

Sacituzumab tirumotecan in previously treated metastatic triple-negative breast cancer: a randomized phase 3 trial

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Supplementary Information

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Table S1. List of OptiTROP-Breast01 Study Principal Investigators

Number	Site Number	Study Institution	Study Investigator
1	01	Cancer Hospital Chinese Academy of Medical Sciences – Leading Site	Binghe Xu, Ying Fan
2	08	The First Affiliated Hospital of Nanjing Medical University – Leading Site	Yongmei Yin
3	02	Sun Yat-sen University Cancer Center	Shusen Wang
4	03	Hunan Cancer Hospital	Quchang Ouyang
5	04	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	Ying Wang
6	05	The First Hospital of Jilin University	Wei Li
7	06	Henan Cancer Hospital	Min Yan
8	07	Zhejiang Cancer Hospital	Xiaojia Wang
9	09	Shandong Cancer Hospital	Lihua Song
10	10	Hubei Cancer Hospital	Xinhong Wu
11	11	The First Affiliated Hospital of Bengbu Medical College	Hongtao Li
12	12	Anhui Provincial Cancer Hospital	Hu Liu
13	14	Nanchang People's Hospital	Wenyan Chen
14	15	Cancer Hospital of China Medical University, Liaoning Cancer Hospital	Tao Sun
15	16	The First Hospital of China Medical University	Yue'e Teng
16	17	Tianjin Medical University Cancer Institute & Hospital	Zhongsheng Tong
17	18	Guangxi Medical University Cancer Hospital	Weimin Xie, Hongxue Wang
18	19	The Second Hospital of Dalian Medical University	Man Li
19	20	West China Hospital of Sichuan University	Xi Yan
20	22	The First Affiliated Hospital of Zhengzhou University	Yuanting Gu
21	23	The Second Affiliated Hospital of Xi'an Jiaotong University	Shuqun Zhang
22	24	The Second People's Hospital of Neijiang	Xujuan Wang
23	25	The First Affiliated Hospital of Chongqing Medical University	Qiao Cheng
24	29	The Second Hospital of Anhui Medical University	Fanfan Li
25	30	Weifang People's Hospital	Guohua Yu
26	31	Shanxi Provincial Cancer Hospital	Fuguo Tian
27	32	The 900 th Hospital of the Joint Logistics	Xi Chen

Number	Site Number	Study Institution	Study Investigator
		Support Force of the People's Liberation Army of China	
28	33	The First Hospital of Lanzhou University	Xiaoling Ling
29	34	Zhongnan Hospital of Wuhan University	Yahua Zhong
30	36	Affiliated Hospital of Hebei University	Hua Yang
31	37	The Affiliated Cancer Hospital of Guizhou Medical University	Zhihong Wang
32	38	Sir Run Run Shaw Hospital	Xian Wang
33	39	Cangzhou Central Hospital	Guozhong Cui
34	40	Chongqing University Cancer Hospital	Xianjun Tang
35	41	General Hospital of Ningxia Medical University	Xinlan Liu
36	42	Sichuan Cancer Hospital	Hui Li
37	43	Jilin Cancer Hospital	Ying Cheng
38	44	The Fourth Hospital of Hebei Medical University	Yunjiang Liu
39	45	The First Affiliated Hospital of Xi'an Jiaotong University	Jin Yang
40	46	Anyang Tumor Hospital	Jing Sun
41	47	Xuzhou Central Hospital	Li Sun
42	48	Xiangyang Central Hospital	Tienan Yi
43	49	The First Medical Center, Chinese PLA General Hospital	Weihong Zhao
44	50	Linyi Cancer Hospital	Jingfen Wang
45	52	Fujian Cancer Hospital	Jian Liu
46	54	Jiangxi Cancer Hospital	Zhengkui Sun
47	55	The First Affiliated Hospital of Henan University of Science and Technology	Xinshuai Wang
48	56	Guizhou Provincial People's Hospital	Yuncong Liu
49	57	Affiliated Hospital of Southwest Medical University	Lijia He

Table S2. Subsequent Anticancer Therapies

	Sac-TMT (N = 130)	Chemotherapy (N = 133)
Patients with any subsequent anticancer therapy, n (%)	66 (50.8)	95 (71.4)
Chemotherapy	55 (42.3)	74 (55.6)
Targeted therapy	33 (25.4)	53 (39.8)
ADC	7 (5.4)	28 (21.1)
Targeting TROP2	0	20 (15.0)
SG	0	12 (9.0)
Dato-DXd	0	5 (3.8)
Other TROP2-targeted ADCs [†]	0	3 (2.3)
Targeting HER2	6 (4.6)	7 (5.3)
T-DXd	5 (3.8)	5 (3.8)
RC48	1 (0.8)	0
Other HER2-targeted ADCs [‡]	0	2 (1.5)
Other targets [§]	1 (0.8)	3 (2.3)
Immunotherapy	8 (6.2)	15 (11.3)
Radiotherapy	8 (6.2)	9 (6.8)
Surgery	4 (3.1)	2 (1.5)
Other therapies	6 (4.6)	17 (12.8)

Data cutoff: November 30, 2023.

[†] Chemotherapy group: BL-M02D1 (n=2), FDA018 (n=1).

[‡] Chemotherapy group: IBI354 (n=1), BB-1701 (n=1).

[§] Sac-TMT group: RC88 (n=1, targeting MSLN); chemotherapy group: BL-B01D1 (n=2, targeting EGFR × HER3), MHB088C (n=1, targeting B7H3).

ADC, antibody-drug conjugate; B7H3, B7 homolog 3; Dato-DXd, datopotamab deruxtecan; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER3, human epidermal growth factor receptor 3; MSLN, mesothelin; RC48, disitamab vedotin; sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TROP2, trophoblast cell-surface antigen 2.

Table S3. Duration of Exposure and Relative Dose Intensity

	Sac-TMT (N = 130)	Chemotherapy (N = 132)
Duration of Exposure, week		
Median	24.86	8.57
Min, Max	2.0, 66.1	1.0, 65.0
Dose Delay, n (%)		
COVID-19	19 (14.6)	10 (7.8)
Relative dose intensity, %		
Median	89.51	95.53
Relative dose intensity [†] , %		
Median	94.64	97.20

Data cutoff: November 30, 2023.

[†] If a patient had a delay in administration due to COVID-19, the relative dose intensity of administration was assumed to be 100%.

Sac-TMT, sacituzumab tirumotecan.

Table S4. Full list of inclusion/exclusion criteria

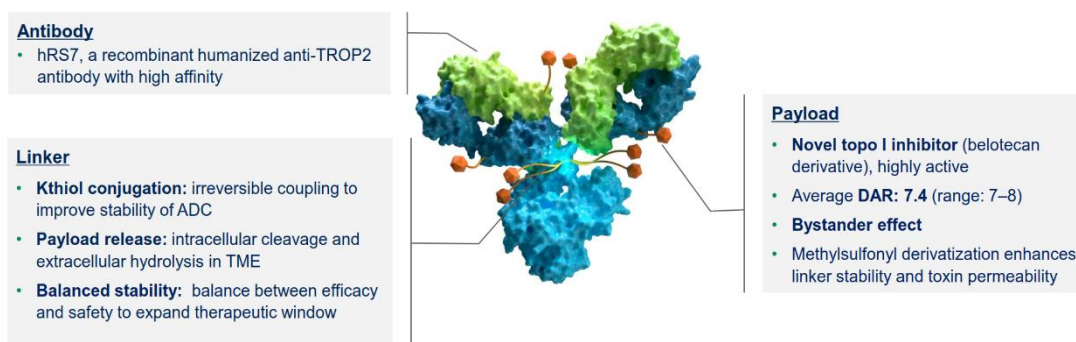
Inclusion Criteria	Subjects will not be included unless they meet all of the following criteria:
1) Males or females aged 18 to 75 years old (inclusive) at the time of signing the informed consent form; 2) Histologically and/or cytologically confirmed TNBC based on pathology reports on recent biopsy specimens or other pathological samples (central laboratory confirmation is not required), including: a) Definition of human epidermal growth factor receptor 2 (HER2) negative: immunohistochemistry (IHC) of 0 or 1+; if HER is 2+ by IHC, negative HER2 expression must be confirmed by fluorescence in situ hybridization (FISH). b) Estrogen and progesterone receptor negative means that less than 1% of the cells express hormone receptors as indicated by IHC; 3) Patients with unresectable locally advanced or metastatic triple-negative breast cancer who have failed at least two lines of standard of care regimens, including: a) Any treatment received by the patients regardless of triple-negative state can be included as one of the standard of care regimens; b) For neoadjuvant and/or adjuvant chemotherapy, if relapse or disease progression to unresectable locally advanced or metastatic disease occurs during treatment or within 12 months after discontinuation of treatment (at least 2 cycles have been completed), it will be considered as one of the standard of care regimens. And the patients must also have received one therapy and have progressed on this therapy during the stage of unresectable locally advanced or metastatic disease; c) For patients with documented germline BRCA1/BRCA2 mutations, if they have been treated with an approved PARP inhibitor, then the PARP inhibitor can be considered as one of the 2 prior standard of care regimens required; d) Patients must have progressed on or been intolerable during or after the last treatment prior to enrollment; 4) All patients must have been previously treated with taxanes; and those who have been treated with taxanes for at least 1 cycle and show contraindications or intolerability during or at the end of the cycle can be included, regardless of the disease stage during this treatment; 5) Patients must have at least one measurable lesion per RECIST v1.1 criteria; those with only skin or bone lesions cannot be included; 6) Subjects with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and with an expected survival of ≥ 12 weeks; 7) Subjects must provide tumor tissues or tissue specimens;	

8) Subjects must have adequate organ and bone marrow function (no blood transfusion, recombinant human thrombopoietin, or colony stimulating factor therapy has been received within 2 weeks prior to the screening), which is defined as follows: a) Hematology: neutrophil count (NEUT) $\geq 1.5 \times 10^9$ /L; platelets (PLT) $\geq 100 \times 10^9$ /L; hemoglobin ≥ 9 g/dL; b) Liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN); total bilirubin (TBIL) $\leq 1.5 \times$ ULN; for patients with liver metastases, ALT and AST must be $\leq 5 \times$ ULN, TBIL $\leq 2 \times$ ULN; for patients with liver or bone metastases, ALP must be $\leq 5 \times$ ULN; c) Albumin ≥ 3 g/dL; d) Renal function: creatinine clearance (Ccr) ≥ 60 ml/min; e) Coagulation function: international normalized ratio (INR), activated partial thromboplastin time (APTT) and prothrombin time (PT) $\leq 1.5 \times$ ULN; 9) Subjects must have recovered from all toxicities (except alopecia) due to prior treatments to $\leq$ grade 1 or the protocol specified inclusion criteria based on the assessment per CTCAE 5.0 criteria; 10) Subjects voluntarily participate in the study, sign the informed consent form, and will be able to comply with the protocol-specified visits and relevant procedures.	
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded:
1) Patients with a history of central nervous system (CNS) metastases or current CNS metastases; 2) Patients with other malignancies, except cured basal or squamous cell skin cancer or in situ cancer of cervix; and patients with other malignancies must have a tumor-free period of at least 5 years; 3) Patients with Gilbert's disease; 4) Patients who have received prior TROP2-targeted therapy; 5) Patients who have received live vaccines within 30 days prior to the first dose; 6) Patients who required the treatment of strong inhibitors or inducers of cytochrome P450 3A4 enzyme (CYP3A4) within 2 weeks prior to the first dose and during the study treatment (strong inhibitors or inducers of CYP3A4 are not allowed in this study). Patients who received continued high dose of systemic corticosteroids within 2 weeks prior to the first dose (low-dose corticosteroids, such as ≤ 10 mg daily prednisone or equivalent, are allowed if the dose is stable for 4 weeks); 7) Patients who have received any chemotherapy, immunotherapy, biological therapy, or other drugs within 4 weeks prior to the first dose of study treatment or within 5 half-lives of the drug used in the previous	

- period (whichever is shorter), or received radiotherapy or treatment with traditional Chinese medicine preparations for approved anti-tumor indications 2 weeks prior to the first dose of study treatment, or received major surgeries 4 weeks prior to the first dose of study treatment;
- 8) With concomitant infections requiring systemic antibiotic therapy within 1 week prior to the first dose of study treatment;
 - 9) Presence of any serious and/or uncontrolled comorbidities that prevent the patient from participating in the study, such as:
 - a) Impaired cardiac function, including any of the following: (not necessarily all of the following):
 - aa) Corrected QT interval (QTcF) between ventricular depolarization to repolarization > 480 ms at baseline;
 - ab) Left ventricular ejection fraction (LVEF) < 50% on echocardiographic (ECHO) scan;
 - b) Clinically significant heart disease within 6 months prior to the first dose of study treatment, including any of the following known medical history:
 - ba) Angina pectoris;
 - bb) Congestive cardiac failure;
 - bc) Myocardial infarction;
 - c) Patients with (noninfectious) interstitial lung disease (ILD) or history of pneumonia requiring steroid therapy; patients with serious pulmonary function impairment due to lung disease;
 - d) Patients with current or previous active chronic inflammatory bowel disease or intestinal obstruction or gastrointestinal (GI) perforation;
 - e) Uncontrolled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg), with a history of unstable hypertension, or with a history of poor compliance with antihypertensive treatment;
 - f) Uncontrolled diabetes (fasting glucose $\geq$ 10 mmol/L and/or glycated hemoglobin (HbA1c) $\geq$ 8%);
 - 10) Active hepatitis B (hepatitis B surface antigen positive, and HBV-DNA above 500 IU/ml or 1x ULN, whichever is higher) or hepatitis C (hepatitis C antibody positive, and HCV-RNA above 1 x ULN); with known history of positive human immunodeficiency virus (HIV) test or known acquired immunodeficiency syndrome (AIDS); positive syphilis antibody test;
 - 11) History of serious drug allergy, with known allergy to macromolecular protein preparations or any component of the study drug formulation (including polysorbate-20). Subjects with a history of severe hypersensitivity reactions to monoclonal antibodies;
 - 12) Pregnant or lactating women; or patients of childbearing potential (male or female) who cannot use effective medical contraception during the study treatment period and for 6 months after the end of the dosing

- period;
- 13) During the screening process prior to the first dose, the condition deteriorated rapidly, such as severe changes in performance status, unstable pain requiring adjustment of analgesic therapy;
 - 14) Other circumstances that, in the opinion of the investigator, are not appropriate for participation in this study.

Figure S1. Design of Sacituzumab Tirumotecan (sac-TMT)

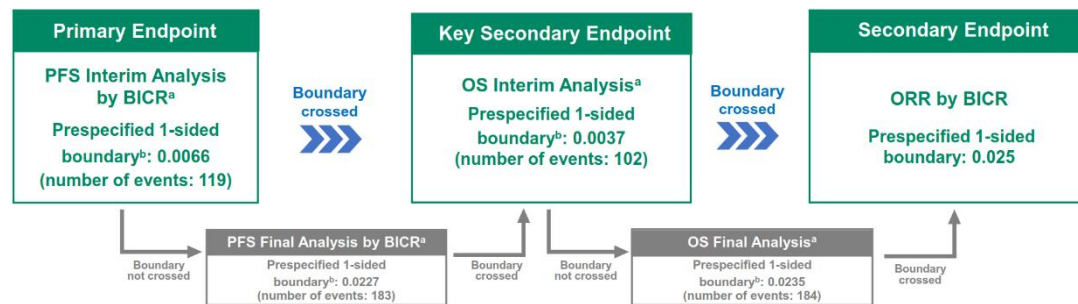


Sac-TMT is a TROP2 ADC developed with a proprietary Kthiol (pyrimidine-thiol) linker conjugated to a novel topoisomerase I inhibitor at DAR 7.4. The features of sac-TMT lead to release of the payload both in the tumor microenvironment (TME) and inside tumor cells, achieving a balance between the safety and efficacy.

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; TME, tumor microenvironment; TROP2, trophoblast cell surface antigen 2.

Figure S2. Statistical Considerations

- The planned sample size of 254 patients was calculated based on the primary endpoint of PFS by BICR per RECIST version 1.1.
 - Median PFS of 2 months in the chemotherapy group (assuming PFS HR = 0.60).
 - 183 PFS events would provide approximately 93% power at one-sided alpha level of 0.025.



^aPFS and OS were analyzed using the stratified log-rank test and stratified Cox proportional hazards model based on all randomized patients.

^bType I error was controlled using Lan-DeMets alpha spending function approximating an O'Brien-Fleming bound.

BICR, blinded independent central review; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.



Clinical Trial Protocol

A Randomized, Controlled, Open-label, Multi-center Phase III Study of SKB264 for Injection Versus Chemotherapy of the Physician's Choice in Patients With Unresectable Locally Advanced, Recurrent or Metastatic Triple-negative Breast Cancer Who Have Failed Second- line or Above Prior Standard of Care

Clinical Trial No. : SKB264-III-03
Version No.: : V2.1
Version Date : June 18, 2023
**Responsible Study Site : Cancer Hospital, Chinese Academy of
Medical Sciences
Jiangsu Province Hospital**
**Principal Investigator : [REDACTED]
[REDACTED]**
**Sponsor : Sichuan Kelun-Biotech Biopharmaceutical
Co., Ltd**
Sponsor's Director : [REDACTED]

Confidentiality Statement

All information contained in this document is the property of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd, and is allowed to be reviewed by all study-related personnel, ethics committee and regulatory authorities. This document shall not be disclosed in any form to any personnel unrelated to the study without written permission.



Statement and Signature Page of Sponsor and Investigator

1. Sponsor Statement

I have read and understood the study protocol. I agree that the study will be conducted in accordance with this study protocol, and I will perform all relevant obligations and follow other relevant requirements related to the Sponsor in compliance with the Good Clinical Practice and the Declaration of Helsinki. I agree to comply with all the standard operating procedures (SOPs) related to the conduct of this study developed by the study sites, the participating institutions, and Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd

Name of Sponsor's
Director: _____



Signature of Sponsor's
Director: _____

Date: _____ (YYYY) _____ (MM) _____ (DD)



2. Investigator's Statement

I have read and understood the protocol and agree to conduct this clinical study in accordance with the design and regulations of this protocol. The study will be conducted in accordance with the moral, ethical and scientific principles set forth in the Declaration of Helsinki and the Good Clinical Practice. I agree to comply with all the SOPs related to the conduct of this study developed by the clinical research facility of this hospital and Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

I will make sure that subjects can be treated promptly in case of adverse events (AEs) during the study. I understand the requirements for proper reporting of SAEs, and I will record and report these events as required.

I guarantee that the data will be accurately, completely and timely recorded in the original documents to ensure the quality of the clinical study. I'm ready to accept the monitoring and auditing conducted by the CRAs and auditors delegated by the Sponsor, as well as the inspections conducted by regulatory authorities.

The information contained herein and in any protocol addendum is confidential and is the property of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. I guarantee that the contents of this protocol will not be used in any other clinical studies, and will not be disclosed to any other individuals or groups unrelated to the study without the prior written permission of Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

Clinical Study Site: _____

Name of Principal
Investigator: _____

Signature of _____ Date: (YYYY) (MM) (DD)
Principal Investigator: _____



Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP) (2020), ICH-GCP (1996 and 2016) and the following regulations and guidelines applicable to clinical studies:

- 1) Drug Administration Law of the People's Republic of China (2019)
- 2) Drug Registration Regulation (2020)
- 3) Declaration of Helsinki (2013)
- 4) Technical Guidelines for the Design of Clinical Trials of Anti-tumor Drugs (2012)

The principal investigator will ensure that the protocol will not be violated or modified without the approval of the Sponsor and the ethics committee, except in the circumstances when modification is warranted to avoid a direct hazard to the subjects.

The application dossier, including the study protocol, informed consent form (ICF), blank case report form, drug regulatory authority's approval for the clinical trial, filing and certificate of analysis, and advertisement for subject recruitment will be submitted to the ethics committee for review and approval. The approval letter from the ethics committee must be received prior to enrollment of subjects. Any amendment to the protocol must be reviewed and approved by the ethics committee before implementation.

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1. Protocol Synopsis

1.1 Abstract

Study Title	A randomized, controlled, open-label, multi-center phase III study of SKB264 for injection versus chemotherapy of the physician's choice in patients with unresectable locally advanced, recurrent or metastatic triple-negative breast cancer who have failed second-line or above prior standard of care
Study Objectives	Primary Objective To assess the efficacy of SKB264 versus chemotherapy of the physician's choice for the treatment of patients with unresectable locally advanced, recurrent or metastatic TNBC who have failed second-line or above prior standard of care based on progression-free survival (PFS). Secondary Objectives 1) To assess the overall survival (OS), objective response rate (ORR), and duration of response (DOR) of SKB264 versus chemotherapy of the physician's choice for the treatment of patients with locally advanced, recurrent or metastatic TNBC; 2) To assess the safety of SKB264 versus chemotherapy of the physician's choice; 3) To assess the pharmacokinetic profile of SKB264; 4) To assess the immunogenicity of SKB264; 5) To assess the quality of life of patients with locally advanced, recurrent, or metastatic TNBC treated with SKB264 versus chemotherapy of the physician's choice.
Study Endpoints	Primary Endpoints The progression-free survival (PFS) assessed by the Independent Review Committee (IRC) as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Secondary Endpoints Efficacy • PFS assessed by the investigator as per RECIST 1.1; • Objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and time to progression (TTP) assessed by IRC and the investigator as per RECIST v1.1; • Overall survival (OS); • Quality of life of patients evaluated using the EORTC QLQ-C30 scale (see Annex). Safety • Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) (as per CTCAE 5.0), abnormal laboratory results, etc. Pharmacokinetics • PK parameters: C_{max}, $C_{max,ss}$, C_{min}, $C_{min,ss}$, etc. Immunogenicity • ADA test results and titer values.
Study	Test group: SKB264 for injection, strength: 200 mg, validity period: tentatively 3 years, storage conditions: 2 to 8°C, light-free.

