemotherapy (85% *vs* 66%). The most common adverse events associated with iza-bren were haematological, including anaemia, white blood cell count decrease, platelet count decrease, and neutrophil count decrease, which could be managed with dose interruption, dose reduction, and standard supportive care. In this study, prophylactic G-CSF was given to 94% of patients receiving iza-bren for mitigating risk of neutropenia. Blood transfusion was used for treating severe anaemia and platelet transfusion was used for treating severe thrombocytopenia in patients receiving iza-bren. With appropriate management, most patients were able to continue iza-bren treatment and only 2% of patients discontinued because of treatment-related adverse events. The rate of treatment-related interstitial lung disease was low (1%) with iza-bren, and

grade 3 or higher interstitial lung disease was not observed. Nevertheless, the high rate of haematological toxicities, including platelet transfusions in 15% of patients, represents a substantial burden and might limit the generalisability of these results to settings where intensive supportive care is not readily available. Further evaluation of optimal dose intensity and prophylactic strategies for thrombocytopenia is warranted.

An open-label design was used in this study based on the following rationale. Given the differences in administration routes of the chemotherapeutic agents in the control group compared with iza-bren, masking was not feasible. Capecitabine, an oral agent, was included as a standard second-line chemotherapy option for patients who preferred oral treatment or had limited access to infusion facilities. The open-label design also avoided the need for blood sample collection from patients in the control group for pharmacokinetic and immunogenicity analyses. Despite the open-label design, all statistical analysis personnel remained masked to treatment allocation until database lock. Prespecified sensitivity and supportive analyses evaluated alternative approaches to handling missed assessments and initiation of new anticancer therapy, and results were consistent with the primary analysis.

When this trial was designed, data on the clinical activity of iza-bren in patients following previous exposure to a topoisomerase I inhibitor-based antibody–drug conjugate were insufficient, and the efficacy and safety profile of iza-bren in this population was not fully understood. Thus, patients who had previously received a topoisomerase I inhibitor-based antibody–drug conjugate were excluded from the trial. In this study, selection of chemotherapy as the control group was based on several considerations. First, this study was designed and initiated in 2024, before approval of Dato-DXd in this population.[18] Second, sacituzumab govitecan was approved only for patients with HR+/HER2– breast cancer who received at least two previous chemotherapies.[19] For patients with HER2-low disease, T-DXd was already approved in China at study initiation but was not included as a control option, which limits direct comparability with current clinical practice.[20] For patients with HER2 IHC 0 disease, T-DXd had no approved indication, and chemotherapy was the appropriate standard of care. Given that T-DXd has since been incorporated into clinical practice for HER2-low breast cancer populations during trial conduct, exclusion of T-DXd from the control group limits direct comparison with current clinical practice.

To date, monospecific antibody–drug conjugates that target HER2 or TROP2 have demonstrated clinical benefit in patients with HR+/HER2– breast cancer who were pretreated with endocrine therapy and chemotherapy. T-DXd incorporates a cleavable tetrapeptide-based linker (Gly-Gly-Phe-Gly) and an exatecan-derivative topoisomerase I inhibitor payload, at a drug-to-antibody ratio of 8:1.[21] Sacituzumab govitecan is composed of the SN-38 payload, which is the active metabolite of irinotecan, and a CL2A linker whose bond is pH sensitive and undergoes release in a low pH environment, at a drug-to-antibody ratio of approximately 8:1.[22] Datopotamab deruxtecan shares the same cleavable tetrapeptide linker and DXd payload as T-DXd, but with a lower drug-to-antibody ratio of 4:1.[23] Iza-bren contains a cleavable tetrapeptide-based linker with structure different from that of T-DXd, sacituzumab govitecan, and datopotamab deruxtecan, as well as a potent cytotoxic payload (Ed-04, a novel camptothecin derivative), with a drug-to-antibody ratio of 8:1. As demonstrated by previous pharmacokinetic results, iza-bren is stable in blood and the concentration–time curves of total antibody and antibody–drug conjugate were nearly identical.[15] The payload of iza-bren showed strong bystander effect and high potency in non-clinical studies, which is probably the cause for haematological toxicities.[8]

Previous clinical studies showed that T-DXd showed a median progression-free survival of 10·1 months, an objective response rate of 52·6%, and a median duration of response of 10·7 months in previously treated HER2-low breast cancer (HER2 IHC 0 population was not included).[20] Dato-DXd showed a median progression-free survival of 6·9 months, an objective response rate of 36·4%, and a median duration of response of 6·7 months in TROPION-Breast01.[24] In patients with HR+/HER2– breast cancer who were pretreated with standard of care and between two and four chemotherapy regimens, sacituzumab govitecan showed a median progression-free survival of 5·5 months, an objective response rate of 21%, and a median duration of response of 7·4 months.[25]

HER2 and TROP2-directed antibody–drug conjugates have shown encouraging clinical activity in advanced HER2-low-expressing breast cancer, emerging as an effective treatment option for this patient population.[26,27] However, previous studies have shown that HER2-low expression is unstable over the disease course of breast cancer, which might limit the use of HER2-directed antibody–drug conjugates in some patients. Hence, antibody–drug conjugates suitable for broader patient populations are needed.[28]