Drugs	Control group: Eribulin, capecitabine, gemcitabine, and vinorelbine; all these drugs will be purchased and provided by the Sponsor.																				
Study Subjects	Patients with unresectable locally advanced, recurrent, or metastatic TNBC who have failed second-line or above prior standard of care																				
Study Phases	Phase III																				
Study Design	This is a randomized, controlled, open-label, multi-center study, in which 254 patients with unresectable locally advanced, recurrent, or metastatic TNBC who have failed second-line or above prior standard of care are planned to be enrolled. Eligible patients will be randomized in a 1:1 ratio to the test group and control group, and stratified by the number of prior therapy lines (2 to 3 vs. > 3); presence or absence of liver metastases (yes vs. no). Method of SKB264 Administration ● Test group: SKB264 will be administered at a dose of 5 mg/kg via intravenous infusion (IV) on Days 1 and 15 of each cycle (4 weeks as a cycle) until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue the study treatment. ● Control group: The control group received any one of the investigator’s choice regimens. Available treatment regimens are listed in the following table: <table><tr><th>Treatment Regimens</th><th>Dose</th><th>Route of Administration</th><th>Dosing Regimen</th></tr><tr><td>Eribulin</td><td>1.4 mg/m²</td><td>Intravenous Infusion</td><td>Dosing on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.</td></tr><tr><td>Capecitabine</td><td>1000-1250 mg/m²</td><td>Oral administration</td><td>The drug will be continuously administered on Days 1 to 14 of each cycle, twice daily, every 3 weeks as a cycle.</td></tr><tr><td>Gemcitabine</td><td>1000 mg/m²</td><td>Intravenous Infusion</td><td>The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.</td></tr><tr><td>Vinorelbine</td><td>25 mg/m²</td><td>Intravenous Infusion</td><td>The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle (Note: Vinorelbine should not be selected as the treatment regimen for patients with Grade 2 peripheral neuropathy).</td></tr></table> Only treatment regimens never received by the patient in prior anti-tumor therapies should be selected. It is not allowed to give patients in the control group only the best supportive care, including palliative radiotherapy. Patient in either treatment group was first assessed as disease progression during the study period, and if the investigator assessed the patient can still continue benefiting from treatment in the test or control group compared to other optional treatment regimens, treatment may continue at the discretion of the investigator as long as the patient still met the eligibility criteria and agreed to continue treatment.	Treatment Regimens	Dose	Route of Administration	Dosing Regimen	Eribulin	1.4 mg/m ²	Intravenous Infusion	Dosing on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.	Capecitabine	1000-1250 mg/m ²	Oral administration	The drug will be continuously administered on Days 1 to 14 of each cycle, twice daily, every 3 weeks as a cycle.	Gemcitabine	1000 mg/m ²	Intravenous Infusion	The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.	Vinorelbine	25 mg/m ²	Intravenous Infusion	The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle (Note: Vinorelbine should not be selected as the treatment regimen for patients with Grade 2 peripheral neuropathy).
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Vinorelbine	25 mg/m ²	Intravenous Infusion	The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle (Note: Vinorelbine should not be selected as the treatment regimen for patients with Grade 2 peripheral neuropathy).																		
Sample Size	In this study, a group sequential design will be used, and the sample size will be calculated using gsDesign package of R software (version 4.1.1). In this study, 254 patients are planned to be enrolled and they will be randomized in a 1:1 ratio to the test group and the control group. According to the study conducted by Bardia et																				

	al, the expected median PFS of the control group is approximately 2 months. Assuming that the hazard ratio (HR) of PFS between the test group and the control group is 0.60, and the PFS follows an exponential distribution, then for 183 PFS events (PD or death), there will be 93% power at a one-sided test level of 0.025 to infer that the test group is superior to the control group. An interim analysis of PFS superiority test is planned for this study when the number of PFS events reaches 65% of the total number, i.e., when there are 119 PFS events. To control the type I errors, the nominal test level α for the interim and final analyses of PFS is set to one-sided 0.0066 and one-sided 0.0227 according to the O' Brien-Fleming spending function, respectively. For the secondary endpoint OS, the expected median OS time of the control group is approximately 7.3 months. Assuming that the hazard ratio (HR) of OS between the test group and the control group is 0.65, and the OS follows an exponential distribution, then for 184 OS events (deaths), there will be 83% power at a one-sided test level of 0.025 to infer that the test group is superior to the control group. The enrollment duration in this study is expected to be 15 months. If the last patient is followed up for the final analysis of OS for approximately 15 months after the first dose, 228 patients are required to be enrolled. Considering the dropout rate of 10%, a total of approximately 254 patients (127 in the test group and 127 in the control group) are required to be enrolled. An interim analysis of OS superiority test is planned for this study at the final analysis of PFS (102 OS events are expected). To control the type I errors in the OS test, the α for testing OS at the PFS interim analysis is set to 0.0001. The nominal test level α (total α is one-sided 0.0249) for the interim and final analyses of OS is set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses. Based on the available clinical study data in Phase I, an ORR of 33% is assumed in the test group. Based on historical study data, an ORR of approximately 6% is assumed in the control group. Based on a type I error α of one-sided 0.025, 114 patients in each group (228 in both groups) will have at least 99% power to infer a statistically significant difference in ORR between the test group and the control group using Fisher's exact test.
Inclusion Criteria	Subjects will not be included unless they meet all of the following criteria: 1) Males or females age ≥ 18 and ≤ 75 years at the time of signing the informed consent form; 2) Histologically and/or cytologically confirmed TNBC based on pathology reports on recent biopsy specimens or other pathological samples (central laboratory confirmation is not required), including: a) Definition of human epidermal growth factor receptor 2 (HER2) negative: immunohistochemistry (IHC) of 0 or 1+; if HER is 2+ by IHC, negative HER2 expression must be confirmed by fluorescence in situ hybridization (FISH). b) Estrogen and progesterone receptor negative means that less than 1% of the cells express hormone receptors as indicated by IHC; 3) Patients with unresectable locally advanced or metastatic triple-negative breast cancer who have failed at least two lines of standard of care regimens, including: a) Any treatment received by the patients regardless of triple-negative state can be included as one of the standard of care regimens; b) For neoadjuvant and/or adjuvant chemotherapy, if relapse or disease progression to unresectable locally advanced or metastatic disease occurs during treatment or within 12 months after discontinuation of treatment (at least 2 cycles have been completed), it will be considered as one of the standard of care regimens. And the

	patients must also have received one therapy and have progressed on this therapy during the stage of unresectable locally advanced or metastatic disease; c) For patients with documented germline BRCA1/BRCA2 mutations, if they have been treated with an approved PARP inhibitor, then the PARP inhibitor can be considered as one of the 2 prior standard of care regimens; d) Patients must have progressed on or were intolerable to the treatment during or after the last treatment prior to enrollment; 4) All patients must have been previously treated with taxanes; and those who have been treated with taxanes for at least 1 cycle and show contraindications or intolerability during or at the end of the cycle can be included, regardless of the disease stage during this treatment; 5) Patients must have at least one measurable lesion per RECIST v1.1 criteria; those with only skin or bone lesions cannot be included; 6) Subjects with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 with an expected survival of ≥ 12 weeks; 7) Subjects must provide tumor tissues or tissue specimens; 8) Subjects must have adequate organ and bone marrow function (no blood transfusion, recombinant human thrombopoietin, or colony stimulating factor therapy has been received within 2 weeks prior to the screening), which is defined as follows: a) Hematology: neutrophil count (NEUT) $\geq 1.5 \times 10^9$ /L; platelets (PLT) $\geq 100 \times 10^9$ /L; hemoglobin ≥ 9 g/dL; b) Liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN); total bilirubin (TBIL) $\leq 1.5 \times$ ULN; for patients with liver metastases, ALT and AST must be $\leq 5 \times$ ULN, TBIL $\leq 2 \times$ ULN; for patients with liver or bone metastases, ALP must be $\leq 5 \times$ ULN; c) Albumin ≥ 3 g/dL; d) Renal function: creatinine clearance (Ccr) ≥ 60 ml/min (see Annex for Cockcroft-Gault formula); e) Coagulation function: international normalized ratio (INR), activated partial thromboplastin time (APTT) and prothrombin time (PT) $\leq 1.5 \times$ ULN; 9) Subjects must have recovered from all toxicities (except alopecia) due to prior treatments to $\leq$ grade 1 or the protocol specified inclusion criteria based on the assessment per CTCAE 5.0 criteria; 10) Subjects voluntarily participate in the study, sign the informed consent form, and will be able to comply with the protocol-specified visits and relevant procedures.
Exclusion Criteria	Subjects who meet any of the following criteria will be excluded: 1) Patients with a history of central nervous system (CNS) metastases or current CNS metastases; 2) Patients with other malignancies, except cured basal or squamous cell skin cancer or in situ cancer of cervix; and patients with other malignancies must have a tumor-free period of at least 5 years; 3) Patients with Gilbert's disease; 4) Patients who have received prior TROP2-targeted therapy; 5) Patients who have received live vaccines within 30 days prior to the first dose; 6) Patients who required the treatment of strong inhibitors or inducers of cytochrome P450 3A4 enzyme (CYP3A4) within 2 weeks prior to the first dose and during the

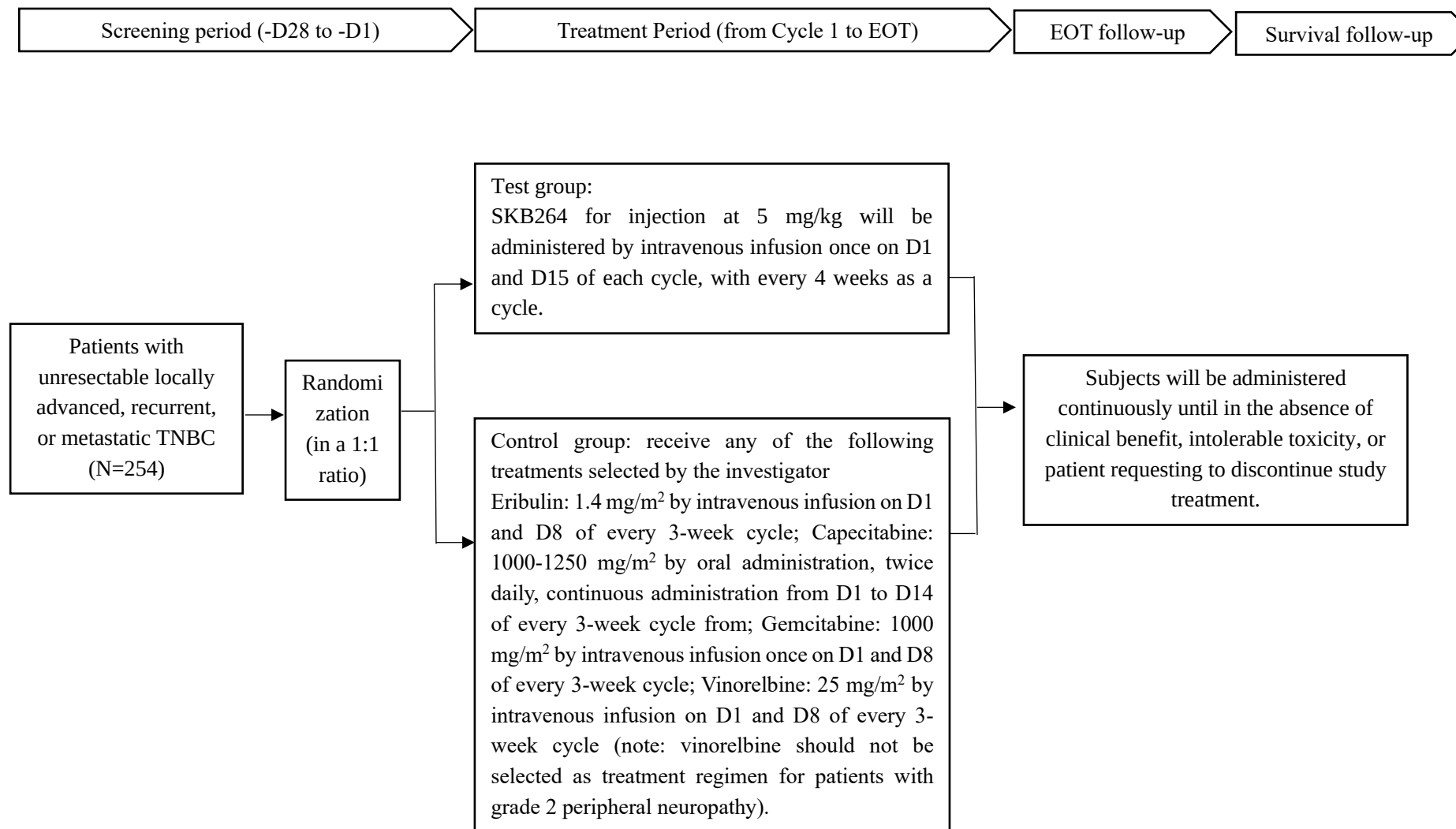
	study treatment (strong inhibitors or inducers of CYP3A4 are not allowed in this study, and representative drugs of strong CYP3A4 inhibitors or inducers are listed in the Annex). Patients who received continued high dose of systemic corticosteroids within 2 weeks prior to the first dose (low-dose corticosteroids, such as ≤ 10 mg daily prednisone or equivalent, are allowed if the dose is stable for 4 weeks); 7) Patients who have received any chemotherapy, hormonal therapy, radiotherapy, immunotherapy, biological therapy or other drugs within 4 weeks prior to the first dose of study treatment or within 5 half-life periods of the drug used in the previous period (whichever is shorter), or received treatment with traditional Chinese medicine preparations for approved anti-tumor indications 2 weeks prior to the first dose of study treatment, or received major surgeries 4 weeks prior to the first dose of study treatment; 8) With concomitant infections requiring systemic antibiotic therapy within 1 week prior to the first dose of study treatment; 9) Presence of any serious and/or uncontrolled comorbidities that prevent the patient from participating in the study, such as: - Impaired cardiac function, including any of the following: (not necessarily all of the following): - Corrected QT interval (QTcF) between ventricular depolarization to repolarization > 480 ms at baseline; - Left ventricular ejection fraction (LVEF) $< 50\%$ as indicated by echocardiography (ECHO) ; - Clinically significant heart disease within 6 months prior to the first dose of study treatment, including any of the following known medical history: - Angina pectoris; - Congestive cardiac failure; - Myocardial infarction; - Patients with (noninfectious) interstitial lung disease (ILD) or history of pneumonia requiring steroid therapy; patients with serious pulmonary function impairment due to lung disease; - Patients with current or previous active chronic inflammatory bowel disease or intestinal obstruction or gastrointestinal (GI) perforation; - Uncontrolled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg), with a history of unstable hypertension, or with a history of poor compliance with antihypertensive treatment; - Uncontrolled diabetes (fasting glucose ≥ 10 mmol/L and/or glycated hemoglobin (HbA1c) $\geq 8\%$); 10) Active hepatitis B (hepatitis B surface antigen positive, and HBV-DNA above 500 IU/ml or 1x ULN, whichever is higher) or hepatitis C (hepatitis C antibody positive, and HCV-RNA above 1x ULN); with known history of positive human immunodeficiency virus (HIV) test or known acquired immunodeficiency syndrome (AIDS); positive syphilis antibody test; 11) History of serious drug allergy, with known allergy to macromolecular protein preparations or any component of the study drug formulation (including polysorbate-20). Subjects with a history of severe hypersensitivity reactions to monoclonal antibodies; 12) Pregnant or lactating women; or patients of childbearing potential (male or female) who cannot use effective medical contraception during the study treatment period and
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	for 6 months after the end of the dosing period (see Annex for specific contraceptive measures); 13) During the screening process prior to the first dose, the condition deteriorated rapidly, such as severe changes in performance status, unstable pain requiring adjustment of analgesic therapy; 14) Other circumstances that, in the opinion of the investigator, are not appropriate for participation in this study.
Efficacy Assessment	The primary efficacy endpoint in this study is the progression-free survival (PFS) assessed by the IRC per RECIST 1.1. Efficacy will be assessed by imaging examinations every 6 weeks (± 1 week) from the start of the first dose of study treatment until disease progression (confirmed by IRC), or every 12 weeks (± 1 week) if the patient has not progressed after receiving 12 months of the investigational product. Imaging examinations will be performed as scheduled regardless of dose delay or modification. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the last imaging examination is more than 4 weeks away, and the subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death. If there is no contraindication to contrast agents, contrast-enhanced CT and/or contrast-enhanced MRI should be preferentially used and the same examination method should be used throughout the study. The sites for CT or MRI scans should include the chest, abdomen, pelvis, and other sites required (as judged by the investigator based on clinical indication).
Pharmacokinetics	Pharmacokinetic Blood Sampling Time Points: Pharmacokinetic blood sampling will be performed only for patients in the test group. Blood samples will be collected prior to the first dose (within -1 h) and within 0.5 h (± 15 min) after the end of dosing in Cycles 1 to 5, prior to the first dose (within -1 h) and within 0.5 h (± 15 min) after the end of dosing every 3 cycles starting from Cycle 6, and at the end of treatment (EOT) visit (if dosing is delayed, the blood sampling time points will be postponed accordingly). Determination of Plasma Concentrations: Enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) will be used for the detection of biological samples in this study. Serum concentrations of SKB264-ADC and SKB264-TAB will be determined by ELISA, and plasma concentrations of unbound KL610023 will be determined by LC-MS/MS. Main Parameters of Pharmacokinetic Analysis: The following PK parameters will be determined in this study: C_{max}, $C_{max,ss}$, C_{min}, $C_{min,ss}$, etc.
Immunogenicity	Immunogenicity Blood Sampling Time Points: Immunogenicity blood sampling will be performed only for patients in the test group. Blood samples will be collected prior to the first dose (within -1 h) in Cycles 1 to 5, prior to the first dose (within -1 h) every 3 cycles starting from Cycle 6, and at the EOT visit (if dosing is delayed, the blood sampling time points will be postponed accordingly). Immunogenicity Test Method: The MSD-based Bridging-ECLA will be used to determine the anti-drug antibodies against SKB264 in patient serum. The neutralizing antibody analysis will be performed based on

	the results of the study.
Quality of Life (QoL)	EORTC QLQ-C30 scale (see Annex) will be used to evaluate the QoL of patients.
Safety Assessment	The safety assessments will be performed at screening period, treatment period, and after the end of the study. The subjects who withdraw prematurely must receive safety evaluation prior to the withdrawal. Safety endpoints include AEs (assessed per NCI CTCAE version 5.0), vital signs, physical examinations, laboratory tests, ECGs, echocardiography, etc.
Data Processing and Statistical Analysis	Data Management In this study, the electronic data capture (EDC) system will be used for data management. Analysis Population Full analysis set (FAS): all subjects who are randomized according to the ITT principle. FAS will be used for baseline and efficacy analyses. Safety set (SS): all subjects who have received at least 1 dose of investigational product and have safety evaluation data. SS will be used for safety analysis. PK concentration set (PKCS): including all subjects who have received at least 1 dose of the investigated product and have at least 1 drug plasma concentration measurement during the study. The PKCS will be used for the analysis of plasma concentrations. Efficacy In order to control total type I errors, this study performed sequential tests (PFS→OS→ORR) for the primary estimand PFS assessed by IRC and the secondary estimands of OS and ORR. An interim analysis of PFS superiority testing is planned for this study at the time of 119 PFS events assessed by IRC. If PFS is not successfully tested at the interim analysis, the final analysis of PFS will be performed at the time of 183 PFS events assessed by IRC. If the PFS test is successful, OS would be compared between the two groups. An interim analysis for OS superiority testing will be performed at the final analysis of PFS or at the time of approximately 102 OS events. If OS is not tested successfully at the interim analysis, the final analysis of OS will be performed at the time of 184 OS events (deaths). To control the type I errors in the OS test, the α for testing OS at the PFS interim analysis is set to 0.0001. The nominal test level α (total α is one-sided 0.0249) for the interim and final analyses of OS is set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses. Primary Estimand In this study, the primary estimand of PFS as assessed by the IRC will be based on the full analysis set (FAS), the median of both groups will be estimated using the Kaplan-Meier method, and the 95% confidence intervals will be calculated using the Brookmeyer-

	Crowley method. The difference in efficacy between the two groups in PFS will be tested using the stratified log rank test method. The hazard ratio between the two groups in PFS will be estimated using the stratified COX model. The stratified log rank test and the stratified COX model will be based on randomization stratification factors. At the time of primary analysis, for patients without disease progression or death, PFS will be censored at the date of the last valid imaging examination. For patients without post-baseline tumor assessments, PFS will be censored at the time of randomization. For patients whose date of first disease progression or death is more than two assessment cycles away from the date of the previous imaging, the date of PFS will be censored to the date of the last valid imaging prior to progression. Secondary Estimands The analysis method for the secondary endpoint of PFS assessed by the investigator will be the same as the that for the primary endpoint. The primary analysis of the secondary estimand of OS will be based on the FAS, and the analysis method will be the same as that of the primary estimand of PFS. The primary analysis of the estimands of ORR and DCR will be based on the FAS. The 95% confidence intervals of ORR and DCR will be estimated using the Clopper-Pearson method, and the differences in ORR and DCR between the two groups as well as the 95% confidence intervals and P value will be calculated using the CMH method. Safety Safety endpoints, including AEs, vital signs, physical examinations, laboratory tests, ECGs, will be analyzed based on the safety dataset. Laboratory test results, electrocardiogram and other test results will be presented in the form of a pre- and post-treatment shift table. Abnormal tests after treatment will be presented in lists. All AEs occurring during this clinical study will be coded using the MedDRA dictionary, and the number and incidence of AEs will be listed in detail by SOC/PT classification. Adverse events of special interest will be presented separately. Pharmacokinetic Profile The concentrations and pharmacokinetic parameters, including C_{max} (measured), $C_{max,ss}$ (measured), C_{min} (measured), $C_{min,ss}$ (measured) of SKB264-ADC, SKB264-TAB in serum and unbound KL610023 in plasma will be statistically described. Population pharmacokinetic analysis will be performed as appropriate in combination with plasma concentration data obtained from other clinical trials of SKB264. Immunogenicity Immunogenicity assessment data will be statistically described. ██████████ ██ ██
Study Sites	Approximately 40 clinical sites are expected to participate in this study.
Study Duration	The duration of enrollment in this study is expected to be approximately 15 months, and the study is expected to end 15 months after the first dose of the last enrolled patient.

1.2 Study Flow Chart





1.3 Study Schedule

Item	Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time	-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months ($\pm$ 14 days) after completion of the EOT Follow-up
Informed consent form	X			
Inclusion/exclusion criteria	X			
Demographic data ^a	X			
Medical history ^b	X			
Imaging ^d	X	See notes		
Brain MRI or CT ^e	X	Conducted as clinically indicated		
Bone scan ^f	X	Conducted as clinically indicated		
Vital signs ^g	X	Treatment groups except capecitabine: before/(during)/after each dose infusion Capecitabine treatment group: at each cycle visit	X	
Physical examination ^h	X	Treatment groups other than capecitabine: prior to each dose Capecitabine treatment group: prior to the first dose of each cycle	X	
Height and weight ⁱ	X	See notes	X	
ECOG score ^j	X	Prior to the first dose of each cycle	X	
Quality of life score ^k	X	Prior to the first dose of each cycle	X	
Laboratory tests ^l	Hematology ^m	Treatment groups other than capecitabine: prior to each dose	X	
	Blood chemistry ⁿ		X	
	Urinalysis ^o	Capecitabine treatment group: prior to the first dose of	X	



Item		Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time		-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months (± 14 days) after completion of the EOT Follow-up
			each cycle Hematology for test group: weekly (every 7±2 days) of the first 2 cycles; prior to the each dose of subsequent cycles		
	Coagulation ^p	X	Prior to the first dose of each cycle	X	
	Glycosylated hemoglobin/fasting glucose ^q	See notes			
	Virological test ^r	X		X	
	Pregnancy test ^s	X	Prior to the first dose of each cycle	X	
Electrocardiogram ^t		X	Prior to the first dose of each cycle	X	
Echocardiogram		X		X	
Randomization ^u		X			
Dosing ^w			X		
Drug dispensing/recovery (Capecitabine group only) ^x			See notes	X	
For patients in the test group only ● PK blood sampling ^y ● Immunogenicity study ^z			See notes	X	
Adverse events ^{aa}		X	X	X	
Concomitant medications ^{bb}		X	X	X	X
Survival Information			X	X	X

a) Demographic data include date of birth, gender, ethnicity, age, etc.;



Item	Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time	-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months ($\pm$ 14 days) after completion of the EOT Follow-up

- b) Medical history includes previous tumor diagnosis information, tumor treatment history (including treatment response), current medical history (other than tumor), past medical history, treatment history (other than tumor), surgical history, allergy history, smoking history, alcohol abuse history, drug abuse history and history of clinical trial participation;

- d) Imaging examinations: CT and/or MRI performed within 28 days prior to the first dose of study treatment will be considered as the baseline data, and the test results obtained before signing the informed consent form (within 28 days prior to the first dose) are acceptable. Tumor response will be assessed by imaging every 6 weeks ($\pm$ 1 week) from the first dose of study treatment until disease progression (confirmed by IRC). Imaging examinations will be performed every 12 weeks ($\pm$ 1 week) if the patient has not progressed after 12-month treatment of the investigational drug. Imaging examinations will be performed as scheduled regardless of dose delay or modification. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the last imaging examination is more than 4 weeks away, and the subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death. If there is no contraindication to contrast agents, contrast-enhanced CT and/or contrast-enhanced MRI should be preferentially used and the same examination method should be used throughout the study. The sites for CT or MRI scans should include the chest, abdomen, pelvis, and other sites required (as judged by the investigator based on clinical indication);
- e) Brain MRI or CT: MRI will be performed at screening and the results obtained prior to signing the informed consent form (within 28 days prior to the first dose) are acceptable; and this imaging examination will be subsequently performed as clinically indicated at the discretion of the investigator. CT can be selected if MRI is contraindicated;
- f) Bone scan: radionuclide bone scan (ECT) will be performed at screening, and the test results within 42 days prior to the first dose and positron emission tomography-computed tomography (PET-CT) are acceptable; subsequent scans will be performed as judged by the investigator based on clinical indication;
- g) Vital signs: including blood pressure, pulse, respiratory rate, and body temperature. For patients in the test group: on dosing days of the first 4 doses of SKB264, vital signs will be measured before infusion (-1 h), at every 15 ($\pm$ 5) min during infusion and immediately (within + 10 min) after the end of infusion of SKB264. In qualified study sites, ECG monitoring is recommended during the first 4 doses of SKB264. For subsequent doses (fifth dose of SKB264 and onwards), vital signs should be measured before infusion (-1 h) and immediately (within +10 min) after the end of infusion of SKB264 if no infusion-related reactions or hypersensitivity reactions occur. On each dosing day, additional assessment of vital signs should be performed at other time points if clinically indicated. Subjects will be monitored for any infusion-related reactions or hypersensitivity reactions for at least 90 minutes following



Item	Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time	-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months ($\pm$ 14 days) after completion of the EOT Follow-up

completion of SKB264 infusion on C1D1. For subsequent doses, subjects will be monitored for at least 60 minutes following completion of SKB264 infusion. Longer observation period after completion of SKB264 infusion is required as clinically indicated in the case of infusion-related reactions or hypersensitivity reactions. For patients in the control group: vital signs will be monitored before infusion and immediately (within + 10 min) after the end of each dose for patients receiving eribulin, gemcitabine or vinorelbine, and at each cycle visit for patients receiving capecitabine;

- h) Physical examination: a complete physical examination should be performed on C1D1. For patients in the treatment groups other than capecitabine treatment group, tailored physical examinations prior to subsequent doses may be performed by the investigator as clinically indicated. For patients in the capecitabine treatment group, tailored physical examinations can be performed in subsequent cycles at the discretions of the investigator as clinically indicated. Physical examination should be performed on or before the dosing day;
- i) Body height: measured at screening only. Body weight: for patients in the test group, body weights will be measured prior to each dose. If the change in the patient's weight is more than $\pm$ 10% from baseline, dose adjustment will be required, and the weight at dose adjustment will be used as the new baseline for calculation. For patients in the control group, those who receive eribulin, gemcitabine, or vinorelbine will be weighed prior to each dose, and those who receive capecitabine will be weighed prior to the first dose in each cycle. The dosage will be adjusted according to the weight change as specified above. Physical examination should be performed on or before the dosing day;
- j) ECOG score: ECOG scoring will be performed for all patients at screening, prior to the first dose of each cycle (on the day of dosing or the day before the dosing day) and at the EOT visit;
- k) Quality of life score: the quality of life score will be performed for all patients at screening, prior to the first dose in each cycle (on the dosing day or one day prior to the dosing day, before any clinical procedure) and at the EOT visit;
- l) Laboratory tests: for all the examinations performed on C1D1, the test results obtained within 7 days before dosing are acceptable. For patients in the treatment group other than capecitabine, the test results obtained within 2 days before dosing are acceptable for subsequent pre-dose examinations. For patients in the capecitabine treatment group, the test results obtained within 2 days before dosing are acceptable for all examinations in subsequent cycles. If there is clinically significant abnormal test value, the frequency of test can be increased by the investigator based on the patient's condition;
- m) Hematology: including red blood cell count, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte count. For the test group, hematology test is performed weekly (every 7 ± 2 days) of the first 2 cycles, the test results obtained outside of site are acceptable if there are special circumstances. Hematology test is performed prior to the each dose of subsequent cycles, and the investigator can evaluate whether to increase the frequency of the test between dosing periods based on the patient's previous hematology results;
- n) Blood chemistry: including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, urea nitrogen/urea, creatinine, uric acid, lactate dehydrogenase, total protein, albumin, glucose, calcium, phosphorus, potassium, sodium, chloride and magnesium;
- o) Urinalysis: including urine protein, urine white blood cells, urine glucose, urine ketone bodies, urine bilirubin, urobilinogen, urine acidity or alkalinity, occult blood and specific gravity;



Item	Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time	-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months ($\pm$ 14 days) after completion of the EOT Follow-up

- p) Coagulation: coagulation tests, including prothrombin time, activated partial thromboplastin time, and international normalized ratio, will be performed at screening, prior to the first dose of each cycle, and at the EOT visit;
- q) Glycosylated hemoglobin/fasting blood glucose: for diabetic patients, glycated hemoglobin (HbA1c) and fasting blood glucose should be tested at screening, and will be subsequently determined by the investigator as clinically indicated;
- r) Virological tests: including five items for hepatitis B, and tests for hepatitis C virus (HCV) antibody, syphilis antibody, and HIV antibody. Test of Hepatitis B virus DNA should be measured additionally in patients with positive hepatitis B surface antigen, and hepatitis C virus RNA should be measured in patients with positive hepatitis C virus antibody;
- s) Pregnancy test: only for women of childbearing potential. Blood pregnancy test (chorionic gonadotropin- β) will be performed at screening, and urine pregnancy test is recommended to be performed prior to the first dose of each cycle and at the EOT visit. On C1D1, blood pregnancy test results within 7 days prior to dosing are acceptable;
- t) ECG: ECG will be performed at screening, prior to the first dose of each cycle (results obtained within 2 days before dosing are acceptable), and at the EOT visit;
- u) Randomization: randomization will be performed after all screening examinations are completed, and randomization should be completed within 2 workdays prior to the first dose of study treatment;

- w) Dosing: SKB264 will be administered at a dose of 5 mg/kg by intravenous infusion on Days 1 and 15 of each cycle every 4 weeks, with an allowable dosing window of 14 ± 2 days between two doses. The requirement on dose delays due to AEs are specified in Section 6.1.3. Patients' chemotherapy regimens should be determined by the investigator before randomization. The chemotherapy of the physician's choice included: eribulin: 1.4 mg/m², intravenous infusion, on Days 1 and 8 of each cycle, every 3 weeks, with assessment of peripheral neuropathy prior to each dose; capecitabine: 1000 to 1250 mg/m², orally, twice daily, continuous dosing on Days 1 to 14 of each cycle, every 3 weeks; gemcitabine: 1000 mg/m², intravenous infusion, once on Days 1 and 8 of each cycle, every 3 weeks; vinorelbine: 25 mg/m² by intravenous infusion on Days 1 and 8 of each cycle, every 3 weeks. The allowable



Item	Screening Period	Treatment Period	End of Treatment (EOT) Follow-up ^{cc}	Survival Follow-up ^{dd}
Time	-D28~ -D1	All patients will receive the study treatment until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue study treatment	After last dose Within 30 days	Every 3 months ($\pm$ 14 days) after completion of the EOT Follow-up

dosing window for eribulin, gemcitabine and vinorelbine is a dosing interval of 7 ± 1 days within one cycle, and the requirements on dose delay caused by AEs are presented in Section 6.1.3;

- x) Drug dispensing/recovery (for patients in the capecitabine group only): drugs for the current cycle will be dispensed prior to the initiation of a new treatment cycle; the used drug packaging, unused drugs, and medication diary cards should be returned at each cycle visit;
- y) PK blood sampling (only for patients in the test group): blood samples will be collected prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing in Cycles 1 to 5, prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing every 3 cycles starting from Cycle 6, and at the EOT visit (if dosing is delayed, the blood sampling time points will be postponed accordingly);
- z) Immunogenicity study (only for patients in the test group): immunogenicity blood samples will be collected prior to the first dose (within -1 h) of Cycles 1 to 5, prior to the first dose (within -1 h) every 3 cycles starting from Cycle 6, and at the EOT Visit (if dosing is delayed, the blood sampling time points will be postponed accordingly);
- aa) Adverse events: adverse events should be observed and recorded from signing the informed consent form until 30 days after the last dose, and only adverse events related to study intervention should be recorded from signing the informed consent form until the first dose. The AEs occurred will be followed up until resolution or becoming stable as judged by the investigator, subjects lost to follow-up, or the event can be otherwise explained;
- bb) Concomitant medications: concomitant medications should be recorded from signing the informed consent form until 30 days after the last dose. Only newly initiated anti-tumor therapies and concomitant medications for the treatment of adverse events will be recorded at the survival visit.
- cc) EOT Visit: the EOT Visit will be performed within 30 days after the last dose or before the initiation of a new anti-tumor therapy, whichever occurs first, and will be close to 30 days after the last dose as far as possible. Laboratory tests, ECGs, and echocardiograms that is performed more than 7 days from the last examination should be repeated at the EOT visit. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the imaging examination is more than 4 weeks away, and subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death.
- dd) Survival Follow-up: from the completion of the EOT visit, follow-up visit will be conducted via telephone every 3 months ($\pm$ 14 days) to collect survival information and information about newly initiated anti-tumor therapies until death or lost to follow-up, whichever occurs first. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), imaging should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up, or death.

2. Introduction

2.1 Study Rationale

The International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) estimated that there will be more than 2.26 million new cases of breast cancer worldwide in 2020, accounting for 11.7% of all malignancies and ranking first in the incidence. Approximately 685,000 people died of breast cancer, accounting for 6.9% of all malignancies and ranking the fifth in the mortality ([Sung et al. 2021](#)). It is estimated that there will be 41,6371 new cases (9.1%) of breast cancer and 117,174 (3.9%) deaths due to breast cancer in 2020, ranking the fourth and seventh among all malignancies, respectively ([WHO 2020](#)). In the United States, these data for 2021 were approximately 28,4200 and 44130, respectively ([Siegel et al. 2021](#)).

Triple-negative breast cancer (TNBC) is a subtype of breast cancer which is characterized by negative expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). According to the statistics released by United States, among breast cancer patients aged over 20 from 2012 to 2016, there were more than 123,156 patients with TNBC, accounting for approximately 10% of all breast cancer patients. This is more common among black women, with approximately 19% of breast cancer patients were diagnosed with TNBC ([DeSantis et al. 2019](#)). In China, TNBC accounts for 9.2% to 22.9% of breast cancers ([Zheng et al. 2014](#), [Zhu et al. 2014](#)).

TNBC is characterized by highly invasiveness, easy recurrence and metastasis, poor prognosis, and is considered as the "most hard-to-treat breast cancer". TNBC is insensitive to both endocrine and HER2-targeted therapies, and chemotherapy remains the main drug therapy due to the lack of specific therapeutic targets. According to the 2022 Chinese Society of Clinical Oncology (CSCO) guidelines for the diagnosis and treatment of breast cancer, for patients with recurrent and metastatic TNBC who are sensitive to taxane therapy, the recommended monotherapy for grade I is albumin-paclitaxel, and docetaxel and paclitaxel can also be selected. The recommended combination therapy for grade I is taxane + capecitabine, taxane + gemcitabine and taxane + platinum. The recommended monotherapy for grade II is capecitabine, vinorelbine, gemcitabine, and etoposide. The recommended combination therapy for grade II is albumin-paclitaxel + PD-1 inhibitors, and taxane + bevacizumab may also be selected. For patients with recurrent and metastatic TNBC who have failed taxane therapy, there is currently no standard chemotherapy regimen. The recommended monotherapy for grade I is eribulin, and vinorelbine, gemcitabine and capecitabine can also be selected. The recommended combination therapy for grade I is vinorelbine + platinum, gemcitabine + platinum, and vinorelbine + capecitabine, utidelone + capecitabine can also be selected. The recommended monotherapy for grade II is albumin-paclitaxel, sacituzumab govitecan, and etoposide can also be selected. The recommended combination therapy for grade II is capecitabine + bevacizumab, and

albumin-paclitaxel + other chemotherapy. For the above recommended chemotherapy regimens, combination chemotherapy usually has a higher objective response rate and progression free survival compared with single-agent chemotherapy. However, combination chemotherapy is more toxic and has limited survival benefits. Therefore, only patients who need rapid tumor shrinkage or symptom relief should choose combination chemotherapy, while patients whose tolerance and quality of life are prioritized should choose single-agent chemotherapy first ([Chinese Society of Clinical Oncology 2022](#)). In conclusion, there is unmet clinical needs among patients with unresectable locally advanced or metastatic TNBC who have received second-line or above standard of care.

Antibody-drug conjugate (ADC), known as "biological missile", is a hot spot in the research field of anti-tumor drugs in recent years. The ADCs combine the targeting specificity of antibodies and the high toxicity of toxin molecules to achieve highly efficient and precise killing of tumor cells. Sacituzumab Govitecan (SG) is a conjugate of a TROP2-targeting antibody and the topoisomerase inhibitor SN-38 developed by Immunomedics. The drug was approved by the FDA for treatment of adult patients with unresectable locally advanced or metastatic TNBC who have received two or more prior systemic therapies, at least one of which is for metastatic disease. SG received an accelerated approval in the US based on the objective response rate (ORR) and duration of response (DOR) obtained in the IMMU-132-01 study. This multi-center, single-arm clinical study enrolled 108 patients with metastatic TNBC who had received two or more prior anti-tumor therapies, and the results showed an ORR of 33.3% and a median DOR of 7.7 months. SG was subsequently fully approved based on the clinical benefit observed in the confirmatory study. ASCENT was a multi-center, open-label phase III clinical study conducted in 529 patients with unresectable locally advanced or metastatic TNBC who had relapsed after receiving at least two prior chemotherapies for breast cancer. In this study, patients were randomized in a ratio of 1: 1 to receive SG or the monotherapy selected by the physician. The results showed that there was a statistically significant increase in PFS (4.8 versus 1.7 months; hazard ratio (HR) = 0.43) and OS (11.8 versus 6.9 months; HR = 0.51) in the SG group compared with the chemotherapy group. In terms of safety, SG could cause severe, life-threatening, or fatal neutropenia and severe diarrhea. Neutropenia occurred in 61% of patients treated with SG, including grade 3-4 neutropenia in 47% patients, and febrile neutropenia in 7% patients. Diarrhea occurred in 65% of patients treated with SG, including grade 3-4 diarrhea in 12% patients, and neutropenic colitis in 0.5% patients. It is noteworthy that SN-38 is metabolized by UGT1A1, and individuals with homozygous UGT1A1*28 alleles are at increased risk of neutropenia, febrile neutropenia, and anemia after the treatment of SG ([Immunomedics 2021](#)).

SKB264 for injection, a technologically innovative product independently developed by Kelun-Biotech, is an antibody drug conjugate directed against TROP2. This product targets TROP2-expressing tumor cells by antibody, then enters tumor cells via endocytosis, and is cleaved in

cytolysosomes, and then releases toxin molecules (belotecan derivatives) to kill tumor cells in an efficient manner. SKB264 is designed to enhance the binding between the antibody and linker, hence prolonging the half-life of ADC molecules in serum and effectively improving the therapeutic index.

As of April 10, 2022, a total of 59 TNBC patients have been treated with SKB264 at the dose levels of 4 mg/kg and 5 mg/kg in the phase II dose expansion phase of the KL264-01 clinical trial. Of them, 55 have completed at least 1 response assessment, the confirmed ORR (1 pending confirmation) was 40% (22/55). The ORR was 42.8% (9/21) and confirmed ORR was 38.1% (8/21) in the 4 mg/kg dose group. The ORR was 44.1% (15/34) and confirmed ORR (1 pending confirmation) was 41.2% (14/34) in the 5 mg/kg dose group. Compared with the currently available therapies as the 3rd line or above treatments, SKB264 showed significant clinical advantages as well as favorable safety and tolerability profiles. In the phase III clinical trial of Sacituzumab Govitecan conducted in patients with unresectable locally advanced or metastatic TNBC who have relapsed after at least two prior chemotherapies for breast cancer, 233 patients without brain metastases in the control group received the investigator selected monotherapies, including 126 patients on eribulin, 47 patients on vinorelbine, 31 patients on capecitabine, and 29 patients on gemcitabine, respectively. The ORRs were 5%, 4%, 6%, and 3%, respectively, the clinical benefit rates were 8%, 6%, 10%, and 14%, the median PFS was 2.1, 1.6, 1.6, and 2.7 months, respectively, and the median OS was 6.9, 5.9, 5.2, and 8.4 months, respectively ([ASCO 2021](#)). Therefore, SKB264 for injection is expected to provide a highly effective and low-toxic treatment option for patients with unresectable locally advanced, recurrent, or metastatic triple-negative breast cancer who have received second-line or above standard of care, and this drug will bring disease improvement and survival benefits to the patients while improving their quality of life.

2.2 Study Background

2.2.1 Mechanism of Action

SKB264 for injection is an antibody drug conjugate targeting TROP2, which targets tumor cells that highly express TROP2 by an antibody and cuts the linker via endocytosis, thereby releasing the toxin molecule KL610023 (topoisomerase inhibitor), blocking the cell cycle progression, and achieving the objective of specifically killing tumor cells.

2.2.2 Nonclinical Studies

The results of nonclinical pharmacodynamic studies showed that SKB264 can bind to TROP2 on the cell surface with high affinity and then it will be endocytosed to release toxin intracellularly, blocking cell cycle progress in the S- or G2/M phase, and causing tumor cell apoptosis. In addition, SKB264 can also kill tumor cells through [REDACTED] the bystander effect. The specificity of SKB264 was mediated by the TROP2-specific antibody SKB264 mAb, whereas the cytotoxicity was mainly

mediated by KL610023. After intravenous administration, the cytotoxin molecule KL610023 was mainly detected in tumor tissues. The results of in vivo studies showed that SKB264 was well tolerated and exhibited modest anti-tumor effects.

The results of nonclinical pharmacokinetic studies showed that SKB264 was mainly distributed in blood vessels, mainly targeting tumors and organs with high TROP2 expression. Within the dose range of 1 to 10 mg/kg, following the single dose administration of the drug in Cynomolgus monkeys, the increase in drug exposure was proportional to the increase, and the unbound KL610023 accounted for less than 3.00% of the systemic exposure (on a molar basis) of SKB264-ADC. Its T_{max} was similar to SKB264 with a $t_{1/2}$ longer than that of SKB264. In the repeat-dose study (SKB264: 3 mg/kg), no accumulation was observed possibly due to the production of ADA. KL610023 was mainly metabolized in the liver and excreted via bile/feces. SKB264 was excreted via the kidney/urine after degradation to polypeptides or amino acids. The metabolite profiles of KL610023 were similar in humans and related species.

The results of the nonclinical safety studies showed that the MTD of SKB264 in the single-dose toxicity study in Cynomolgus monkeys was 90 mg/kg. The HNSTD of SKB264 was 50 mg/kg in the 7-week repeat-dose toxicity study in Cynomolgus monkeys. SKB264 had no hemolysis effect and local irritation, hence meeting the requirements for injection administration. The safety pharmacology studies demonstrated that SKB264 was well tolerated in Sprague-Dawley rats and Cynomolgus monkeys. KL610143, a prodrug of SKB264, had no effect on the functions of CNS and respiratory system in Sprague-Dawley rats. SKB264 had no effect on cardiovascular and respiratory function in Cynomolgus monkeys.

The nonclinical pharmacodynamic, pharmacokinetic and toxicological study data of this product are detailed in the latest version of the Investigator's Brochure.

2.2.3 Clinical Studies

A phase I to II clinical study (Clinical Trial No.: KL264-01) of SKB264 for Injection is ongoing. This study is divided into two phases, namely phase I dose escalation phase and phase II dose expansion phase. Based on the data obtained as of February 28, 2022, SKB264 demonstrated preliminary good efficacy in patients with unresectable locally advanced or metastatic solid tumors refractory to available standard of care, especially in patients with metastatic triple-negative breast cancer who have received second-line or above standard of care, and showed good safety profile.

The clinical efficacy, pharmacokinetic and safety study data of this product are detailed in the latest version of the Investigator's Brochure.

2.2.4 Development of Similar Drugs

Among ADC drugs targeting TROP2, Sacituzumab Govitecan (IMMU-132), developed by Immunomedics, received accelerated approval by FDA in April 2020 for the treatment of triple

negative breast cancer, and it was formally approved in April 2021. The latest development phase of DS-1062 developed by the Daiichi Sankyo is a phase III clinical study.

Status of TROP2-ADC development in China: the marketing application of Sacituzumab Govitecan was submitted to NMPA by Everest Medicines in May 2021, the IND application for DAC-002 jointly developed by Hangzhou DAC Biotechnology and Shanghai Junshi Biosciences was approved in July 2020, the IND application for FDA018 antibody conjugate for injection developed by Fudan-Zhangjiang Bio-Pharmaceutical was approved in June 2021, and the IND application for ESG401 developed by Shanghai Shijian Biological/TOT Biopharm was approved in July 2021. DS-1062a, developed by Daiichi Sankyo, was approved for conducting clinical trials in China for the indication of non-small cell lung cancer in September 2021, and for breast cancer in November 2021.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

As of February 28, 2022, a total of 173 patients at the dose levels of 4 mg/kg and 5 mg/kg have been administered with SKB264 in the KL264-01 clinical study.

Investigational drug-related adverse events were reported in 157 (90.8%) patients. Of these, those with the incidence of $\geq 20\%$ included anemia (68.2%), white blood cell count decreased (56.1%), neutrophil count decreased (49.7%), stomatitis (39.3%), platelet count decreased (31.8%), rash (31.8%), alopecia (30.6%), nausea (27.7%) and vomiting (24.3%).

83 (48.0%) patients experienced $\geq$ grade 3 drug-related adverse events, of which the incidence of $\geq 5\%$ included neutrophil count decreased (20.8%), anemia (19.7%), white blood cell count decreased (17.3%), platelet count decreased (9.2%), and stomatitis (7.5%).

40 (23.1%) patients experienced drug-related serious adverse events except death, of which the incidence of $\geq 1\%$ included: anemia (8.1%), platelet count decreased (6.4%), neutrophil count decreased (5.8%), white blood cell count decreased (5.8%), stomatitis (3.5%), mucosal inflammation (1.7%), agranulocytosis (1.2%) and bone marrow failure (1.2%). No drug-related adverse events leading to death occurred.

As of May 2, 2023, in clinical studies of SKB264 (N=563, excluding SKB264-III-03 study), 18 patients (3.2%) had infusion related reactions / hypersensitivity reactions. Grade ≥ 3 adverse events occurred in 6 patients (1.1%), including 3 grade 3 (0.5%, 2 hypersensitivity and 1 infusion related reaction), 2 grade 4 (0.4%, both were SAE, including 1 anaphylactic reaction and 1 anaphylactic shock), and 1 grade 5 event (0.2%, anaphylactic shock, see below for details). One Grade 4 SAE of anaphylactic shock was reported in SKB264-III-03 (N=262, randomly assigned in 1:1 ratio to receive SKB264 or treatment of physician's choice) from pharmacovigilance database.

The SAE (anaphylactic shock) resulted in fatal outcome occurred on the administration date of second dose with premedication of antihistamine but no steroid. The patient experienced Grade

4 anaphylactic shock within four minutes right after the infusion. The patient recovered from sinus tachycardic rhythm with improved hypotension after treatment but remained in a coma. The patient decompensated and died 2 days later. Further details of clinical data update are provided in the latest Investigator's Brochure.

A corresponding treatment plan has been developed to address the potential risks of this product, as detailed in the latest version of the Risk Control Plan.

2.3.2 Known Potential Benefits

The results of nonclinical pharmacodynamic studies showed that SKB264 can bind to TROP2 on the cell surface with high affinity and then it will be endocytosed to release toxin intracellularly, blocking cell cycle progress in the S- or G2/M phase, and causing tumor cell apoptosis. In addition, SKB264 can also kill tumor cells through [REDACTED] the bystander effect. The specificity of SKB264 was mediated by the TROP2-specific antibody SKB264 mAb, whereas the cytotoxicity was mainly mediated by KL610023. After intravenous administration, the cytotoxin molecule KL610023 was mainly detected in tumor tissues. The results of in vivo studies showed that SKB264 was well tolerated and exhibited modest anti-tumor effects.

As of April 10, 2022, a total of 59 TNBC patients have been treated with SKB264 at the dose levels of 4 mg/kg or 5 mg/kg in the phase II dose expansion phase of the KL264-01 clinical trial. Of them, 55 have completed at least 1 response assessment, the confirmed ORR (1 pending confirmation) was 40% (22/55). The ORR was 42.8% (9/21) and confirmed ORR was 38.1% (8/21) in the 4 mg/kg dose group. The ORR was 44.1% (15/34) and confirmed ORR (1 pending confirmation) was 41.2% (14/34) in the 5 mg/kg dose group.

2.3.3 Assessment of Potential Risks and Benefits

This product is an investigational product currently under clinical development that has not been approved for marketing. Any drug tested in clinical trials and during study stage may bring discomforts and pose unpredictable risks to the subjects. In this study, subjects will be treated by physicians and nurses to ensure the safety of the subjects.

In summary, this study will adopt appropriate measures to reduce the potential risks and minimize the risk to the subjects. Moreover, based on the results of previous studies and clinical use experience from similar products, it is expected that the potential benefit to subjects is significantly greater than the potential and controllable risks.

3. Study Objectives, Endpoints and Estimands

3.1 Study Objectives

3.1.1 Primary Objectives

To assess the efficacy of SKB264 for injection versus chemotherapy of the physician's choice for the treatment of patients with unresectable locally advanced, recurrent or metastatic TNBC who have failed second-line or above prior standard of care based on progression-free survival (PFS).