Findings from this trial provided important clinical implications for the potential positioning of iza-bren within the evolving therapeutic landscape. First, to date, in patients with HER2 IHC 0 disease, no HER2-directed antibody–drug conjugates have demonstrated clinical benefit. In our study, patients who had HER2 IHC 0 breast cancer were included and iza-bren demonstrated consistent progression-free survival improvement across HER2 0 to 2+ subgroups, indicating that the clinical activity of iza-bren is independent of HER2 expression. Thus, for patients who have HR+/HER2– breast cancer (HER2 0 to 2+) at initial diagnosis and cannot undergo re-biopsy for determining HER2 status, iza-bren is a treatment option. Second, in our study, an HR of 0·43

was observed in the HER2-low subgroup, which compares favourably to that of T-DXd in DESTINYBreast04 (HR 0·51). However, indirect comparisons across trials need to be made with caution due to differences in previous lines of therapy, endocrine resistance status, and control group composition. Head-to-head evaluation is needed to determine relative efficacy. Furthermore, although iza-bren is associated with a higher incidence of haematological toxicities than observed with chemotherapy, the majority of patients could continue iza-bren treatment and only 2% of patients discontinued the treatment due to adverse events, indicating that iza-bren was well tolerated. The incidence of interstitial lung disease related to iza-bren treatment was much lower (1%, one case of grade 1 and one case of grade 2) than that reported with T-DXd (overall incidence, 12·1%; grade 5, 0·8%).[20] Thus, iza-bren might be the preferred treatment option for patients with pre-existing pulmonary disease or high interstitial lung disease risk. In addition, iza-bren might be used in patients who received T-DXd and have mild interstitial lung disease before disease progression. For future studies, the clinical efficacy and safety of iza-bren in patients who progressed on or after T-DXd treatment need to be assessed. Additionally, a phase 3 study (NCT07648914) is already ongoing assessing the efficacy and safety of iza-bren versus chemotherapy in patients who have HR+/HER2– breast cancer following previously unsuccessful endocrine therapy.

Overall, iza-bren offers a significant progression-free benefit (HR 0·41) in a population with few treatment options, but this benefit is not accompanied by a quality-of-life improvement, overall survival data are immature, and the incidence of haematological toxicities with iza-bren is higher than observed with chemotherapy. By European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) criteria, the magnitude of benefit observed in PANKU-Breast01 corresponds to a score of 2.[29] Final ESMO-MCBS scoring for iza-bren will require mature overall survival data and the current score should be interpreted in the appropriate context.

This study has several limitations. First, the progression-free survival is a surrogate endpoint and overall survival data remain immature, which requires further follow-up. Second, the study was conducted exclusively in China; therefore, the generalisability of the results to other populations requires further validation. Finally, the control group received physician's choice chemotherapy; future head-to-head clinical trials comparing iza-bren with sacituzumab govitecan or datopotamab deruxtecan are warranted.

In conclusion, iza-bren demonstrated a significant improvement in progression-free survival compared with chemotherapy in patients with HR+/HER2– breast cancer who had received endocrine therapy, CDK inhibitors, and one or two lines of chemotherapy (including taxanes). No new safety concerns were identified. The results of PANKU-Breast01 suggest iza-bren could be a new treatment option for this population in China and further evaluation of iza-bren in global populations and in earlier lines of therapy for HER2-negative breast cancer is warranted.

#### Contributors

BX, BLa, YS, XS, FW, SW, and SX conceived and designed the study. BLa, YS, XS, FW, SW, WX, QZ, QO, JC, XLing, HYu, HL, XT, SD, CH, BZ, YLi, HYa, MY, GH, XW, FL, PP, CG, YLiu, JG, YY, ML, YT, JZ, YG, JW, JL, XH, XLi, BLi, SZ, BLiu, and BX enrolled patients and collected the data. HZ was responsible for performing the statistical analyses, and all authors participated in data interpretation. BLa, LY, SX, and BX accessed and verified the data reported in the manuscript. The manuscript was drafted, reviewed, and revised by all authors. The final version was approved to be submitted by all authors. All authors confirm they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

#### Declaration of interests

BX has served as advisor or consultant for Novartis and AstraZeneca. LY and SX are full-time employees of Baili-Bio (Chengdu) Pharmaceutical. HZ is a full-time employee of SystImmune. YZ is a full-time employee of Sichuan Biokin Pharmaceutical. All other authors declare no competing interests.

#### Data sharing

The unredacted study protocol and statistical analysis plan of this study are available in the appendix (pp 33–270). Individual patient data after de-identification will be available upon reasonable request after publication of this paper. Requests should be directed to the corresponding author Prof Binghe Xu (xubinghe@medmail.com.cn). Signing of a data use agreement will be required to ensure protection of patient privacy. Requests need to be reviewed and approved by the corresponding author and sponsor of this study, Baili-Bio (Chengdu) Pharmaceutical.

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