3.1.2 Secondary Objectives

- 1) To assess the overall survival (OS), objective response rate (ORR), and duration of response (DOR) of SKB264 for injection versus chemotherapy of the physician's choice for the treatment of patients with locally advanced, recurrent or metastatic TNBC;
- 2) To assess the safety of SKB264 for injection versus chemotherapy of the physician's choice;
- 3) To assess the pharmacokinetic profile of SKB264 for injection;
- 4) To assess the immunogenicity of SKB264 for injection;
- 5) To assess the quality of life of patients with locally advanced, recurrent, or metastatic TNBC treated with SKB264 for injection versus chemotherapy of the physician's choice.

3.2 Study Endpoint

3.2.1 Primary Study Endpoint

The progression-free survival (PFS) assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

3.2.2 Secondary Study Endpoints

Efficacy

- PFS assessed by the investigator per RECIST 1.1;
- Objective response rate (ORR), duration of response (DOR), disease control rate (DCR), and time to response (TTR) assessed by IRC and the investigator per RECIST v1.1;
- Overall survival (OS);
- Quality of life of patients evaluated using the EORTC QLQ-C30 scale (see Annex).



Safety

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) (as per CTCAE 5.0), abnormal laboratory results, etc.

Pharmacokinetics

- PK parameters: $C_{\max}$, $C_{\max,ss}$, $C_{\min}$, $C_{\min,ss}$, etc.

Immunogenicity

- ADA test results and titer values.

[REDACTED]

[REDACTED]

3.3 Estimands

In accordance with the E9 (R1) guidelines entitled "Estimands and Sensitivity Analyses in Clinical Trials", this study will consider the concomitant events occurred in patients after drug administration, and use the framework of estimands for clinical trial design, analysis, and interpretation of results. The analysis of the estimands is detailed in Chapter 9 and in the statistical analysis plan.

In this study, 1 primary estimand and 4 secondary estimands will be established considering concomitant events according to the study objectives and the details are presented in the table below.

Table 1 Estimands

Attribute	Primary Estimand (PFS Assessed by IRC)	Secondary Estimands (PFS Assessed by Investigator)	Secondary Estimands (ORR)	Secondary Estimands (DCR)	Secondary Estimands (OS)
Population	Patients with unresectable locally advanced, recurrent, or metastatic triple-negative breast cancer who meet the eligibility criteria and who have received second-line or above prior standard of care.				
Treatment	SKB264 for Injection or the chemotherapy of the physician's choice				
Endpoints	PFS is defined as the time from randomization to disease progression or death, whichever occurs first. Disease progression is assessed by IRC per RECIST 1.1.	PFS is defined as the time from randomization to disease progression or death, whichever occurs first. Disease progression is assessed by the investigator per RECIST 1.1.	ORR is defined as the proportion of patients with confirmed complete response (CR) or partial response (PR) as the best overall response assessed by RECIST 1.1.	DCR is defined as the proportion of patients with CR or PR or stable disease (SD) as the best overall response assessed by RECIST 1.1.	OS is defined as the time from randomization to death due to any cause.
Summarized at population level	HR and 95% CI	HR and 95% CI	Rate difference and 95% CI of ORR	Rate Difference and 95% CI of DCR	HR and 95% CI

Intercurrent event (ICE) and management strategies	ICE1: use of the protocol-prohibited anti-tumor therapy prior to disease progression.	ICE1: use of the protocol-prohibited anti-tumor therapy prior to disease progression.	ICE1: use of the protocol-prohibited anti-tumor therapy during study treatment.	ICE1: use of the protocol-prohibited anti-tumor therapy during study treatment.	ICE1: use of the protocol-prohibited anti-tumor therapy.
	Hypothetical strategy: the date of the last valid imaging examination performed prior to the initiation of the prohibited anti-tumor therapy should be censored.	Hypothetical strategy: the date of the last valid imaging examination performed prior to the initiation of the prohibited anti-tumor therapy should be censored.	On-treatment strategy: the efficacy evaluation results after the use of the prohibited anti-tumor therapy should be ignored.	On-treatment strategy: the efficacy evaluation results after the use of the prohibited anti-tumor therapy should be ignored.	Treatment strategy: the impact of the prohibited anti-tumor therapy should be disregarded, and collection and analysis of efficacy data should be continued until lost to follow-up or death.
	ICE2: premature discontinuation of treatment due to intolerability and clinical progression.	ICE2: premature discontinuation of treatment due to intolerability and clinical progression.	ICE2: premature discontinuation of treatment due to intolerability and clinical progression.	ICE2: premature discontinuation of treatment due to intolerability and clinical progression.	ICE2: premature discontinuation of treatment due to intolerability and inadequate response.
	Treatment strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to	Treatment strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up,	Treatment strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up, or death.	Treatment strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up, or death.	Treatment strategy: the impact of study treatment discontinuation should be disregarded, and collection of OS data should be continued.
			ICE3: death (no disease	ICE3: death (no disease	



	follow-up, or death. ICE3: death (no disease progression observed). Covariate strategy: death should be included in the definition of PFS.	or death. ICE3: death (no disease progression observed). Covariate strategy: death should be included in the definition of PFS.	progression observed). On-treatment strategy: the efficacy evaluation results prior to death should be collected and analyzed.	progression observed). On-treatment strategy: the efficacy evaluation results prior to death should be collected and analyzed.	
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4. Study Design

4.1 Overall Design

This is a randomized, controlled, open-label, multi-center study, in which 254 patients with unresectable locally advanced, recurrent, or metastatic TNBC who have failed second-line or above prior standard of care are planned to be enrolled. Eligible patients will be randomized in a 1:1 ratio to the test group and control group, and stratified by the number of prior lines of therapy received (2 to 3 vs. > 3); presence or absence of liver metastases (yes vs. no).

Patients in the test group will be given SKB264 at a dose level of 5 mg/kg by intravenous infusion on Days 1 and 15 of each cycle every 4 weeks until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue the study treatment. Patients in the control group will be given any of the chemotherapy of the physician's choice (eribulin, capecitabine, gemcitabine, and vinorelbine).

4.2 Rationale for Study Design

According to the 2022 CSCO Guidelines for the Diagnosis and Treatment of Breast Cancer, for patients with recurrent and metastatic TNBC who are sensitive to taxane therapy, taxanes-based regimens are generally preferred, and monotherapy or combinational regimens can be selected as the first-line treatment, but there is currently no standard of care regimen for the second- and third-line treatment, and the recommended optional agents include capecitabine, gemcitabine, and vinorelbine, etc. For patients with recurrent and metastatic TNBC who have failed taxane therapy, there is currently no standard chemotherapy regimen, and previously unused mono-chemotherapy or combinational regimen can be considered. However, combinational chemotherapy is highly toxic and has limited survival benefit. Considering the tolerability and quality of life in patients with advanced diseases, mono-chemotherapy is recommended as a preference. Capecitabine, vinorelbine, gemcitabine and eribulin can be considered as monotherapy options. In conclusion, four recommended mono-chemotherapy, including eribulin, capecitabine, gemcitabine, and vinorelbine, will be used as the chemotherapy of the physician's choice in this study, and will be used as the control drugs for evaluating the efficacy of SKB264 in patients with unresectable locally advanced, recurrent, or metastatic triple-negative breast cancer who have received two or more prior lines of standard of care.

This is a randomized study, which will help reduce the selection bias generated by investigators when grouping patients. In addition, stratified randomization of patients will be performed according to the number of prior lines of therapy they received and the status of liver metastases as considering that the factors such as disease status and prior therapy may have an important impact on the prognosis, which will facilitate the evaluation of the study results. In this study, patients in the control group are required to receive investigator-selected anti-tumor monotherapy, and double-blind design is not appropriate because of the significant differences

on dosing regimens and administration routes of chemotherapeutic drugs.

In this study, the PFS assessed by the IRC will be used as the primary efficacy indicators to objectively reflect the effect of the investigational product on tumor growth so as to avoid the bias in the assessment. In addition, PFS is a commonly used surrogate endpoint in randomized studies and can reflect the toxicity and side effects of the investigational product to some extent. Overall survival (OS), objective response rate (ORR) and duration of response (DOR) will also be analyzed as secondary efficacy indicators in this study.

In conclusion, this is a randomized, controlled, open-label, multi-center study to evaluate the efficacy of SKB264 for injection versus chemotherapy of the physician's choice in patients with unresectable locally advanced, recurrent, or metastatic triple-negative breast cancer who have received two or more prior lines of standard of care. PFS assessed by the IRC per RECIST 1.1 will be selected as the primary efficacy indicators.

4.3 Rationale for Dose Selection

Dose expansion study of SKB264 at 4 and 5 mg/kg has been conducted in patients with TNBC. Based on the available efficacy, safety and PK data, the ORRs of the current SKB264 at 4 and 5 mg/kg in TNBC patients who received three or more lines of therapies were significantly higher than that of the current clinical standard of care as three or more lines of therapy, and the safety profile of these 2 dose groups is good. Considering the benefits and risks of patients, the effective dose that can be maintained after dose adjustment, and the correlation between efficacy and dose of ADC, 5 mg/kg (Q2W) is proposed to be selected as the recommended dose for the study.

Efficacy: in the 5 mg/kg (Q2W) dose group, the ORR in the patient population with advanced TNBC who received the last line of treatment was 44.1% (15/34), confirmed ORR (1 pending confirmation) was 41.2% (14/34), which was significantly superior to currently clinically available agents. In the phase III clinical trial of Sacituzumab Govitecan conducted in patients with unresectable locally advanced or metastatic TNBC who have relapsed after at least two prior chemotherapies for breast cancer, 233 patients without brain metastases in the control group received the investigator selected monotherapies, including 126 patients on eribulin, 47 patients on vinorelbine, 31 patients on capecitabine, and 29 patients on gemcitabine, respectively. The ORRs were 5%, 4%, 6%, and 3%, respectively, the clinical benefit rates were 8%, 6%, 10%, and 14%, the median PFS was 2.1, 1.6, 1.6, and 2.7 months, respectively, and the median OS was 6.9, 5.9, 5.2, and 8.4 months, respectively ([ASCO 2021](#)).

Safety: SKB264 has high safety and may have advantages over other similar drugs (IMMU132, DS1062) in terms of causing interstitial pneumonia, hematotoxicity, and gastrointestinal toxicity. Investigational product-related AEs were mainly anemia, decreased neutrophil count, decreased white blood cell count, decreased platelet count, etc., and all the events could be recovered after symptomatic treatment.

PK: Based on the results from the comparison of PK data obtained from the phase I dose escalation study of the KL264-01 clinical trial with that of the similar drug IMMU-132 as well as the preclinical study results, it can be concluded that 1) in the SKB264 4.0 mg/kg or above dose group, the mean AUC_{INF_obs} of ADC after a single dose in the first cycle was comparable or higher to the AUC_{0-168h} of the similar drug IMMU-132 (Trodelyv) at the clinically approved dose of 10 mg/kg (data derived from FDA approved label), and it was much higher than AUC_{INF_obs} at the effective dose of 1.0 mg/kg in HCC1806 tumor-bearing mice observed in the preclinical study; 2) in the SKB264 4.0 mg/kg or above dose group, the sustained plasma concentrations immediately to 240 h after a single dose were higher than the mean IC_{50} of 9 positive TROP2-expressing cell lines *in vitro* in the preclinical study. 3) SKB264 has shown linear pharmacokinetic characteristics in the dose range of 2.0-6.0 mg/kg.

4.4 Definition of End of Study

The study will be ended when the following conditions are met:

- All the patients have completed the study treatment and the Sponsor considers that the survival benefit data obtained from this study are mature.
- Or the primary analysis has been completed and the Sponsor has initiated an extension study to ensure that patients remained in the study can continue to receive treatment.

5. Study Population

5.1 Inclusion Criteria

Subjects will not be included unless they meet all of the following criteria:

- 1) Males or females age 18 to 75 years old (inclusive) at the time of signing the informed consent form;
- 2) Histologically and/or cytologically confirmed TNBC based on pathology reports on recent biopsy specimens or other pathological samples (central laboratory confirmation is not required), including:
 - a) Definition of human epidermal growth factor receptor 2 (HER2) negative: immunohistochemistry (IHC) of 0 or 1+; if HER is 2+ by IHC, negative HER2 expression must be confirmed by fluorescence in situ hybridization (FISH).
 - b) Estrogen and progesterone receptor negative means that less than 1% of the cells express hormone receptors as indicated by IHC;
- 3) Patients with unresectable locally advanced or metastatic triple-negative breast cancer who have failed at least two lines of standard of care regimens, including:
 - a) Any treatment received by the patients regardless of triple-negative state can be included as one of the standard of care regimens;
 - b) For neoadjuvant and/or adjuvant chemotherapy, if relapse or disease progression to unresectable locally advanced or metastatic disease occurs during treatment or within 12 months after discontinuation of treatment (at least 2 cycles have been completed), it will be considered as one of the standard of care regimens. And the patients must also have received one therapy and have progressed on this therapy during the stage of unresectable locally advanced or metastatic disease;
 - c) For patients with documented germline BRCA1/BRCA2 mutations, if they have been treated with an approved PARP inhibitor, then the PARP inhibitor can be considered as one of the 2 prior standard of care regimens required;
 - d) Patients must have progressed on or been intolerable during or after the last treatment prior to enrollment;
- 4) All patients must have been previously treated with taxanes; and those who have been treated with taxanes for at least 1 cycle and show contraindications or intolerance during or at the end of the cycle can be included, regardless of the disease stage during this treatment;
- 5) Patients must have at least one measurable lesion per RECIST v1.1 criteria; those with only skin or bone lesions cannot be included;
- 6) Subjects with a Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and with an expected survival of ≥ 12 weeks;

- 7) Subjects must provide tumor tissues or tissue specimens;
- 8) Subjects must have adequate organ and bone marrow function (no blood transfusion, recombinant human thrombopoietin, or colony stimulating factor therapy has been received within 2 weeks prior to the screening), which is defined as follows:
 - a) Hematology: neutrophil count (NEUT) $\geq 1.5 \times 10^9$ /L; platelets (PLT) $\geq 100 \times 10^9$ /L; hemoglobin ≥ 9 g/dL;
 - b) Liver function: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN); total bilirubin (TBIL) $\leq 1.5 \times$ ULN; for patients with liver metastases, ALT and AST must be $\leq 5 \times$ ULN, TBIL $\leq 2 \times$ ULN; for patients with liver or bone metastases, ALP must be $\leq 5 \times$ ULN;
 - c) Albumin ≥ 3 g/dL;
 - d) Renal function: creatinine clearance (Ccr) ≥ 60 ml/min (see Annex for Cockcroft-Gault formula);
 - e) Coagulation function: international normalized ratio (INR), activated partial thromboplastin time (APTT) and prothrombin time (PT) $\leq 1.5 \times$ ULN;
- 9) Subjects must have recovered from all toxicities (except alopecia) due to prior treatments to $\leq$ grade 1 or the protocol specified inclusion criteria based on the assessment per CTCAE 5.0 criteria;
- 10) Subjects voluntarily participate in the study, sign the informed consent form, and will be able to comply with the protocol-specified visits and relevant procedures.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded:

- 1) Patients with a history of central nervous system (CNS) metastases or current CNS metastases;
- 2) Patients with other malignancies, except cured basal or squamous cell skin cancer or in situ cancer of cervix; and patients with other malignancies must have a tumor-free period of at least 5 years;
- 3) Patients with Gilbert's disease;
- 4) Patients who have received prior TROP2-targeted therapy;
- 5) Patients who have received live vaccines within 30 days prior to the first dose;
- 6) Patients who required the treatment of strong inhibitors or inducers of cytochrome P450 3A4 enzyme (CYP3A4) within 2 weeks prior to the first dose and during the study treatment (strong inhibitors or inducers of CYP3A4 are not allowed in this study, and representative drugs of strong CYP3A4 inhibitors or inducers are listed in the Annex). Patients who received continued high dose of systemic corticosteroids within

- 2 weeks prior to the first dose (low-dose corticosteroids, such as ≤ 10 mg daily prednisone or equivalent, are allowed if the dose is stable for 4 weeks);
- 7) Patients who have received any chemotherapy, immunotherapy, biological therapy, or other drugs within 4 weeks prior to the first dose of study treatment or within 5 half-lives of the drug used in the previous period (whichever is shorter), or received radiotherapy or treatment with traditional Chinese medicine preparations for approved anti-tumor indications 2 weeks prior to the first dose of study treatment, or received major surgeries 4 weeks prior to the first dose of study treatment;
 - 8) With concomitant infections requiring systemic antibiotic therapy within 1 week prior to the first dose of study treatment;
 - 9) Presence of any serious and/or uncontrolled comorbidities that prevent the patient from participating in the study, such as:
 - a) Impaired cardiac function, including any of the following: (not necessarily all of the following):
 - aa) Corrected QT interval (QTcF) between ventricular depolarization to repolarization > 480 ms at baseline;
 - ab) Left ventricular ejection fraction (LVEF) $< 50\%$ on echocardiographic (ECHO) scan;
 - b) Clinically significant heart disease within 6 months prior to the first dose of study treatment, including any of the following known medical history:
 - ba) Angina pectoris;
 - bb) Congestive cardiac failure;
 - bc) Myocardial infarction;
 - c) Patients with (noninfectious) interstitial lung disease (ILD) or history of pneumonia requiring steroid therapy; patients with serious pulmonary function impairment due to lung disease;
 - d) Patients with current or previous active chronic inflammatory bowel disease or intestinal obstruction or gastrointestinal (GI) perforation;
 - e) Uncontrolled hypertension (systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 100 mm Hg), with a history of unstable hypertension, or with a history of poor compliance with antihypertensive treatment;
 - f) Uncontrolled diabetes (fasting glucose ≥ 10 mmol/L and/or glycated hemoglobin (HbA1c) $\geq 8\%$);
 - 10) Active hepatitis B (hepatitis B surface antigen positive, and HBV-DNA above 500 IU/ml or 1x ULN, whichever is higher) or hepatitis C (hepatitis C antibody positive, and HCV-RNA above 1 x ULN); with known history of positive human

immunodeficiency virus (HIV) test or known acquired immunodeficiency syndrome (AIDS); positive syphilis antibody test;

- 11) History of serious drug allergy, with known allergy to macromolecular protein preparations or any component of the study drug formulation (including polysorbate-20). Subjects with a history of severe hypersensitivity reactions to monoclonal antibodies;
- 12) Pregnant or lactating women; or patients of childbearing potential (male or female) who cannot use effective medical contraception during the study treatment period and for 6 months after the end of the dosing period (see Annex for specific contraceptive measures);
- 13) During the screening process prior to the first dose, the condition deteriorated rapidly, such as severe changes in performance status, unstable pain requiring adjustment of analgesic therapy;
- 14) Other circumstances that, in the opinion of the investigator, are not appropriate for participation in this study.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screening Failures

Screening failure is defined as the subject's premature withdrawal from the study prior to drug administration after signing the ICF. Subjects who have failed in the screening test should complete the original documents and record the necessary information in the EDC system without attending any further follow-up.



6. Study Treatment

6.1 Study Drug Administration

6.1.1 General Information of Investigational Product

- **Test group:**

Product name: SKB264 for Injection

Dosage form: Injection

Strength: 200 mg/vial

Ingredient: SKB264

Shelf life: 3 years (tentative)

Storage conditions: stored at 2°C to 8°C and protected from light

R&D and manufacturing unit: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd

The manufacturing date and expiry date of the investigational product are provided at the time of use, please check.

- **Control group:**

Eribulin, capecitabine, gemcitabine, and vinorelbine; all these drugs will be purchased and provided by the Sponsor; and the manufacturer, strength, manufacturing date will be subjected to the actual supply.

- Eribulin

Dosage form: Injection

Strength: 2 mL:1 mg

- Capecitabine

Dosage Form: Tablets

Strength: 0.15 g, 0.5 g

- Gemcitabine

Dosage form: Injection

Strength: 0.2 g, 1.0 g

- Vinorelbine

Dosage form: Injection

Strength: 1 mL:10 mg, 5 mL:50 mg, 10 mg, 15 mg, 20 mg

6.1.2 Dose and Administration

- **Test group:**

Dosage and Administration: SKB264 will be administered at a dose of 5 mg/kg by intravenous infusion on Days 1 and 15 of each cycle every 4 weeks until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue the study treatment. The allowable dosing window is the dosing interval of 14 ± 2 days between two doses, and the rules of dosing delay due to AEs are presented in [Section 6.1.3](#). Patient in either treatment group was first assessed as disease progression during the study period, and if the investigator assessed the patient can still continue benefiting from treatment in the test or control group compared to other optional treatment regimens, treatment may continue at the discretion of the investigator as long as the patient still met the eligibility criteria and agreed to continue treatment.

[REDACTED]

[REDACTED]

[REDACTED]

● Control group:

The control group received any one of the chemotherapies of the physician's choice. The allowable dosing window for eribulin, gemcitabine and vinorelbine is a dosing interval of 7 ± 1 days within one cycle, and the requirements on dose delay caused by AEs are presented in [Section 6.1.3](#).

Available treatment regimens are listed in the following table:

Treatment Regimens	Dose	Route of administration	Dosing Regimen
Eribulin	1.4 mg/m ²	Intravenous Infusion	Dosing on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.
Capecitabine	1000-1250 mg/m ²	Oral administration	The drug will be continuously administered on Days 1 to 14 of each cycle, twice daily, every 3 weeks as a cycle.
Gemcitabine	1000 mg/m ²	Intravenous Infusion	The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle.
Vinorelbine	25 mg/m ²	Intravenous Infusion	The drug will be administered on Days 1 and 8 of each cycle, once daily, every 3 weeks as a cycle (Note: Vinorelbine should not be selected as the treatment regimen for patients with Grade 2 peripheral neuropathy).

Only treatment regimens never received by the patient in prior anti-tumor therapies should be selected. It is not allowed to give patients in the control group only the best supportive care, including palliative radiotherapy.

6.1.3 Dose Modification and Drug Discontinuation Criteria

● Test group:

Toxicities will be graded according to NCI CTCAE V5.0, and all patients should be closely monitored for toxic reactions and active symptomatic treatment will be provided. If a patient experiences a toxic reaction, the dose for the patient can be modified or interrupted according to the table below. In principle, the dosing delay due to an AE should not exceed 3 weeks (the interval between delayed dosing and the last dosing should not exceed 5 weeks).

In case of SKB264-related AEs, the dosage is allowed to be reduced by 1 mg/kg each time, with a maximum of 2 times. After a dose reduction, it is not allowed to upregulate again.

The investigator may make dose modifications according to the table below and take appropriate treatment measures according to the actual situation. If the proposed dose modification scheme is inconsistent with the table below, the investigator should discuss the handling details with the Sponsor in a timely manner.

[illegible]



The specific investigational product-related AEs is recommended to be managed as follows:

Event name: stomatitis

Recommended treatment: see patient education on stomatitis and treatment recommendations for stomatitis.

Event name: rash

Recommended treatment: see patient education on skin-related side effects and treatment recommendations for rash.

Event name: nausea

Recommended treatment: antiemetics.

Event name: vomiting

Recommended treatment: antiemetics.

Event name: diarrhea

Recommended treatment: loperamide or atropine/diphenoxylate or other adjunctive antidiarrheal therapy is allowed to be used and should be recorded if used.

Event name: neutropenia

Recommended treatment: use of prophylactic antibiotics (preferably quinolones) and granulocyte or granulocyte-macrophage colony-stimulating factor at the discretion of the investigator.

Event name: anaemia

Recommended treatment: infusion of red blood cells or administration of erythropoietin.

Event name: peripheral neuropathy

Recommended treatment: non-steroidal anti-inflammatory drugs, anti-epileptic drugs (pregabalin) or antidepressants (duloxetine) if the event grade is higher.

● **Control group:**

➤ **Eribulin**

Dose modification scheme and drug discontinuation criteria are provided for reference, and detailed information is provided in the corresponding package insert of drugs or operation manual.

Assess for peripheral neuropathy prior to each dose.

Recommended dose delays

Do not administer eribulin on Day 1 or Day 8 for any of the following:

- $ANC < 10^9/L$
- $Platelets < 75 \times 10^9/L$
- Grade 3 or 4 non-hematological toxicities

The Day 8 dose may be delayed for a maximum of 1 week.

- If toxicities do not resolve or improve to $\leq$ Grade 2 severity by Day 15, omit the dose.
- If toxicities resolve or improve to $\leq$ Grade 2 severity by Day 15, administer eribulin at a reduced dose and initiate the next cycle no sooner than 2 weeks later.

Recommended dose reductions

If a dose has been delayed for toxicity and toxicities have recovered to Grade 2 severity or less, resume eribulin at a reduced dose as set out below.

- Do not re-escalate eribulin dose after it has been reduced.
- Permanently reduce the 1.4 mg/m^2 eribulin dose to 1.1 mg/m^2 for any of the following:
 - $ANC < 0.5 \times 10^9/L$ for >7 days
 - $ANC < 10^9/L$ with fever or infection

- Platelets $< 25 \times 10^9/L$
- Platelets $< 50 \times 10^9/L$ requiring transfusion
- Non-hematologic Grade 3 or 4 toxicities
- Omission or delay of Day 8 eribulin dose in previous cycle for toxicity
- Dose reduce to 0.7 mg/m^2 for any event requiring permanent dose reduction while receiving 1.1 mg/m^2
- Discontinue eribulin for any occurrence of any event requiring permanent dose reduction while receiving 0.7 mg/m^2

➤ Capecitabine

Dose modification scheme and drug discontinuation criteria are provided for reference, and detailed information is provided in the corresponding package insert of drugs or operation manual.

Capecitabine dose modification scheme described below is recommended for the management of adverse reactions.

Toxicity NCIC Grades	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 0-1	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	-
Grade 3		
1st appearance	Interrupt until resolved to Grade 0-1	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	-
Grade 4		
1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%

➤ Gemcitabine

Dose modification scheme and drug discontinuation criteria are provided for reference, and detailed information is provided in the corresponding package insert of drugs or operation manual.

Recommended dose modifications for gemcitabine for myelosuppression on day of treatment are described below.

Treatment Day	Absolute neutrophil count ($\times 10^9/L$)		Platelet count ($\times 10^9/L$)	% of full dose
Day 1	≥ 1.5	and	≥ 100	100%
	< 1.5	or	< 100	Hold

Day 8 and Day 15	≥ 1.2	and	> 75	100%
	1.000-1.199	or	50-75	75%
	0.700-0.999	and	≥ 50	50%
	< 0.7	or	< 50	Hold

Dose Modifications for Non-Hematologic Adverse Reactions

- Withhold Gemzar or reduce dose by 50% for other severe (Grade 3 or 4) non-hematological toxicity until resolved.
- No dose modifications are recommended for alopecia, nausea, or vomiting.

Permanently discontinue Gemzar for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-uremic syndrome
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

➤ Vinorelbine

Dose modification scheme and drug discontinuation criteria are provided for reference, and detailed information is provided in the corresponding package insert of drugs or operation manual.

Dose Modifications for Hematologic Toxicity: Neutrophil counts should be $> 10^9/L$ prior to the administration of vinorelbine. Adjustments in the dosage of vinorelbine should be based on neutrophil counts obtained on the day of treatment according to the following table.

Dose Adjustments Based on Neutrophil Counts	
Neutrophils on Day of Treatment ($\times 10^9/L$)	Percentage of Starting Dose of vinorelbine
≥ 1.5	100%
1.000-1.499	50%
< 1.0	Do not administer. Repeat neutrophil count in 1 week. If 3 consecutive weekly doses are held because neutrophil count is $< 10^9/L$, discontinue vinorelbine.
Note: For patients who, during treatment with vinorelbine, experienced fever and/or sepsis while neutropenic or had 2 consecutive weekly doses held due to neutropenia, subsequent doses of vinorelbine should be:	
≥ 1.5	75%
1.000-1.499	37.5%
< 1.0	See above

Dose Modifications for Hepatic Insufficiency: vinorelbine should be administered with caution to patients with hepatic insufficiency. In patients who develop hyperbilirubinemia during treatment with vinorelbine, the dose should be adjusted for total bilirubin (see below).

Dose Modification Based on Total Bilirubin	
Total Bilirubin (mg/dL)	Percentage of Starting Dose of vinorelbine
≤ 2.0	100%
2.1-3.0	50%
> 3.0	25%

Dose Modifications for Concurrent Hematologic Toxicity and Hepatic Insufficiency: In patients with both hematologic toxicity and hepatic insufficiency, the lower of the doses based on the corresponding starting dose of vinorelbine determined from Tables above should be administered.

Dose Modifications for Renal Insufficiency: No dose adjustments for vinorelbine are required for renal insufficiency.

Dose Modifications for Neurotoxicity: If Grade > 2 neurotoxicity develops, vinorelbine should be held until the toxicity resolves to < grade 1 and then restarted at a 50% of the starting dose of vinorelbine. If > Grade 2 neurotoxicity reoccurs after dose reduction to 50%, vinorelbine should be held until the toxicity resolves to < Grade 1 and then restarted at a 25% of the starting dose of vinorelbine. If > Grade 2 neurotoxicity reoccurs after dose reduction to 25%, vinorelbine should be discontinued.

Permanently reduce the vinorelbine dose to 50% of the starting dose for any of the following: Non-hematologic Grade 3 or 4 toxicities.

6.1.4 Infusion-Related Reactions

SKB264 may cause severe or life-threatening infusion-related reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines associated infusion reaction are provided in [Table 3](#). Infusion-related reaction caused by SKB264, it should follow the dose modification and treatment guidelines as specified in the table for the drug. Premedication measures for infusion-related reactions of SKB264 are described in [Section 6.1.2](#).

Subjects will be closely monitored during and after infusions for signs and symptoms of infusion-related reactions (e.g., fever and/or shiver, flushing and/or pruritus, changes in heart rate and blood pressure, dyspnea or chest discomfort, rash, etc.), severe systemic hypersensitivity reactions (e.g., generalized urticaria, angioedema, asthma, hypotension, tachycardia, etc.). If a subject develops symptoms or signs of severe systemic hypersensitivity reactions, the subject should be treated with appropriate medications: epinephrine should be given immediately, followed by corticosteroids, anti-allergic agents, bronchodilators and oxygen inhalation, etc. Appropriate medical equipment and medications should be readily available at all sites.

Table 3 Infusion-related Reaction Dose Modification and Treatment Guidelines for

SKB264

[illegible]



6.2 Management of Investigational Product

6.2.1 Receipt and Reconciliation of Investigational Product

A designated personnel at the study site is responsible for the receipt, storage, dispensing and recovery of the drug, and making records. Clinical study personnel must ensure that the drug can only be used in this clinical study.

The drugs, packaging and labels used in the study will be provided by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., and transferred to the study site for use. Relevant documents for drug receipt should be signed by the study site personnel in a timely manner.

The drugs shall be managed by a designated personnel, and the drug storage record should be completed by the drug management personnel, and no drug shall be used after the expiry date. Take appropriate measure to prevent damages caused by fire, theft, heating, mould, insects and mice. The investigational product should be stored in strict accordance with the storage conditions, and subject to a 24-h monitoring and the data will be record.

Prior to the start of study drug administration, the study nurse or pharmacist is responsible for preparing the investigational product and completing the drug preparation record form. The study personnel will administer the drug to the subjects according to the study protocol, and the actual medication will be truthfully recorded by the study personnel after administration. All the drugs can only be used for this clinical study and not for any other purposes.

After the end of the study, the study nurse or pharmacist should return the remaining drugs to the drug administrator and complete handover records. The used drug empty vials and residual liquids should be destroyed at the study site, and those that do not meet the destruction criteria should be uniformly recovered and destroyed by the Sponsor. The used drug packaging and unused drugs will be uniformly recovered and destroyed by the Sponsor.

6.2.2 Packaging and Labeling of Investigational Product

The packaging and labeling of the investigational product SKB264 for this study will be provided by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

The label of the investigational product will be marked with the words "for clinical study only", and will be indicated with the name, strength, batch No., manufacturing date, expiry date, storage conditions, manufacturer and clinical trial No..

6.2.3 Product Storage and Stability

SKB264 for injection: 2 to 8°C, protected from light.

Eribulin, capecitabine, gemcitabine, and vinorelbine: subjected to the label of the drug product actually provided.

6.2.4 Preparation

➤ SKB264 for Injection

1. Calculation of the administered dose

The dose to be administered will be determined based on the dose level (mg/kg) and subject's body weight (kg) and the SKB264 vials of required number will be prepared. If the dose is 5 mg/kg, for a subject with the body weight of 60 kg, 300 mg of the drug will be administered. If the strength of the drug is 200 mg/vial, 2 vials need to be prepared.

2. Reconstitution

Ten mL of sterile water for injection will be slowly injected into a 200 mg SKB264 vial with a sterile syringe, then the vial will be gently rotated (shaking should be avoided) until the drug is completely dissolved, and a 20 mg/mL solution of SKB264 is obtained. Multiple vials of drug will be reconstituted according to the administered dose. The reconstituted solution should be colorless to pale yellow, clear, and free from visible particles. Do not use the solution if it contains visible particles, or is turbid or discolored.

It is recommended to use the reconstituted solution immediately after reconstitution with sterile water for injection. If it is not used immediately, the reconstituted solution can be stored in a refrigerator at 2°C to 8°C. However, it cannot be stored for more than 4 hours. Do not shake or freeze the drug after reconstitution.

3. Dilution

The saline will be pipetted from the 250 mL saline intravenous infusion bag with the same volume as that of the required SKB264 solution, and the corresponding volume of reconstituted solution [required volume (mL) = subject's body weight (kg) × dose level (mg/kg)/20 (mg/mL)] will be drawn from the vial and injected into the saline infusion bag. The solution will be mixed by gently inverting the infusion bag, and the drug concentration after dilution should be within the range of 0.4 to 6.0 mg/mL.

It is recommended to use the diluent immediately within 4 h after preparation. If it cannot be used immediately, it should be stored at 2°C to 8°C or room temperature (25 ± 5°C). Do not freeze or shake the solution. The time interval from the completion of the dilution to the end of the infusion should not exceed 4 hours.

The unused portions left in the vials or wastes should be disposed of according to hospital procedures.

The specific operation is detailed in the corresponding operation manual.

➤ Eribulin

The required volume of eribulin will be pipetted based on the required dose and administered by intravenous infusion for 2 to 5 min; or the drug can be diluted in 100 mL of 0.9% sodium chloride injection for intravenous infusion.

The specific operation is detailed in the corresponding package insert or operation manual.

➤ **Capecitabine**

Capecitabine tablets should be swallowed in whole with water within 30 minutes after a meal.

➤ **Gemcitabine**

Gemcitabine lyophilized powder should be dissolved with an appropriate amount of 0.9% sodium chloride injection, then further diluted with 0.9% sodium chloride injection, and infused intravenously for 30 minutes.

The specific operation is detailed in the corresponding package insert or operation manual.

➤ **Vinorelbine**

The drug should be diluted with 0.9% sodium chloride injection, and administered via intravenous infusion within a short time, and the vein should be washed with a large amount of 0.9% sodium chloride injection after administration.

The specific operation is detailed in the corresponding package insert or operation manual.

6.3 Method to Minimize Deviation: Randomization and Blinding

6.3.1 Randomization

A total of 254 patients are planned to be enrolled in this study. The subjects will be randomized using a central randomization system by stratified block randomization, and all the study sites will compete with each other to recruit patients. Stratification factors include: ① The number of prior lines of therapy a patient has received (2 to 3 vs. > 3); ② Status/Presence of liver metastases (yes vs. no). The randomization schedule of subjects will be generated by an unblinded statistician in a 1:1 ratio between the test group and the control group using the SAS statistical analysis software (version 9.4 or above). After subjects pass the eligibility screening tests, i.e. they meet all the inclusion criteria and do not meet any of the exclusion criteria, the investigator will log in the central randomization system and enter the subjects' information according to the order in which the subjects entered the study to obtain the subjects' random numbers. Patients randomized to the control group will be given the chemotherapy of the physician's choice, and the drug preparer/dispenser will be informed of the name of the drug to be dispensed to the patients based on the randomization results and the chemotherapy of the physician's choice.

6.3.2 Blinding

Not applicable for this study.

6.4 Subject Compliance

The administration of all drugs (including investigational product) must be recorded in the corresponding section in the subject's original documents and electronic case report form (eCRF), and the CRA will review the records to determine the subject's protocol compliance.

6.5 Concomitant Treatments

All concomitant medications (including start/discontinuation date and purpose of administration) must be recorded in the subject's original document and in the corresponding section of the eCRF, and drugs such as solvents and tube flushing agents that do not have preventive or therapeutic intentions are not required to be entered into the eCRF.

6.5.1 Permitted Concomitant Therapies

- Patients are allowed to receive the best supportive care but anti-tumor therapy is not included. Medications that are judged by the investigator to be in compliance with the protocol (e.g., concomitant medications for the treatment of disease-related symptoms and various AEs) are allowed to be used.
- Medications and therapies to treat complications or relieve symptoms of complications, such as antihypertensives, antibacterials and antihistamines are allowed to be used, but the modification of dose and administration mode should be minimized during the study.
- Radiotherapy for non-target lesions (mainly for pain relief) and bisphosphate therapy for bone metastases are allowed.
- Necessary local radiotherapy (total dose ≤ 1500 cGy) (eg, for painful skeletal lesions) is allowed.

6.5.2 Prohibited Concomitant Treatments

- From the time of patient signing the ICF to the EOT visit, patients are prohibited from using anti-tumor therapy not specified in the protocol, including extensive radiotherapy or radiotherapy and/or local therapy confined to target lesions, surgical treatment, chemotherapy, hormonal therapy for tumor treatment, biological agents, traditional Chinese medicine preparations (see Annex for the detailed list), or other investigational drugs.
- If other anti-tumor therapies are required during the study, patients should immediately discontinue the investigational product and complete the EOT visit before receiving any other anti-tumor therapy.
- Strong inhibitors or inducers of CYP3A4 are not allowed to be used in this study, and the representative drugs of strong CYP3A4 inhibitors or inducers are listed in the annex.

6.5.3 Rescue Medications

Not applicable.

6.6 Study Procedures

6.6.1 Screening Period

During the process of obtaining the informed consent form from the subjects, the investigator must give a detail explanation about the nature, purpose, procedures, expected duration, potential risks and benefits of the study, and any discomfort that may occur to each subject during the study. Each subject must be informed that their participation in the study is voluntary and that he/she may withdraw from the study at any time, and his/her rights and interests will not be affected.

After the basic contents of the study have been explained and the investigator confirms that each subject candidate understands the purpose of the study, each subject who will participate in the study or his/her guardian should be asked to sign and date the ICF and leave the contact information. Subjects or their guardians should carefully read and think over before signing and indicating the date, and sign the ICF after understanding the course of the study and agreeing to participate in the study, and the investigator should sign on the ICF at the same time. The ICF is in duplicate, with one to be archived for the country's regulatory authority and the other to be kept by the subject. Subjects who fail to give informed consent or sign the ICF are not allowed to enroll in the study.

Subjects will participate in the physical examination conducted during screening after signing the ICF, and they will be assigned the "screening numbers" in the order in which the ICF is signed. Subjects are not allowed to undergo repeated screenings, but subjects whose laboratory results do not meet the inclusion criteria may undergo a retest within the screening window.

Screening will be performed within 28 days prior to dosing, and the eligible subjects will be randomized within 2 workdays prior to dosing. The following information or procedures should be recorded or performed: the demographic data and medical history of the subject, [REDACTED] imaging examination, brain MRI or CT, bone scan, vital signs, physical examination, body height and body weight, ECOG score, quality of life score, hematology, blood chemistry, urinalysis, coagulation, glycosylated hemoglobin/fasting glucose (for diabetic patients), virological test, pregnancy test (for women of childbearing potential only), ECGs, echocardiograms, as well as AEs related to study intervention, and concomitant medications. The items to be completed for screening within -28 days to -1 days prior to dosing are shown in the table below.

Table 4 Screening Items

Item	Requirements and Observed Indicators
Demographic data	Date of birth, gender, ethnicity, age, etc.

Item	Requirements and Observed Indicators
Medical history	Previous tumor diagnosis information, tumor treatment history (including treatment response), current medical history (other than tumor), past medical history, treatment history (other than tumor), surgical history, allergy history, smoking history, alcohol abuse history, drug abuse history and history of clinical trial participation;
Imaging examination	The sites for computerized tomography (CT) and/or magnetic resonance imaging (MRI) will include the chest, abdomen, pelvis, and other sites required (as judged by the investigator based on clinical indication). If there is no contraindication to contrast agents, contrast-enhanced CT and/or contrast-enhanced MRI should be preferentially used.
Brain MRI or CT	MRI will be performed; however, CT can be selected if there is any contraindication.
Bone scan	Radionuclide bone scan (ECT)
Vital signs	Blood pressure, pulse, respiratory rate, and body temperature
Physical examination	Including skin, mucosa, lymph nodes, head, neck, chest, abdomen, spine/extremities, and nervous system examinations, etc.
Body height and body weight	/
ECOG score	Record the score
Quality of life score	Quality of life of patients will be evaluated using the EORTC QLQ-C30 scale (see Annex), and the scores will be recorded
Hematology	Red blood cell count (RBC), hemoglobin (HGB), platelet count (PLT), white blood cell count (WBC), neutrophil count (NEUT) and lymphocyte count (LYM)
Blood chemistry	Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), urea nitrogen (BUN)/urea (Urea), creatinine (CRE), uric acid (UA), lactate dehydrogenase (LDH), total protein (TP), albumin (ALB), glucose (GLU), calcium (Ca), phosphorus (P), potassium (K), sodium (Na), chlorine (Cl) and magnesium (Mg)
Urinalysis	Urine protein (PRO), white blood cell (WBC), glucose (GLU), ketone body (KET), bilirubin (BIL), urobilinogen (URO), PH (PH), occult blood (BLD) and specific gravity (SG)
Coagulation	Prothrombin time (PT), activated partial thrombin time (APTT), international normalized ratio (INR)
Glycosylated hemoglobin/fasting glucose	Glycosylated hemoglobin (HbA1c) and fasting glucose
Virology test	Hepatitis B (five items), HCV antibody, syphilis antibody, HIV antibody. Test of Hepatitis B virus DNA should be measured additionally in patients with positive hepatitis B surface antigen, and hepatitis C virus RNA should be measured in patients with positive hepatitis C virus antibody.
Pregnancy test	Blood chorionic gonadotropin- β (HCG- β)

Item	Requirements and Observed Indicators
Electrocardiogram	/
Echocardiogram	Left ventricular ejection fraction (LVEF)
Adverse Event	Only adverse events related to study intervention will be recorded
Concomitant medication	Recording of concomitant medications

Eligibility will be assessed according to the inclusion/exclusion criteria, and eligible subjects will be enrolled in this study.

6.6.2 Visits during Treatment Period

- 1) Imaging examination: tumor response will be assessed every 6 weeks (± 1 week) from the first dose of study treatment until disease progression (confirmed by IRC). Imaging examinations will be performed every 12 weeks (± 1 week) if the patient has not progressed after 12-month treatment of investigational product. Imaging examinations will be performed as scheduled regardless of dose delay or modification. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the last imaging examination is more than 4 weeks away, and the subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death. If there is no contraindication to contrast agents, contrast-enhanced CT and/or contrast-enhanced MRI should be preferentially used and the same examination method should be used throughout the study. The sites for CT or MRI scans should include the chest, abdomen, pelvis, and other sites required (as judged by the investigator based on clinical indication);
- 2) Monitoring of vital signs: For patients in the test group: on dosing days of the first 4 doses of SKB264, vital signs will be measured before infusion (-1 h), at every 15 (± 5) min during infusion and immediately (within + 10 min) after the end of infusion of SKB264. In qualified study sites, ECG monitoring is recommended during the first 4 doses of SKB264. For subsequent doses (fifth dose of SKB264 and onwards), vital signs should be measured before infusion (-1 h) and immediately (within +10 min) after the end of infusion of SKB264 if no infusion-related reactions or hypersensitivity reactions occur. On each dosing day, additional assessment of vital signs should be performed at other time points if clinically indicated. Subjects will be monitored for any infusion-related reactions or hypersensitivity reactions for at least 90 minutes following completion of SKB264 infusion on C1D1. For subsequent doses, subjects will be monitored for at least 60 minutes following completion of SKB264 infusion.

Longer observation period after completion of SKB264 infusion is required as clinically indicated in the case of infusion-related reactions or hypersensitivity reactions. For patients in the control group: vital signs will be monitored before infusion and immediately (within +10 min) after the end of each dose for patients receiving eribulin, gemcitabine or vinorelbine, and at visits during each cycle for patients receiving capecitabine;

- 3) Physical examination: a complete physical examination should be performed on C1D1. For patients in the treatment groups other than capecitabine treatment group, tailored physical examinations prior to subsequent doses may be performed by the investigator as clinically indicated. For patients in the capecitabine treatment group, tailored physical examinations can be performed in subsequent cycles at the discretions of the investigator as clinically indicated. Physical examination should be performed on or before the dosing day;
- 4) Body weight measurement: for patients in the test group, body weights will be measured prior to each dose. If the change in the patient's weight is more than $\pm 10\%$ from baseline, dose adjustment will be required, and the weight at dose adjustment will be used as the new baseline for calculation. For patients in the control group, those who receive eribulin, gemcitabine, or vinorelbine will be weighed prior to each dose, and those who receive capecitabine will be weighed prior to the first dose in each cycle. The dosage will be adjusted according to the weight change as specified above. Physical examination should be performed on or before the dosing day;
- 5) ECOG scoring: ECOG scoring will be performed for all patients before the first dose during each cycle (on the dosing day or one day prior to the dosing day);
- 6) Quality of life scoring (EORTC QLQ-C30): quality of life scoring will be performed for all patients before the first dose (on the dosing day or one day prior to the dosing day, before any clinical procedure) during each cycle;
- 7) Laboratory tests: hematology (for test group: weekly (every 7 ± 2 days) of the first 2 cycles; prior to the each dose of subsequent cycles), blood chemistry, urinalysis and coagulation function, pregnancy (urine pregnancy test is recommended, only for women of childbearing potential) (coagulation function and pregnancy will be tested only before the first dose during each cycle), and the test results obtained within 7 days prior to dosing are acceptable for tests on C1D1. For patients in the treatment group other than capecitabine, the test results obtained within 2 days before dosing are acceptable for subsequent pre-dose examinations. For patients in the capecitabine treatment group, the test results obtained within 2 days before dosing are acceptable for all examinations in subsequent cycles. If there is clinically significant abnormal

test value, the frequency of test can be increased by the investigator based on the patient's condition;

- 8) ECG: ECG will be performed prior to the first dose of each cycle (results obtained within 2 days before dosing are acceptable);

[REDACTED]

- 10) Dosing: SKB264 will be administered at a dose of 5 mg/kg by intravenous infusion on Days 1 and 15 of each cycle every 4 weeks, with an allowable dosing window of 14 ± 2 days between two doses. The requirement on dose delays due to AEs are specified in [Section 6.1.3](#). Patients' chemotherapy regimens should be determined by the investigator before randomization. The chemotherapy of the physician's choice included: eribulin: 1.4 mg/m², intravenous infusion, on Days 1 and 8 of each cycle, every 3 weeks, with assessment of peripheral neuropathy prior to each dose; capecitabine: 1000 to 1250 mg/m², orally, twice daily, continuous dosing on Days 1 to 14 of each cycle, every 3 weeks; gemcitabine: 1000 mg/m², intravenous infusion, once on Days 1 and 8 of each cycle, every 3 weeks; vinorelbine: 25 mg/m² by intravenous infusion on Days 1 and 8 of each cycle, every 3 weeks. The allowable dosing window for eribulin, gemcitabine and vinorelbine is a dosing interval of 7 ± 1 days within one cycle, and the requirements on dose delay caused by AEs are presented in [Section 6.1.3](#);
- 11) Drug dispensing/recovery (for patients in the capecitabine group only): drugs for the current cycle will be dispensed prior to the initiation of a new treatment cycle; the

used drug packaging, unused drugs, and medication diary cards should be returned at each cycle visit;

- 12) PK blood sampling (only for patients in the test group): blood samples will be collected prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing in Cycles 1 to 5, prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing every 3 cycles starting from Cycle 6 (if dosing is delayed, the blood sampling time points will be postponed accordingly);
- 13) Immunogenicity study (only for patients in the test group): immunogenicity blood samples will be collected prior to the first dose (within -1 h) of Cycles 1 to 5, prior to the first dose (within -1 h) every 3 cycles starting from Cycle 6 (if dosing is delayed, the blood sampling time points will be postponed accordingly);
- 14) Adverse events: observe and record adverse events;
- 15) Concomitant medications: record concomitant medications;
- 16) Survival information.

6.6.3 End of Treatment Visit

The EOT Visit will be performed within 30 days after the last dose or before the initiation of a new anti-tumor therapy, whichever occurs first, and will be close to 30 days after the last dose as far as possible. Laboratory tests, ECGs, and echocardiograms that is performed more than 7 days from the last examination should be repeated at the EOT visit.

- 1) Imaging examination: for patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the imaging examination is more than 4 weeks away, and subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death.
- 2) Vital signs monitoring;
- 3) Physical examination: a tailored physical examination may be performed by the investigator as clinically indicated;
- 4) Body weight measurement;
- 5) ECOG score;
- 6) Quality of life score (EORTC QLQ-C30);
- 7) Laboratory tests: hematology, blood chemistry, urinalysis, coagulation, virology test, pregnancy (urine pregnancy test is recommended, for women of childbearing potential

- only);
- 8) Electrocardiogram;
 - 9) Echocardiography;
 - 10) Drug dispensing/recovery (for patients in the capecitabine group only): the used drug packaging, unused drugs, and medication diary cards will be recovered at each cycle visit;
 - 11) PK blood sampling (only for patients in the test group);
 - 12) Immunogenicity study (only for patients in the test group);
 - 13) Adverse events: observe and record adverse events;
 - 14) Concomitant medications: record concomitant medications;
 - 15) Survival information.

6.6.4 Survival Visit

From the completion of the EOT visit, follow-up visit will be conducted via telephone every 3 months ($\pm$ 14 days) to collect survival information and information about newly initiated anti-tumor therapies until death or loss to follow-up, whichever occurs first.

- 1) Imaging examinations: for patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), imaging should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up, or death.
- 2) Concomitant medications: only new anti-tumor therapies and concomitant medications for the treatment of adverse events will be recorded;
- 3) Survival information.

6.6.5 Unscheduled Visits

During the study, considering the safety of the subjects, if a subject experiences an adverse event or has any laboratory abnormality, the investigator may increase the number of follow-up visits for the subject, i.e. unscheduled visits, as needed. The investigator must accurately record each unscheduled visit of the subject in the unscheduled follow-up section of the subject's original documents and eCRFs.

6.7 Processing and Testing of Biological Samples

6.7.1 Biological Sample Collection

Blood sampling time points:

- Pharmacokinetic blood sampling time points (only for patients in the test group)

Blood samples will be collected prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing in Cycles 1 to 5, prior to the first dose (within -1 h) and within 0.5 h ($\pm$ 15 min) after the end of dosing every 3 cycles starting from Cycle 6, and at the EOT visit (if dosing is delayed, the blood sampling time points will be postponed accordingly).

- Immunogenicity blood sampling time points (only for patients in the test group)

Blood samples will be collected prior to the first dose (within -1 h) in Cycles 1 to 5, prior to the first dose (within -1 h) every 3 cycles starting from Cycle 6, and at the EOT visit (if dosing is delayed, the blood sampling time points will be postponed accordingly).

Collection of tumor tissue samples (for all eligible patients):

Eligible patients must provide 5 tumor tissue slides for TROP2 testing before randomization, preferably newly obtained tissues. If newly obtained tissues cannot be provided, archival paraffin tissues/sections must be provided, which must be collected within 2 years (if it is more than 2 years, it is up to the Sponsor to decide whether or not it can be used).

Sample Collection, Processing, Shipment and Storage:

The specific operation is detailed in the corresponding operation manual.

All the steps involved in the biological sample collection should be recorded accordingly to ensure accurate and complete data, including but not limited to handover, storage, handling, delivery and destruction.

6.7.2 Analytical Procedures for Biological Samples

Biological samples will be tested by enzyme-linked immunosorbent assay (ELISA) and liquid chromatography with tandem mass spectrometry (LC-MS/MS). Serum concentrations of SKB264-ADC and SKB264-TAB will be determined by ELISA, and plasma concentrations of unbound KL610023 will be determined by LC-MS/MS.

The MSD-based Bridging-ECLA will be used to determine the anti-SKB264 anti-drug antibodies in patients' serum. The neutralizing antibody analysis will be performed based on the results of the study.

[REDACTED]

7. Treatment Discontinuation and Discontinuation/Withdrawal from the Study

7.1 Treatment Discontinuation of Subjects

Subjects must discontinue the study treatment if one of the following conditions occurs:

- 1) Disease progression;
- 2) Discontinuation of study treatment requested by the subject and/or his/her guardian;
- 3) Occurrence of an AE, which is judged by the investigator to be inappropriate for continuing the treatment;
- 4) Loss to follow-up;
- 5) Death;
- 6) Inadequate response;
- 7) Poor compliance and inability to comply with the study requirements during the study;
- 8) Pregnancy;
- 9) Study terminated by the Sponsor;
- 10) Others.

Discontinuation of study treatment requested by a subject does not imply an end of study procedures and subsequent study procedures, including the end-of-treatment visit and survival follow-up, which should be completed as specified in the protocol. In any event, the reason for discontinuation of study treatment should be recorded in the subject's original document and the electronic case report form (eCRF).

7.2 Discontinuation/Withdrawal from the Study

Subjects have the right to withdraw from the study at any time during any period of the study. Any enrolled subject must discontinue/withdraw from the study if he or she experiences the following conditions during the course of the study :

- 1) Withdrawal from the study at the request of the subject and/or his/her guardian;
- 2) Loss to follow-up;
- 3) Death;
- 4) Study terminated by the Sponsor;
- 5) Others.

In any event, the reason for discontinuation/withdrawal from the study should be recorded in the subject's original document and the electronic case report form (eCRF).

7.3 Lost to Follow-up

Lost to follow-up refers to the situation that the investigator fails to contact the subject using the contact information provided by the subject at different time intervals for multiple times (more than three times). Any efforts made should be recored in the documents.

8. Study Assessments

8.1 Efficacy Assessment

The primary efficacy endpoint in this study is the progression-free survival (PFS) assessed by the IRC per RECIST 1.1.

Efficacy will be assessed by imaging examinations every 6 weeks (± 1 week) from the start of the first dose of study treatment until disease progression (confirmed by IRC), or every 12 weeks (± 1 week) if the patient has not progressed after receiving 12 months of the investigational product. Imaging examinations will be performed as scheduled regardless of dose delay or modification. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the last imaging examination is more than 4 weeks away, and the subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up, or death. If there is no contraindication to contrast agents, contrast-enhanced CT and/or contrast-enhanced MRI should be preferentially used and the same examination method should be used throughout the study. The sites for CT or MRI scans should include the chest, abdomen, pelvis, and other sites required (as judged by the investigator based on clinical indication).

8.2 Assessment of Other Study Objectives

8.2.1 Pharmacokinetic Evaluation

For patients in the test group only: in this study, the concentrations of SKB264-ADC and SKB264-TAB in serum and unbound KL610023 in plasma must be measured.

8.2.2 Immunogenicity Evaluation

For patients in the test group only: in this study, anti-SKB264 anti-drug antibodies in serum will be measured, and the neutralizing antibody analysis will be performed based on the study results.

[REDACTED]

[REDACTED]

[REDACTED]

8.2.4 Quality of Life Assessment

In this study, the quality of life of patients will be evaluated using the EORTC QLQ-C30 scoring scale (see Annex).

8.3 Safety Evaluation

Safety evaluation will be performed at screening, during the study and after the end of the study. Subjects who prematurely withdraw from the study are required to undergo safety evaluations prior to withdrawal.

Safety indicators include the AEs, vital signs, physical examinations, laboratory tests, electrocardiograms and echocardiography.

- 1) AEs: definition, evaluation and follow-up requirements of AEs are detailed in [Section 8.4](#);
- 2) Vital signs: blood pressure, pulse rate, respiratory rate and body temperature will be measured according to the study schedule described in [Section 1.3](#) and the study procedures described in [Section 6.6](#);
- 3) Physical examination: a complete or specific physical examination will be performed according to the study schedule described in [Section 1.3](#) and the study procedures described in [Section 6.6](#), and the complete examination items include skin, mucosa, lymph nodes, head, neck, chest, abdomen, spine/extremities and neurological examination;
- 4) Laboratory tests: hematology, blood chemistry, urinalysis and coagulation will be determined according to the study schedule described in [Section 1.3](#) and the study procedures described in [Section 6.6](#);
- 5) Electrocardiogram: electrocardiogram will be performed according to the study schedule described in [Section 1.3](#) and the study procedures described in [Section 6.6](#);
- 6) Echocardiography: echocardiography will be performed according to the study schedule described in [Section 1.3](#) and the study procedures described in [Section 6.6](#);
- 7) Throughout the course of the study, additional safety tests may be performed by the investigator as clinically indicated for the safety of subjects.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events

An adverse event (AE) is defined as any untoward medical event that occurs after a subject receives the investigational product, and this AE may be manifested as symptoms, signs, diseases, or laboratory abnormalities, but may not necessarily have a causal relationship with the investigational product.

Only AEs related to study intervention will be recorded from the time of the subject signing the ICF to the first dose. Newly found abnormal observations considered to be of clinical significance by the investigator after the first dose will be recorded as AEs, including physical examination results, clinically relevant abnormal vital signs, clinically relevant laboratory abnormalities and clinically relevant electrocardiogram results. Conditions in which the original

symptoms become aggravated in nature, severity, or frequency after the first dose should also be recorded as AEs. Any disease, condition, or laboratory abnormality that exists prior to the screening visit or detected at the screening visit without further worsening should be considered pre-existing ones and should be recorded on the eCRF as a medical history.

Criteria to determine whether an abnormal laboratory result should be reported as an AE are as follows:

- The test results are accompanied with symptoms, and (or);
- The test results require further diagnostic examination or medical/surgical intervention, and (or);
- The test results lead to a change in the dose or discontinuation of the investigational product, a significant concomitant drug treatment or other therapy, and/or;
- The test results constitute an AE in the opinion of the investigator.

A test that is conducted only for the purpose of retesting an abnormality and does not meet any of the above conditions does not constitute an AE. Any abnormal laboratory result judged to be an error is also not required to be reported as an AE.

8.4.1.1 Definition of Serious Adverse Events

A serious adverse event (SAE) is an AE that meets any of the following criteria:

- 1) Leading to death;
- 2) Is life-threatening*;
- 3) Requiring hospitalization or prolongation of a hospitalization;
- 4) Resulting in permanent or serious disability/loss of function;
- 5) Resulting in a congenital anomaly/birth defect;
- 6) Other important medical events. Any medical occurrence that is not immediately life-threatening, fatal, or leading to hospitalization, but may jeopardize the health of the subject or requires medical interventions to prevent one of the above outcomes based on the appropriate medical diagnosis is generally considered a serious AE.

*Note: "Life-threatening" is defined as an immediate risk of death posed to a subject due to an AE, rather than an event that is hypothesized to result in death if the condition is exacerbated.

8.4.1.2 Adverse Events of Special Interest (AESIs)

AESI is the event of clinical interest in terms of science and medicine for sponsor's product or project, which can be serious or non-serious adverse event and requires ongoing monitoring and prompt communication with sponsor by the investigator. Such events may require further research to understand their characteristics. In the event of ECI specified in the clinical research protocol, regardless of the severity, the investigator should immediately report to the sponsor or designee so that the sponsor can timely monitor, identify and address possible emerging risks.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.4.2 Collection, Recording and Description of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest

8.4.2.1 Recording and Description of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest

All AEs observed or mentioned by the subject during the study should be accurately recorded by the investigator in the original medical records and entered into the "AEs" page of the eCRF.

The rules to be followed for recording and describing AEs are: 1) completeness: the description in the original medical record should include, but is not limited to, the basic information of the clinical study and the subject, the use of the investigational product, the occurrence of AE, treatment measures taken for the AE, and the action taken with the investigational product, outcome of the AE, causality determination and rationale and concomitant medications; 2) readability: use of abbreviations of medical terms should be avoided to reduce ambiguity.

Contents to be entered include, but are not limited to:

- Name of AE;
- Onset date;
- Severity;
- Action taken;
- Action taken with investigational product;
- Relationship with the investigational product;
- Whether it is a SAE;
- Outcome of AE;
- End date.

8.4.2.2 Determination of Adverse Event/Serious Adverse Event/Adverse Event of Special Interest Name

The name of an AE should be a medical term and a medical diagnosis should be used preferentially. That is, if multiple symptoms, signs and laboratory abnormalities can be referred to or classified as the manifestations of a disease or a damage, they will be considered as an AE. If a definitive diagnosis is not possible, symptoms/signs will be used; when a diagnosis is later confirmed, the record will be updated to replace the previous symptoms/signs with the diagnosis.

When determining the name of the AE, it should be ensured that the name of each AE consists of a single event, and that a diagnosis, symptom/sign represents an AE.

Terms such as hospitalization, surgery and death are not AEs per se, whereas the causes of these conditions need to be recorded as AEs. When the causes of the above-mentioned conditions are not yet determined, the known information, such as hospitalization and death, can be used as the name of the AE and updated in the subsequent follow-ups.

8.4.2.3 Severity of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest

The investigator will assess the AEs with reference to the NCI CTCAE (version 5.0) and grade the severity of each AE. If the severity of an AE is not clarified in the guidelines, the investigator may assess it according to the general definition of Grade 1 to 5 and in combination with medical judgment. General Grading of Adverse Events:

Grade 1: Mild; asymptomatic or with slight symptoms; with clinical or diagnostic observations only; requiring no treatment.

Grade 2: Moderate; requiring less intense, non-invasive or local treatment, or age-related instrumental activities of daily living are limited*.

Grade 3: Severe or medically significant but not immediately life-threatening; leading to hospitalization or prolongation of hospitalization; disabling; limitations on self-care activities of daily living**.

Grade 4: Life-threatening; requiring urgent treatment.

Grade 5: AE-related death.

*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone and managing money.

**Self-care activities of daily living refer to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not bedridden.

8.4.2.4 Judgment of Relationship of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest With Investigational Product

The relationship between AEs and the investigational product will be classified based on the five criteria for the analysis of AEs into five categories, i.e. definitely related, probably related, possibly related, unlikely related and definitely unrelated. Of these, "definitely related, probably related, possibly related" will be considered related to the investigational product.

Definitely related: consistent with the known type of reactions of the suspected drug; consistent with a reasonable chronological order after drug administration; alleviation or disappearance of the AE after dose reduction or drug discontinuation, and re-occurrence after re-administration.

Probably related: consistent with the known type of reactions of the suspected drug; consistent with a reasonable chronological order after administration; alleviation or disappearance of the

AE after dose reduction or drug discontinuation, but the event can also result from the subject's clinical status or other reasons.

Possibly related: consistent with the known type of reactions of the suspected drug; consistent with a reasonable chronological order after administration; alleviation or with less manifestation of the AE after dose reduction or drug discontinuation, but the event can be explained by the subject's clinical status or other reasons.

Possibly unrelated: not so consistent with the known type of reactions of the suspected drug; not so consistent with a reasonable chronological order after administration; the event can also result from subject's clinical status or other reasons.

Definitely unrelated: not consistent with the known type of reactions of the suspected drug; not consistent with a reasonable chronological order after administration; the event can also be explained by subject's clinical status or other reasons; the event is alleviated or disappears after the clinical symptoms or other reasons are resolved/excluded.

8.4.2.5 Timeline and Frequency of Adverse Event Assessment and Follow-up

AEs should be observed and recorded from signing the ICF until 30 days after the last dose, and only AEs related to study intervention should be recorded from signing the ICF to the first dose. The AEs occurred will be followed up until resolution or becoming stable as judged by the investigator, subjects lost to follow-up, or the event can be otherwise explained.

8.4.2.6 End Time of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest

The end time of an AE should be the time when the AE is resolved, becomes stable, can be reasonably explained, or when the AE is judged by the investigator to be definitely ended. If the end time is not collected due to the death of the subject, and the AE which is not the direct cause of death persists, the recording of the end time of the AE should be left blank indicating the status of "ongoing". If the AE is judged to be the direct or primary cause of death, the end time is defined as the death time.

8.4.3 Management of Serious Adverse Events/Adverse Events of Special Interest

8.4.3.1 Reporting of Serious Adverse Events/Adverse Events of Special Interest

In case of SAEs/AESIs, the investigator should immediately take appropriate and active rescue and protective measures for the subjects, and may decide whether to discontinue the study based on patients' conditions. Any SAE/AESI (whether related to investigational product or not) occurring during the study should be completed in the Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Report Form by the investigator and reported to the Sponsor within 24 h of awareness. The Sponsor's e-mail address is sae@kelun.com.

For reports involving death events, the investigator must report such SAEs to the Sponsor and

the Ethics Committee within 24 hours of awareness. The investigator should provide the Sponsor and the Ethics Committee with other information required, such as autopsy report and the final medical report.

The Sponsor will judge the expectedness of SAEs and promptly report any suspected unexpected serious adverse reactions (SUSARs) to all investigators participating in the clinical trial, as well as clinical study sites and the ethics committee. In addition, the Sponsor should report the SUSARs to drug regulatory authorities and health authorities.

The investigator should read and sign relevant safety information of the clinical study provided by the Sponsor in a timely manner, then consider whether the treatment for the subject should be adjusted as appropriate, communicate with the subject as soon as possible when necessary, and report the SUSARs provided by the Sponsor to the ethics committee and the study sites.

8.4.3.2 Follow-up of Serious Adverse Events/Adverse Events of Special Interest

All SAEs/AESIs should be followed up until resolution or becoming stable as judged by the investigator, subjects lost to follow-up, or the event can be otherwise explained, and the frequency of follow-up will be determined by the investigator according to the specific conditions of the SAE.

8.4.3.3 Determination of Expectedness of Serious Adverse Events

The assessment of expectedness should be based on serious adverse reactions observed in clinical studies, and the determination of expectedness of SAEs occurring during the study in subsequent clinical studies will be based on the expected serious adverse reactions listed in the section of the Reference Safety Information in the Investigator's Brochure (see the most recent version of the Investigator's Brochure for details of the drug Reference Safety Information).

8.4.3.4 Disease Progression

Unequivocal symptoms or signs of tumor progression should not be recorded as AEs (with a clear diagnostic rationale) unless they are more severe than expected or are considered by the investigator to be related to study drug administration or study procedures. If a new primary malignancy occurs, such an event should be reported as a SAE.

All SAEs of death (including death due to disease progression) should be reported from signing the ICF to 30 days after the last dose.

Since overall survival (OS) is used as the primary endpoint in this clinical trial and has been approved by regulatory authorities after communication, the event of death due to disease progression will not be reported as an SAE.

8.4.3.5 Hospitalization

In this clinical study, the AEs that lead to hospitalization or prolongation of existing hospitalization should be considered as SAEs. Any first hospitalization to a medical facility

(even if less than 24 hours) meets this criterion.

Hospitalization does not include the following conditions:

- 1) Admitted by routine emergency room;
- 2) Day surgery (e.g., outpatient/day/ambulatory surgery) (observation in outpatient departments for less than 24 hours);
- 3) Nursing homes;
- 4) Rehabilitation facilities;
- 5) Hospice care facilities (e.g. nursing homes);
- 6) Hospitalization due to a pre-existing disease that does not become worsened without the onset of any new AEs (e.g., hospitalization due to laboratory abnormalities that occur prior to the study and still persist);
- 7) Hospitalization due to administrative reasons (e.g., annual routine physical examination);
- 8) On-study hospitalization as specified in the protocol (e.g., protocol-specified procedures);
- 9) Elective hospitalization unrelated to worsening of the AEs (e.g. elective cosmetic surgery);
- 10) Pre-scheduled treatment or surgery which should be recorded in the protocol and/or in the subject's baseline data.

Diagnostic or therapeutic invasive (e.g., surgery) and non-invasive procedures should not be reported as AEs. However, disease conditions leading to the operation of this procedure should be reported as AEs if they meet the definition of AEs. For example, acute appendicitis that occurs during the reporting period of an AE should be reported as an AE, therefore, the appendectomy performed for the disease should be recorded as the treatment for this AE.

8.4.4 Pregnancy Reports

Pregnancy of a female subject or partner of a male subject during the study should be reported to the Sponsor and the ethics committee of the study site within 24 hours of awareness.

Female subjects who become pregnant are required to discontinue study treatment immediately, and will be recorded, reported, and followed up in accordance with the Standard Operating Procedures (SOPs) of the clinical study site; male subjects are not required to discontinue study treatment after their partners become pregnant; however, the pregnancy of their partners should be recorded, reported and followed up in the same manner as pregnant female subjects.

Pregnancy per se will not be considered as an AE or SAE, but any of the following complicated conditions that occur during pregnancy will be recorded, reported and followed up as the "SAE" in accordance with the provisions of the protocol. Complicated conditions include: spontaneous abortion (threatened abortion, inevitable abortion, complete abortion, incomplete abortion,

habitual abortion); stillbirth; fetal/neonatal congenital anomaly or deformity; and termination of pregnancy for medical reasons.

8.4.5 Overdose

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose (including accidental or intentional overdose) for:

SKB264: any dose $\geq 20\%$ over the prescribed dose specified in the protocol.

No specific information is available on the treatment of overdose of SKB264. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the subject to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the subject for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

An accidental overdose is not an AE per se, and any adverse medical event resulting from an accidental overdose is an AE. Overdose and any adverse medical event should be recorded in the original medical record and eCRF.

For all overdoses of SKB264, whether or not they lead to adverse events, the investigator must fill in the Overdose Report Form or overdose page in EDC, and report to the sponsor or designee within 24 hours of awareness. Detailed contacts can be found in a separate document.

If an overdose is accompanied by an SAE, it should be reported according to the SAE process.

9. Statistical Considerations

9.1 Statistical Assumptions

The primary endpoint of this study is progression-free survival (PFS) assessed by IRC per RECIST 1.1.

Assumptions

H0: HR of test group vs. control group = 1

H1: HR of test group vs. control group < 1

α level: one-sided 0.025

9.2 Sample Size Estimation

In this study, a group sequential design will be used, and the sample size will be calculated using gsDesign package of R software (version 4.1.1).

In this study, 254 patients are planned to be enrolled and they will be randomized in a 1:1 ratio to the test group and the control group. According to the study conducted by Bardia et al, the expected median PFS of the control group is approximately 2 months. Assuming that the hazard ratio (HR) of PFS between the test group and the control group is 0.60, and the PFS follows an exponential distribution, then for 183 PFS events (PD or death), there will be 93% power at a one-sided test level of 0.025 to infer that the test group is superior to the control group. An interim analysis of PFS superiority test is planned for this study when the number of PFS events reaches 65% of the total target number, i.e., when there are 119 PFS events. To control the type I errors, the nominal test level α for the interim and final analyses of PFS is set to one-sided 0.0066 and one-sided 0.0227 according to the O'Brien-Fleming spending function, respectively. For the secondary endpoint OS, the expected median OS time of the control group is approximately 7.3 months. Assuming that the hazard ratio (HR) of OS between the test group and the control group is 0.65, and the OS follows an exponential distribution, then for 184 OS events (deaths), there will be 83% power at a one-sided test level of 0.025 to infer that the test group is superior to the control group. The enrollment duration in this study is expected to be 15 months. If the last patient is followed up for the final analysis of OS for approximately 15 months after the first dose, 228 patients are required to be enrolled. Considering the dropout rate of 10%, a total of approximately 254 patients (127 in the test group and 127 in the control group) are required to be enrolled. An interim analysis of OS superiority test is planned for this study at the final analysis of PFS (102 OS events are expected). To control the type I errors in the OS test, the α for testing OS at the PFS interim analysis is set to 0.0001. The nominal test level α (total α is one-sided 0.0249) for the interim and final analyses of OS is set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses.

Based on the available clinical study data in Phase I, an ORR of 33% is assumed in the test group. Based on historical study data, an ORR of approximately 6% is assumed in the control

group. Based on a type I error α of one-sided 0.025, 114 patients in each group (228 in both groups) will have at least 99% power to infer a statistically significant difference in ORR between the test group and the control group using Fisher's exact test.

9.3 Populations for Analyses

- 1) Full analysis set (FAS): including all subjects who are randomized according to the ITT principle. The FAS will be used for baseline and efficacy analyses.
- 2) Safety set (SS): all subjects who have received at least 1 dose of the investigational product and have safety evaluation data. SS will be used for safety analysis.
- 3) PK concentration set (PKCS): including all subjects who have received at least 1 dose of the investigated product and have at least 1 drug plasma concentration measurement during the study. The PKCS will be used for the analysis of plasma concentrations.
- 4) Immunogenicity set (IMGS): all patients who have received at least 1 dose of the investigational product and have at least 1 post-baseline immunogenicity measurement during the study.

9.4 Statistical Analysis

9.4.1 General Methods

All statistical programming will be completed using SAS (version 9.4 or above). In this study, the data will be summarized using statistical descriptive methods in accordance with the following general principles unless otherwise specified. The descriptive statistics for continuous variables will be performed using number, mean, standard deviation (SD), maximum, minimum and median, and the descriptive statistics for categorical variables will be performed using incidence and frequency or number and percentage of patients.

9.4.2 Analysis of Estimands

Specific descriptions of the primary and secondary study endpoints, including the strategies to manage concomitant events, are provided in [Section 3.3](#).

9.4.2.1 Analysis of Primary Estimands

The primary estimand of PFS as assessed by the IRC will be based on the FAS, the median of both groups will be estimated using the Kaplan-Meier method, and the 95% confidence intervals will be calculated using the Brookmeyer-Crowley method. The difference in efficacy between the two groups in PFS will be tested using the stratified log rank test method. The hazard ratio between the two groups in PFS will be estimated using the stratified COX model. The stratified log rank test and the stratified COX model will be based on randomization stratification factors. At the time of primary analysis, for patients without disease progression or death, PFS will be censored at the date of the last valid imaging examination. For patients

without post-baseline tumor assessments, PFS will be censored at the time of randomization. For patients whose date of first disease progression or death is more than two assessment cycles away from the date of the previous imaging, the date of PFS will be censored to the date of the last valid imaging prior to progression. Sensitivity analyses will be performed based on the FAS, with the date of first disease progression or death assessed by IRC as the calculated date of PFS, and the analysis method will be the same as that used for the primary analysis.

9.4.2.2 Analysis of Secondary Estimands

The analysis method for the secondary endpoint of PFS assessed by the investigator will be the same as the that for the primary endpoint. The primary analysis of the secondary estimand of OS will be based on the FAS, and the analysis method will be the same as that of the primary estimand of PFS.

The primary analysis of the estimands of ORR and DCR will be based on the FAS. The 95% confidence intervals of ORR and DCR will be estimated using the Clopper-Pearson method, and the differences in ORR and DCR between the two groups as well as the 95% confidence intervals and P value will be calculated using the CMH method. The sensitivity analysis will be conducted based on the FAS, and the results will be assessed by the investigator, and the analysis method will be the same as that used for the primary analysis.

9.4.2.3 Analysis of Other Secondary Efficacy Endpoints

The analyses of DOR and TTR assessed by IRC and the investigator will be based on the patients with CR and PR in the FAS and Kaplan-Meier method will be used to estimate the median for each group, and the corresponding 95% confidence interval for each group will be calculated using the Brookmeyer-Crowley method. For patients without progression or death, DOR and TTR will be censored at the date of the last valid imaging examination.

9.4.2.4 Multiple Comparisons

In this study, 1 interim analysis for superiority testing will be performed for the primary estimand of PFS assessed by the IRC. In order to control Type I errors, the nominal test level of α for the interim analysis and the final analysis will be set at one-sided $\alpha=0.0066$ and one-sided $\alpha=0.0227$ using the O' Brien-Fleming spending function, respectively. If the actual number of PFS events differs from the planned number, the nominal test level α for the PFS interim analysis and final analysis may need to be adjusted according to the O' Brien-Fleming spending function based on the actual number of PFS events for the interim and final analysis.

In order to control total type I errors, this study performed sequential tests (PFS→OS→ORR) for the primary estimand PFS assessed by IRC and the secondary estimands of OS and ORR. An interim analysis of PFS superiority testing is planned for this study at the time of 119 PFS events assessed by IRC. If PFS is not successfully tested at the interim analysis, the final analysis of PFS will be performed at the time of 183 PFS events assessed by IRC. If the PFS test is successful, OS would be compared between the two groups. An interim analysis for OS

superiority testing will be performed at the final analysis of PFS or at the time of approximately 102 OS events. If OS is not tested successfully at the interim analysis, the final analysis of OS will be performed at the time of 184 OS events (deaths). To control the type I errors in the OS test, the α for testing OS at the PFS interim analysis is set to 0.0001. The nominal test level α (total α is one-sided 0.0249) for the interim and final analyses of OS is set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses.

9.4.2.5 Imputation of Missing Values

In this study, missing values of the primary analysis of the primary endpoint PFS and the secondary endpoints ORR and DCR will not be imputed. For patients with missing or incomplete death dates, the imputation rules for death dates are detailed in the statistical analysis plan.

9.4.3 Analysis of Other Study Objectives

9.4.3.1 Pharmacokinetic Analyses

The concentrations and pharmacokinetic parameters, including $C_{\max}$ (measured value), $C_{\max,ss}$ (measured value), $C_{\min}$ (measured value), $C_{\min,ss}$ (measured value) of SKB264-ADC and SKB264-TAB in serum and unbound KL610023 in plasma will be statistically described.

9.4.3.2 Immunogenicity Analysis

Immunogenicity assessment data will be statistically described.

[REDACTED]

[REDACTED]

[REDACTED]

9.4.3.4 Quality of Life Assessment

The quality of life scores and changes from baseline at each assessment time point in the two groups will be statistically described.

9.4.4 Safety Analysis

Safety endpoints, including AEs, vital signs, physical examinations, laboratory tests, ECGs, will be analyzed based on the safety dataset. Laboratory test results, electrocardiogram and other test results will be presented in the form of a pre- and post-treatment shift table. Abnormal tests after treatment will be presented in lists. All AEs occurring during this clinical study will be coded using the MedDRA dictionary, and the number and incidence of AEs will be listed in detail by SOC/PT classification. Adverse events of special interest will be presented separately.

9.4.5 Baseline Descriptive Analysis

Baseline is defined as the last examination data obtained prior to the first dose. Baseline

characteristics of patients, including demographic and baseline characteristics, will be analyzed using descriptive statistical methods.

9.4.6 Planned Interim Analysis

An interim analysis for superiority testing is planned for this study at the time of the occurrence of 119 PFS events. An interim analysis for OS superiority testing will be performed at the final analysis of PFS or at the time of approximately 102 OS events. The nominal test levels for the interim and final analyses of PFS and OS are provided in [Section 9.4.2.4](#).

9.4.7 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established in this study to analyze adverse events and efficacy data during the study, as well as to make recommendations. The IDMC consists of experts in relevant fields, including those in relevant areas of clinical trial indications, serious adverse events as well as biostatisticians. Recommendations made by the IDMC following review of the data will be assessed for acceptance and decided by the Sponsor. More detailed regulations and contents will be addressed in the IDMC charter.

9.4.8 Subgroup Analysis

Subgroup analysis will be performed for potential impact factors/confounding variables, including but not limited to age, prior lines of treatment received, and status of liver metastases.

9.4.9 Listing of Data by Subject

Patient enrollment, baseline characteristics, dosing, efficacy, safety, plasma concentrations, immunogenicity test results, and [REDACTED] results will be tabulated.

10. Supporting Documents and Operational Considerations

10.1 Regulations, Ethics and Regulatory Considerations of Clinical Trials

10.1.1 Process of Informed Consent

Each subject should sign the informed consent form before participating in the study, as detailed in [Section 6.6.1](#).

10.1.2 Study Discontinuation and Termination

10.1.2.1 Study Discontinuation

Study discontinuation means that the clinical study has not been ended in accordance with the protocol and has been stopped during the process.

Generally speaking, the study may be temporarily discontinued when the investigator, the ethics committee, the Sponsor, and/or the regulatory authority determine that continuation of the study may affect the safety of the subjects. Whether the study can be resumed will be jointly decided by the investigator, the Sponsor, and/or relevant authorities based on discussion.

10.1.2.2 Study Termination

This clinical study will be terminated if any of the following circumstances occur:

- 1) The regulatory authority, ethics committee, investigator, and/or the Sponsor consider the study harbors significant safety risks;
- 2) The Sponsor may terminate the study for any scientific, medical or ethical reasons, but sufficient considerations should be given to the rights and interests, safety and health of the study subjects. In addition, the sponsor reserves the right to discontinue the development of this product at any time;
- 3) Other reasons for which the Sponsor or the investigator determines that it is inappropriate to continue the study.

10.1.3 Confidentiality and Privacy

This study will only collect and process data from subjects that the use of which are limited to the evaluation of efficacy, safety, quality, and clinical application of the investigational product.

The confidentiality of these data will be sufficiently protected and the relevant laws and regulations protecting the privacy of subjects will be followed when the data are collected and used.

10.1.4 Future Use of Stock Samples and Data

Not applicable.

10.1.5 Key Roles and Study Management

The Sponsor is responsible for providing the study sites with information such as the study-

related Investigator's Brochure and research fundings, qualified study drugs and study materials (including copies or instructions of the Sponsor's business license, drug production license, good manufacturing practice (GMP) certificate, original certificate of analysis, etc.) free of charge. And the Sponsor and the investigator will jointly formulate the study protocol, which will be mutually approved by the two sides. This study will be conducted by the investigator according to the protocol and in accordance with the current national regulations.

The study sites should strictly keep all information provided by the Sponsor confidential, and other study participants and ethics committees should also be required to take the same confidentiality measures. Information provided to the study sites must not be disclosed to others without written permission from the Sponsor.

10.1.6 Safety Monitoring

The doctors and nurses of the study sites will be responsible for the monitoring of adverse events throughout the study. Subjects who experience any discomfort during the study can contact their doctors promptly.

10.1.7 Monitoring of Clinical Trial

The CRA should monitor the conduct of the study in accordance with the requirements of GCP, including but not limited to:

- Before the initiation of this clinical study, the CRA should confirm that the investigator has sufficient qualifications and resources to complete the study, and that the clinical study site has appropriate conditions for completing the study, including personnel and training, and fully equipped and well operating laboratories as well as various study-related testing conditions.
- The CRA should verify the following conditions: the investigational product is within the validity period; the storage conditions are acceptable; the supply will be adequate during the clinical study; the investigational product will only be provided to eligible subjects at the dose specified in the protocol; subjects have received instructions for proper use, handling, storage and return of the investigational product; the receipt, use and return of the investigational product by the clinical study sites are appropriately controlled and documented; the disposition of unused investigational product by the clinical study sites complies with relevant laws and regulations and the requirements of the Sponsor.
- The CRA should verify the implementation of the protocol by the investigator during the conduct of the clinical study; he or she should confirm that all subjects or their guardians have signed the ICF before participating the study; he or she should ensure that the investigator has received the latest version of the Investigator's Brochure, all study-related documents, and essential supplies for conducting the study and the study is implemented in accordance with the requirements of relevant laws and regulations;

and he or she should ensure that the investigator has adequate knowledge for conducting the clinical study.

- The CRA should check the accuracy and completeness of the data entered into the CRF and compare the data against the source documents;
- The CRA should confirm that all the AEs have been reported within the specified period in accordance with the requirements of relevant laws and regulations, the study protocol, the ethics committee and the Sponsor.

10.1.8 Quality Assurance and Quality Control

The Sponsor is responsible for the development, implementation and timely updating of the in-house standard operating procedures for quality assurance and quality control systems for this clinical trial. The Sponsor should ensure that the conduct of the clinical trial, data generation, records and reporting comply with the requirements of the protocol, the Good Clinical Practice as well as relevant laws and regulations.

Before the participation of all the relevant parties to the clinical trial, the Sponsor should verify that they have corresponding qualifications, clarify their responsibilities, rights and interests, and indicates these items in the signed contract.

Participants involved in each step of the clinical trial should be authorized, provided with trainings corresponding to the authorized contents, and have the required professional knowledge, training experience and technical competence for conducting the study.

All instruments, equipment, reagents, standards related to the conduct of this clinical trial should strictly meet the requirements of specifications. Instruments and equipment to be calibrated should be calibrated periodically and ensure that they can operate under normal conditions.

All the parties involved in this trial should establish a complete set of procedures to ensure that they can perform their study-related responsibilities and functions and follow these study procedures to ensure that reliable data can be generated.

The Sponsor should supervise the work undertaken by all parties on an ongoing basis, and assign independent auditors to the study sites to have direct access of the source data, source documents and reports, and the audit report should be kept within the facility of the Sponsor. If significant compliance issues are found, which may have a significant impact on the safety and rights and interests of subjects, or on the reliability of the study data, relevant personnel should be organized to identify the root causes and take appropriate corrective and preventive actions.

At the time when the drug regulatory authorities initiate an inspection on all parties involved in this study, the relevant parties should immediately notify the Sponsor, and both the Sponsor and the inspected institutions should send personnel to participate the inspections, actively cooperate with the inspectors to ensure that the inspectors have direct access to the study-related



source data and source documents.

10.1.9 Data Processing and Record Retention

10.1.9.1 Data Collection and Management Responsibilities

The purpose of clinical data management is to collect and clean of true and complete study data in a timely manner, and to submit the standardized data in the database to the statistical analysis team for use. Data collection is mainly based on the EDC system, and data entry will be completed by the investigator or a personnel designated by the investigator. Data cleaning and check of entered data will be performed by professional data manager/medical monitor in accordance with the data management plan/medical monitoring plan. In case data issues are identified, they will be submitted in the form of queries in the EDC system, which shall be answered by the investigator or his/her authorized personnel. In addition, the project operation staff will be responsible for the comparison between the data entered in the EDC system and the original medical records, and any discrepancies found will also be submitted using the same method as that used for submitting queries and answered or modified by the investigator or his/her authorized personnel.

In addition, the scope of data management also includes study data outside the EDC system, including but not limited to: central laboratory test results, central imaging diagnosis results, even including the consistency comparison and verification of data stored in the working system of other clinical project function sections and the data in the EDC system.

Data safety management will be achieved based on three-level control regime of EDC account authorization control, database data backup management and disaster management of company data server to ensure the safety of data obtained from the clinical trial projects.

All the key links in the data management system will be documented accordingly, including but not limited to the data management plan (DMP), blank case report forms, annotated case report forms, data verification plans, and data management reports.

10.1.9.2 Retention of Study Records

All the study materials and data of this study will be archived and managed at the study sites, sub sites, analytical testing units, statistical and data management units, respectively, and the study data will be preserved for at least 2 years after the production approval letter of the investigational product is obtained. Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. will preserve the study data for at least 5 years after the approval letter for the investigational product is obtained. All the materials and data of this clinical study are the properties owned by Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd., and the documents obtained by the study sites cannot be damaged before the prior written agreement is reached between the study site and the Sponsor. The Sponsor must be consulted in advance if the investigator decides to provide the master study file to any third party or to transfer the file to another location. The master study



file cannot be provided to any third party in any form and by any institution or individual without the prior written permission of the Sponsor, except at the request of the national regulatory authority.

10.1.10 Protocol Deviation

A protocol deviation is defined as any noncompliance with the requirements of the study protocol, the Good Clinical Practice, or the operating manual. Noncompliance may arise from subjects, the investigator, or the staff of the test facility. Corrective actions should be taken to address the deviations and completed in a timely manner.

10.1.11 Study Results Publication and Data Sharing Policy

This study is a clinical study of a drug and should be registered and study data should be submitted in accordance with relevant regulatory requirements.

Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. and the CRA monitors will have access to the study data for monitoring purposes. When relevant personnel not directly involved in the conduct of the study need to audit the data or the data are inspected by the regulatory authorities, the study site should provide the data in a timely manner.

Regarding the publication of the results of this study, whether in part or in whole, consent should be obtained from Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd. The investigator are not allowed to publicate or publish any data and information related to the study without the written authorization from Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

10.2 Other Considerations

Not applicable.

10.3 History Record of Protocol Amendments

- If revisions are warranted after the protocol has been approved by the ethics committee, a statement of protocol amendments should be prepared with signature of the principal investigator, and the protocol can only be revised after obtaining the approval from the Sponsor.
- Any protocol amendment should not be implemented without the review by or file with the ethics committee.
- Revision record:

Version change from V1.0/20211217 to V2.0/20220415		
Section	Description of changes	Rationale
Title and full text	Version No. and version date was changed	Version update
1.1 Abstract, 1.2 Study Flow Chart, 1.3 Study Schedule,	The randomization should be completed within "2 workdays" prior to the first dose, and the chemotherapy regimens should be determined by	The time of randomization, the time to determine the chemotherapy regimens, and the

6.1.2 Dose and Administration and 6.6 Study Procedures	the investigator before randomization. The dosage of gemcitabine was defined as 1000mg/m ² , and the dosing cycle Q4W was modified to Q3W.	dosage of gemcitabine were determined, and the dosing cycle for gemcitabine was revised considering the recovery time of toxicity.
1.3 Study Schedule	PET-CT is acceptable for bone scans.	Updated bone scans based on clinical operations.
1.3 Study Schedule, 6.6.2 Visit during Treatment Period	The relevant description for calculating dosage based on body weight was revised.	Updated statements for clarity.
1.3 Study Schedule, 6.6.2 Visit during Treatment Period	Quality of life score should be performed “before any clinical procedure”.	Clarified time points for quality of life assessment.
1.3 Study Schedule, 6.6.2 Visit during Treatment Period	Hematology for test group will be performed weekly of the first 2 cycles, and the frequency of laboratory tests could be increased based on the patients' conditions by the investigator.	Considering the frequent occurrence of hematological AEs for SKB264, the hematology tests of the first 2 cycles were added, and investigators could increase the frequency of tests based on subsequent circumstances.
1.3 Study Schedule, 6.6.2 Visit during Treatment Period and 6.6.3 End of Treatment Visit	The time window of pregnancy test and recommended test items during the treatment period were defined more clearly.	Updated pregnancy test based on clinical operations.
1.1 Abstract, 5.1 Inclusion Criteria, 5.2 Exclusion Criteria	The inclusion criteria were adjusted, mainly by deleting the description of intolerable regimens included as one of the prior therapies.	Updated inclusion criteria considering the efficacy of study drug is related to the number of chemotherapy regimens the patients have previously received.
1.1 Abstract, 1.2 Study Flow Chart, 1.3 Study Schedule, 4.1 Overall Design, 6.1 Study Drug Administration, 6.6 Study Procedures, 8.1 Efficacy Assessment	PD assessed by the investigator needs to be confirmed by IRC.	Consider how to maximize patients' imaging results, reduce bias, and prevent patients from prematurely receiving new antitumor therapies.
1.1 Abstract, 6.1.2 Dose and	Continuing treatment after PD was added.	From an ethical point of view.

Administration		
2.1 Study Rationale, 4.2 Rationale for Study Design	Updated background.	Updated background according to the latest CSCO breast cancer.
2.1 Study Rationale, 2.2.3 Clinical Studies, 2.3.1 Known Potential Risks, 2.3.2 Known Potential Benefits	Updated clinical efficacy and safety data.	Updated clinical efficacy and safety data, the DCO is the latest.
Full text	Revised the dosage of SKB264 from 4mg/kg to 5mg/kg.	Revised the dosage of SKB264 according to the project strategy.
4.3 Rationale for Dose Selection	Revised the rationale for dose selection.	Revised the rationale for dose selection synchronously.
6.1.3 Dose Modification and Drug Discontinuation Criteria	The delay of dosing should not exceed “3 weeks”, and the dose modification and discontinuation criteria were modified.	The dose modification scheme was modified based on the safety characteristics of SKB264.
1.1 Abstract, 9.2 Sample Size Estimation, 9.4 Statistical Assumptions	Improved the basis of sample size calculation and the detailed provisions of the test in the order of (PFS→OS→ORR).	Updated the basis of sample size calculation and the detailed provisions of the test in the order of (PFS→OS→ORR).

Version change from V2.0/20220415 to V2.1/20230618

Section	Description of changes	Rationale
Title and full text	Version No. and version date was changed	Version update
1.1 Abstract, 1.2 Study Flow Chart, 1.3 Study Schedule, 6.1.2 Dose and Administration, 6.2.4 Preparation and 6.6.2 Visits during Treatment Period	The route of administration of eribulin was revised to intravenous infusion.	The route of administration of eribulin was revised based on actual circumstance.
11.1 Abstract, 5.2 Exclusion Criteria	It is clear that the excipients of SKB264 include polysorbate-20. Criteria were added to exclude subjects with a history of severe hypersensitivity to monoclonal antibodies.	Refined exclusion criteria.
1.3 Study Schedule, 6.1.2 Dose and Administration and 6.6.2 Visits during Treatment Period	① For safety considerations, refined the infusion and monitoring regulations of SKB264, and strictly regulated the infusion duration, vital signs and adverse reaction monitoring time.	1) Revised the infusion regimen of SKB264 based on clinical safety data. 2) Updated the requirements for premedications to reduce the risk of anaphylactic reaction.

	② The premedications before dosing of SKB264 were refined, including the drugs that should be used and recommended to be used, the dosing time of the drugs, and the recommendations for the drugs for subjects at high risk.	
2.3.1 Known Potential Risks	Updated clinical safety data of infusion-related reactions.	Updated risk of infusion-related reactions.
6.1.3 Dose Modification and Drug Discontinuation Criteria	Combined with clinical practice, it was clear that dosing should be suspended before recovery to ≤ grade 2. In cases where the same Grade 3 toxicity or Grade 4 neutropenia occurs again, a dose reduction is required.	Revised dose modification and discontinuation criteria for SKB264.
6.1.4 Infusion-Related Reactions	Added infusion-related reaction dose modification and treatment guidelines for SKB264.	Added infusion-related reaction dose modification and treatment guidelines for SKB264.
8.4.1 Definition of Adverse Events, 8.4.2 Collection, Recording and Description of Adverse Events/Serious Adverse Events/ Adverse Events of Special Interest, 8.4.3 Management of Serious Adverse Events/Adverse Events of Special Interest	① Added the definition of AESIs. ② Added collection, record, follow-up, reporting and other management provisions for AESIs.	Added the definition of AESIs and related management provisions combining clinical data.
8.4.5 Overdose	Added the definition of overdose, treatment for overdose, and procedures for reporting overdose.	Related regulations and reporting requirements for overdose were added in accordance with clinical practice.

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Appendices

Annex 1: Principal Study Site and Sponsor

Project Title	A randomized, controlled, open-label, multi-center phase III study of SKB264 for injection versus chemotherapy of the physician's choice in patients with unresectable locally advanced, recurrent or metastatic triple-negative breast cancer who have failed second-line or above prior standard of care
Clinical Study Director	
Sponsor's Director	

Annex 2:Abbreviation

ADA	anti-drug antibody
ADC	antibody-drug conjugate
AE	adverse event
AESI	adverse event of special interest
ALB	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BIL	bilirubin
BLD	occult blood
BS	biomarker set
BUN	blood urea nitrogen
Ca	calcium iron
Ccr	creatinine clearance rate
cGy	centigray
Cl	chloride ion
C _{max}	maximum observed plasma concentration
C _{max,ss}	steady-state maximum observed plasma concentration
C _{min}	minimum blood plasma concentration
C _{min,ss}	steady-state minimum blood plasma concentration
CNS	central nervous system
CR	complete response
CRE	creatinine
CSCO	Chinese Society Of Clinical Oncology
CT	computed tomography
CTCAE	common terminology criteria adverse events
CYP3A4	cytochrome P450 3A4
DCR	disease control rate
DMP	data management plan
DNA	deoxyribonucleic acid
DOR	duration of response
ECHO	echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ECT	emission computed tomography
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
EOT	end of treatment
ER	estrogen receptor
FAS	full analysis set
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GI	gastrointestinal

GLU	glucose
GMP	Good Manufacture Practice of Medical Products
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCG- β	human chorionic gonadotrophin- β
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HGB	hemoglobin
HIV	human immunodeficiency virus
HR	hazard ratio
IARC	International Agency for Research on Cancer
ICE	Intercurrent event
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMGS	immunogenicity set
INR	international normalized ratio
IRC	Independent Review Committee
K	potassium
KET	ketone
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	lactate dehydrogenase
LVEF	left ventricular ejection fraction
LYM	lymphocyte count
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulation Activities
Mg	magnesium
MRI	magnetic resonance imaging
Na	sodium iron
NCI	National Cancer Institute
NEUT	neutrophil count
NMPA	National Medical Products Administration
ORR	objective response rate
OS	overall survival
P	phosphorus
PD	progressive disease
PFS	progression-free survival
PH	hydrogen-ion concentration - acid/alkaline
PK	pharmacokinetics
PKCS	pharmacokinetics concentration set
PKPS	pharmacokinetics parameter set
PLT	platelet
PPS	per protocol set
PR	partial response
PR	progesterone receptor
PRO	proteinuria

PT	prothrombin time
PT	preferred term
QTc	QT interval corrected for heart rate
RBC	red blood cell count
RDE	recommended dose of extension
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RP2D	recommended phase 2 dose
SAE	serious adverse event
SD	stable disease
SD	Standard Deviation
SG	specific gravity
SOC	system organ class
SOP	standard operating procedure
SS	safety set
TAB	total antibody
TBIL	total bilirubin
T _{max}	time of maximum observed plasma concentration
TNBC	triple-negative breast cancer
TP	total protein
TROP2	trophoblast cell-surface antigen 2
TTR	time to response
t _{1/2}	(terminal phase elimination) half-life
UA	uric acid
URO	urobilinogen
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	upper limit of normal
WBC	white blood cell count
WHO	World Health Organization

Annex 3: Definition of Women of Childbearing Potential, Contraceptive Requirements

1. Definition of Women of Childbearing Potential

A woman of childbearing potential is defined as any woman who has experienced menarche, has not undergone successful sterilization (i.e., bilateral tubal ligation, bilateral oophorectomy, or total hysterectomy) and has not been postmenopausal.

2. Contraceptive Requirements

- 1) From signing the informed consent form until 6 months after the last dose, the subject and his/her sexual partner must agree to adopt one of the following measures:
 - Total abstinence from sexual activities. Periodic abstinence (e.g., calendar method, ovulation method, symptothermal method, post-ovulation method) is not allowed;
 - Or use condoms correctly;
 - Or correctly use one of the contraceptive methods listed below:
 - Intrauterine device (IUD) with an annual failure rate < 1%
 - Tubal sterilization;
 - Male subjects or male partners have undergone vasectomy.
- 2) In addition to the above contraceptive measures, subjects and their sexual partners may also use the following contraceptive measures within 6 months after the last dose:
 - Subcutaneous implants and injections containing hormones;
 - Compound oral contraceptives;
 - Compound transdermal patches.
- 3) Male subjects must agree to refrain from donating sperm to females from the date of signing the informed consent form until 6 months after the last dose.

Annex 4: Calculation of Creatinine Clearance

Calculation of creatinine clearance using Cockcroft-Gault formula

Please select the formula correctly according to the different units used in serum creatinine test:

If serum creatinine concentration is calculated in mg/dl

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{body weight})}{72 \times \text{serum creatinine concentration}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{body weight})}{72 \times \text{serum creatinine concentration}}$$

If serum creatinine concentration is calculated in $\mu\text{mol/L}$:

$$\text{Male creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times (\text{body weight})}{0.818 \times \text{serum creatinine concentration}}$$

$$\text{Female creatinine clearance (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{body weight})}{0.818 \times \text{serum creatinine concentration}}$$

Note: age is expressed in year, and bodyweight in kg.

Annex 5: ECOG Performance Status Grading Scale

ECOG Grading Scale (Corresponding to Karnofsky Scale)

ECOG Score	Karnofsky score	Patient Status
0 score	90 to 100 scores	Fully active, able to carry on all pre-disease performance without restriction.
1 score	70 to 80 scores	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2 scores	50 to 60 scores	Ambulatory and capable of all selfcare but unable to carry out any work activities. Ambulatory for up and about more than 50% of waking hours.
3 scores	30 to 40 scores	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4 scores	10 to 20 scores	Completely disabled; Cannot carry on any selfcare; Totally confined to bed or chair.
5 scores	0 score	Death.

Annex 6: Response Evaluation Criteria in Solid Tumors RECIST Version 1.1

1. Measurability of tumour at baseline

1.1 Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT

or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by methods of measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new

lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilisation of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumour response evaluation

2.1 Assessment of overall tumour burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2 Baseline documentation of ‘target’ and ‘non-target’ lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm×30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

2.3 Response criteria

2.3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the ‘sum’ of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become ‘too small to measure’. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being ‘too small to measure’. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the

measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions ‘fragment’, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the ‘coalesced lesion’.

2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve ‘unequivocal progression’ on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest ‘increase’ in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of

change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
 If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
 If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
 If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the ‘best overall response’.

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table a on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table b is to be used.

Table a Time point response: patients with target (+/–non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR

Target lesions	Non-target lesions	New lesions	Overall response
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR= complete response, PR= partial response, SD= stable disease, PD= progressive disease, NE=inevaluable

Table b Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR= complete response, PD= progressive disease, NE= inevaluable

*Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at

second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response is required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table c.

Table c Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR= complete response, PR= partial response, SD= stable disease, PD= progressive disease, NE= inevaluable

a: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables a-c.

Conditions that define ‘early progression, early death and inevaluability’ are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5 Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If ‘time to an event’ (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory measurement/duration of response

2.6.1 Confirmation

In non-randomised trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is



an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.



Annex 7: Examples of Representative Traditional Chinese Medicine

Preparations with Anti-tumor Effects

Huazheng Huisheng Tablets, Brucea Javanica Oil Soft Capsules, Zhemu Syrup, Compound Cantharidi Capsules, Cinobufacini Tablets, Cinobufacini Capsules, Cinobufacini Injection, Chansu Injection, Kangai Injection, Kanglaite Injection, Kanglaite Soft Capsules, Zhongjiefeng Injection, Zhongjiefeng Tablets, Aidi Injection, Awei Huapi Gao, Kang'aiping Pills, Xiao'aiping Tablets, Xiao'aiping Injection, Xiao'aiping Oral Liquid, Pingxiao Capsules, Pingxiao Tablets, Shendan Sanjie Capsules, Ankangxin Capsules, Bosheng Aining, Kanglixin Capsules and Cidan Capsules.

**Annex 8: Examples of Representative CYP3A4 inhibitors and inducers**

Strong inhibitors of CYP3A4	Boceprevir, Cobicistat, Danoprevir and Ritonavir, Elvitegravir and Ritonavir, Grapefruit juice, Indinavir and Ritonavir, Itraconazole, Ketoconazole, Lopinavir and Ritonavir, Paritaprevir and Ritonavir and (Ombitasvir and/or Dasabuvir), Posaconazole, Ritonavir, Saquinavir and Ritonavir, Telaprevir, Tipranavir and Ritonavir, Telithromycin, Troleandomycin, Voriconazole, Clarithromycin, Idelalisib, Nefazodone, Nelfinavir
Strong inducers of CYP3A	Apalutamide, Carbamazepine, Enzalutamide, Mitotane, Phenytoin, Rifampin, St. John's wort

Annex 9: EORTC QLQ-C30, version 3

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your first letter: _____

Date of birth: _____(YYYY)_____(MM)_____(DD)

Date of today: _____(YYYY)_____(MM)_____(DD)

	Not at All	A Little	Quite a Bit	Very Much
1、 Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2、 Do you have any trouble taking <u>a long walk</u> ?	1	2	3	4
3、 Do you have any trouble taking <u>a short walk</u> outside of the house?	1	2	3	4
4、 Do you need to stay in bed or a chair during the day?	1	2	3	4
5、 Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	Not at All	A Little	Quite a Bit	Very Much
6、 Were you limited in doing either your work or other daily activities?	1	2	3	4
7、 Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8、 Were you short of breath?	1	2	3	4
9、 Have you had pain?	1	2	3	4
10、 Did you need to rest?	1	2	3	4
11、 Have you had trouble sleeping?	1	2	3	4
12、 Have you felt weak?	1	2	3	4
13、 Have you lacked appetite?	1	2	3	4
14、 Have you felt nauseated?	1	2	3	4
15、 Have you vomited?	1	2	3	4
16、 Have you been constipated?	1	2	3	4
17、 Have you had diarrhea?	1	2	3	4
18、 Were you tired?	1	2	3	4
19、 Did pain interfere with your daily activities?	1	2	3	4
20、 Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21、 Did you feel tense?	1	2	3	4
22、 Did you worry?	1	2	3	4



	Not at All	A Little	Quite a Bit	Very Much			
23、 Did you feel irritable?	1	2	3	4			
24、 Did you feel depressed?	1	2	3	4			
25、 Have you had difficulty remembering things?	1	2	3	4			
26、 Has your physical condition or medical treatment interfered with your family life?	1	2	3	4			
27、 Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4			
28、 Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4			
For the following questions please circle the number between 1 and 7 that best applies to you:							
29、 How would you rate your <u>overall health</u> during the past week?	Very poor					Excellent	
	1	2	3	4	5	6	7
30、 How would you rate your <u>overall quality of life</u> during the past week?	Very poor					Excellent	
	1	2	3	4	5	6	7

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Annex 10: Hy's Law

Hy's Law cases are defined as follows:

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
- Among trial subjects showing such AT elevations, often with ATs much greater than $3 \times \text{ULN}$, one or more also show elevation of serum TBL to $>2 \times \text{ULN}$, and no evidence of cholestasis (e.g. elevated serum ALP).
- No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Once the above 3 conditions are confirmed, a series of tests are required to rule out any other causes of liver damage. First, the initial abnormal laboratory tests must be confirmed. Then rule out a viral cause. Abdominal ultrasound and/or CT scan may be performed. In this case, consult a hepatologist should be considered. The treatment will be suspended until the investigation is completed.

According to relevant guidelines, ALT, AST, ALP, and TBL should be repeatedly tested every 2 to 4 weeks for several months. If ALT levels at certain checkpoints in the study were elevated to $\geq 3 \times \text{ULN}$, which should be reviewed every 2 to 3 days.

STATISTICAL ANALYSIS PLAN

A Randomized, Controlled, Open-label, Multi-center Phase III Study of SKB264 for Injection Versus Chemotherapy of the Physician's Choice in Patients With Unresectable Locally Advanced, Recurrent or Metastatic Triple-negative Breast Cancer Who Have Failed Second-line or Above Prior Standard of Care

SKB264-III-03

Experimental Drug:	SKB264 for injection
Control Drugs:	Eribulin, Capecitabine, Gemcitabine, Vinorelbine
Indication:	Triple-Negative Breast Cancer
Stage:	Phase 3
Type:	Statistical analysis plan
Version:	2.0
Finalized date:	July 10, 2023

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Revision History			
Revision	Date	Description of Change	Initial Version
1.0	December 22, 2022	NA	-
2.0	July 10, 2023	Below is a detailed list of all notable changes: Study object: The definition of Visceral metastasis was updated. The definitions of liver metastasis and prior lines of therapy were added. The calculation of body mass index was added. The summary of pre-treatment before administration was added. The analysis dataset based on FAS of prior and concomitant medications, prior and concomitant non-drug therapy, radiotherapy during treatment, and subsequent anti-tumor therapy based on was updated to SS. PK: The definition of PKCS was updated, “if the blood concentration of the subject before the first dose is greater than 5% of the first cycle C_{max}, the subject’s data will be excluded from PKCS.” is added into the definition. The content of pharmacokinetics analysis was updated, and the restriction on statistical description of PK data was added. [REDACTED] [REDACTED] [REDACTED] Safety analysis: The definition and analysis of AEFI were adjusted. The definition of infusion-related reactions/hypersensitivity reactions was updated. The summary of echocardiography was deleted. The listings of safety endpoints of abnormal clinically significant were updated. Immunogenicity: The immunogenicity analysis is updated, and the analysis of the correlation between efficacy, safety and PK was updated.	1.0 (December 22, 2022)

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List of Abbreviations

Abbreviation	Full Term
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALP	Alkaline Phosphate
ALT	Alanine transaminase
AST	Aspartate transferase
ATC classification	Anatomical Therapeutic Chemical classification
BQL	Below the Quantification Limit
BS	Biological Sample
BSA	Body Surface Area
C _{max}	Maximum Concentration
C _{min}	Minimum Concentration
CR	Complete Remission
DCR	Disease Control Rate
DOR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ER	Estrogen Receptor
FAS	Full Analysis Set
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
ICE	Immediate Consequent Event
IMGS	Immunogenicity Set
IRC	Independent Review Committee
IRT	Interactive Response Technology
LLOQ	Lower Limit of Detection
LVEF	Left Ventricle Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
Nab	Neutralizing Antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
OS	Overall Survival
ORR	Objective Response Rate
PD	Progression of Disease
PFS	Progression Free Survival
PK	Pharmacodynamics
PKCS	Pharmacodynamics Concentration Set
PT	Preferred Term
PN	Pharmaceutical Name
RECIST	Response evaluation criteria in solid tumors
PR	Partial Response

Rac_C _{max}	Observed Accumulation Ratio for C _{max}
SAE	Serious Adverse Events
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Classification
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TRAE	Treatment Related Adverse Event
TROP2	Tumor-associated calcium signal transducer 2

1. Study Overview

This Statistical Analysis Plan (SAP) describes in detail the statistical analyses and data processing principles of the study entitled “*A Randomized, Controlled, Open-label, Multi-center Phase III Study of SKB264 for Injection Versus Chemotherapy of the Physician's Choice in Patients With Unresectable Locally Advanced, Recurrent or Metastatic Triple-negative Breast Cancer Who Have Failed Second-line or Above Prior Standard of Care*”, which is conducted by Sichuan Kelun Biotech Biopharmaceutical Co., Ltd with Protocol No. of SKB264-III-03.

The preparation for this statistical analysis plan is based on the SKB264-III-03 clinical study protocol version 2.1 (June 18, 2023).

1.1 Study Objectives

Primary Objective

To compare the efficacy of SKB264 for injection versus chemotherapy of the physician's choice in patients with unresectable locally advanced, recurrent or metastatic TNBC who have failed second-line or above prior standard of care based on progression-free survival (PFS).

Secondary Objectives

- To compare the overall survival (OS), objective response rate (ORR), and duration of response (DOR) of SKB264 for injection to chemotherapy of the physician's choice in patients with locally advanced, recurrent, or metastatic TNBC.
- To assess the safety of SKB264 for injection chemotherapy of the physician's choice.
- To assess the pharmacokinetics (PK) profile of SKB264 for injection;
- To assess the immunogenicity of SKB264 for injection;
- To assess the quality of life of patients with locally advanced, recurrent, or metastatic TNBC treated with SKB264 for injection versus chemotherapy of the physician's choice.
- To assess the relationship between tumor tissue biomarker (TROP2) and efficacy.

1.2 Study Endpoints

1.2.1 Primary Study Endpoints

The progression-free survival (PFS) assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

1.2.2 Secondary Study Endpoints

Efficacy

- PFS assessed by the investigator per RECIST 1.1.
- ORR, DOR, DCR, and TTR assessed by IRC and the investigator per RECIST 1.1, respectively;
- OS;
- [REDACTED]

Safety

- Incidence and severity of adverse events (AE) and serious adverse events (SAE) (as per CTCAE 5.0), abnormal laboratory results, etc.

Pharmacokinetics

- PK parameters: maximum concentration ($C_{\max}$), minimum concentration ($C_{\min}$), and accumulation ratio calculated based on $C_{\max}$ ($R_{ac_C_{\max}}$).

Immunogenicity

- ADA test results and titer values.

[REDACTED]

[REDACTED]

1.3 Study Design

1.3.1 Overall Design

This is a randomized, controlled, open-label, multicenter study, in which 254 patients with unresectable locally advanced, recurrent, or metastatic TNBC who have failed second-line or above prior standard of care are planned to be enrolled. Eligible patients will be randomized in a 1:1 ratio to the experimental group and control group, and stratified by the number of prior lines of therapy received (2 to 3 vs. > 3); and presence or absence of liver metastases (yes vs. no).

Patients in the experimental group will be given SKB264 at a dose of 5 mg/kg by infusion on Days 1 and 15 of each cycle every 4 weeks until in the absence of clinical benefit, intolerable toxicity, or patient requesting to discontinue the study treatment. Patients in the control group will be given any of the chemotherapy choices by the physician (Eribulin, Capecitabine, Gemcitabine, Vinorelbine).

Efficacy will be assessed by imaging examinations every 6 weeks (± 1 week) from the start of the first dose of study treatment until disease progression (confirmed by IRC), or

every 12 weeks (± 1 week) if the patient has not progressed after receiving 12 months of study drug. Imaging examinations will be performed as scheduled regardless of dose delay or modification. For patients who discontinue treatment for reasons other than disease progression or due to disease progression assessed by investigator (but not confirmed by IRC), the assessment should be repeated at the EOT visit if the last imaging examination is more than 4 weeks away, and the subsequent imaging examinations should be performed as scheduled as far as possible until disease progression (confirmed by IRC), initiation of new anti-tumor therapy, patient requests to discontinue the study treatment, loss to follow-up, or death.

A detailed flow chart of the clinical trial is given in the study schedule of the protocol.

1.3.2 Determination of Sample Size

In this study, a group sequential design will be used, and the sample size will be calculated using the gsDesign package of R software (version 4.1.1).

In this study, 254 patients are planned to be enrolled and they will be randomized in a 1:1 ratio to the experimental group and the control group. The expected median PFS of the control group is approximately 2 months. Assuming that the hazard ratio (HR) of PFS between the experimental group and the control group is 0.60, and the PFS follows an exponential distribution, then for 183 PFS events (PD or death), there will be 93% power at a one-sided test level of 0.025 to infer that the experimental group is superior to the control group. An interim analysis of the PFS superiority test is planned for this study when the number of PFS events reaches 65% of the total target number, i.e., when there are 119 PFS events. To control the type I errors, the nominal test level alpha for the interim and final analyses of PFS is set to one-sided 0.0066 and one-sided 0.0227 according to the O'Brien-Fleming spending function, respectively.

For the secondary endpoint OS, the expected median OS time of the control group is approximately 7.3 months. Assuming that the hazard ratio (HR) of OS between the experimental group and the control group is 0.65, and the OS follows an exponential distribution, then for 184 OS events (deaths), there will be 83% power at a one-sided test level of 0.025 to infer that the experimental group is superior to the control group. The enrollment duration in this study is expected to be 15 months, and the last patient is followed up for the final analysis of OS for approximately 15 months after the first dose, then 228 patients are required to be enrolled. Considering the dropout rate of 10%, a total of approximately 254 patients (127 in the experimental group and 127 in the control group) are required to be enrolled. An interim analysis of the OS superiority test is planned for this study at the final analysis of PFS (approximately 102 OS events). To control the type I errors, the alpha for the superiority test of OS is set to be 0.0001. The nominal test level alpha (total alpha is one-sided 0.0249) for the interim and final analyses of OS will be set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses.

Based on phase I clinical data, assuming that the experimental group can achieve an ORR of 33%, and assuming that the control group can achieve an ORR of approximately 6% based on historical study data. 114 patients of each arm (in total 228 patients) would achieve 99% power to infer a statistically significant difference in ORR between the

experimental group and the control group by applying Fisher's Exact test, based on a type I error alpha of one-sided 0.025.

1.3.3 Randomization and Blinding

The patients will be randomized using a stratified block randomization method. Stratification factors include the number of prior lines of therapy a patient has received (2~3 vs >3), the presence of liver metastases (yes vs no). Eligible subjects after the screening will be randomly assigned in a 1:1 ratio to the experimental group or control group.

This is an open label study complying with the *Guideline on Blinding in Drug Clinical Trials(Draft for Comment)*. To effectively reduce potential bias, the following procedures are implemented in this study:

1. PFS assessed by the blinded IRC is to be the primary endpoint.
2. To avoid artificial decisions on patient assignment by investigators being informed of patient groups in advance; the random assignment table will be generated and securely stored by random statisticians, and the patients will be randomized according to their screening order using the IRT (Interactive Response Technology) system.
3. Strictly control EDC access rights. Keep blind to the participants involved in the patient enrollment and the data analysts.
4. Analysis or summaries generated through randomized treatment assignment and actual treatment received will be strictly limited before the final analysis of PFS except that IDMC or IST (independent statistician team) analyzes or summaries according to the charter of IDMC.

An interim analysis of PFS superiority testing is planned for this study when there are 119 PFS events. After communication with CDE, the sponsor was agreed to submit a pre-new drug application (Pre-NDA) based on the results of the interim efficacy analysis of the primary endpoint PFS. To avoid potential bias when the sponsor submits a pre-NDA, the sponsor will set up an unblinding team to be responsible for the application when the study gets a statistically significant conclusion by IDMC based on PFS assessed by IRC. The blinding team continues to comply with the *Guideline on Blinding in Drug Clinical Trials (Draft for Comment)* to implement the study. To prevent the blinding team from accessing the unblinding documents, the "firewall" is set up between the blinding and unblinding team, see *Data Integrity Protection Plan* for details.

2. Estimands

In this study, 1 primary estimand and 3 secondary estimands will be established considering concomitant events according to the study objectives, and the details are presented in the table below.

Table 1 Estimands

Attribute	Primary estimand (PFS assessed by	Secondary estimand (ORR)	Secondary estimand (DCR)	Secondary estimand
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	ICR)			(OS)
Population	Patients with unresectable locally advanced, recurrent or metastatic TNBC who have failed second-line or above prior standard of care.			
Treatment	SKB264 for injection or Chemotherapy of the Physician's Choice in Patients			
Variable	PFS is defined as the time from randomization to disease progression or death, whichever occurs first. PFS is assessed by the IRC per RECIST 1.1	ORR is defined as the proportion of patients with complete response (CR) or partial response (PR) as the best overall response assessed by IRC per RECIST 1.1.	DCR is defined as the proportion of patients with CR, PR, or stable disease (SD) as the best overall response assessed by IRC per RECIST 1.1.	OS is defined as the time from randomization to death due to any cause.
summarized at population level	Conditional hazard ratio (HR) and 95%CI based on covariate adjustment	ORR rate difference and 95%CI based on covariate adjustment	DCR rate difference and 95%CI based on covariate adjustment	HR and 95%CI based on covariate adjustment
Intercurrent event (ICEs) and management strategies	ICE1: use of the protocol-prohibited anti-tumor therapy prior to disease progression. Hypothetical strategy: the date of the last valid imaging examination performed prior to the initiation of the prohibited anti-tumor therapy should be censored. ICE2: premature discontinuation of treatment due to intolerability and clinical progression. Treatment policy strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy,	ICE1: use of the protocol-prohibited anti-tumor therapy. While on treatment strategy: the efficacy evaluation results after the use of the prohibited anti-tumor therapy should be ignored. ICE2: premature discontinuation of treatment due to intolerability and clinical progression. Treatment policy strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to follow-up, or death.	ICE1: use of the protocol-prohibited anti-tumor therapy during study treatment. While on treatment strategy: the efficacy evaluation results after the use of the prohibited anti-tumor therapy should be ignored. ICE2: premature discontinuation of treatment due to intolerability and clinical progression. Treatment policy strategy: collection and analysis of efficacy data should be continued until radiologically confirmed disease progression, initiation of new anti-tumor therapy, withdrawal from the study at the patient's request, loss to	ICE1: use of the protocol-prohibited anti-tumor therapy. Treatment policy strategy: the impact of the prohibited anti-tumor therapy should be disregarded, and collection and analysis of efficacy data should be continued until lost to follow-up or death. ICE2: premature discontinuation of treatment due to intolerability and inadequate response. Treatment policy strategy: the impact of study treatment discontinuation should be

	withdrawal from the study at the patient's request, loss to follow-up, or death. ICE3: death (no disease progression observed). While on treatment strategy: the efficacy evaluation results prior to death should be collected and analyzed. Composite variable strategy: death should be included in the definition of PFS.	follow-up, or death. ICE3: death (no disease progression observed). While on treatment strategy: the efficacy evaluation results prior to death should be collected and analyzed.\	disregarded, and collection of OS data should be continued.
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3. General Specifications for Statistical Analyses

3.1 General Considerations

All statistical analyses will be conducted using SAS Version 9.4 or higher.

In this study, data will be summarized using statistical descriptive methods according to general principles unless otherwise specified. Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation, minimum, maximum, and median). Categorical data will be described using the patient count and percentage in each category. If applicable, geometric mean and coefficient of variation will be used to analyze blood concentration and PK parameters.

In the study, unless otherwise specified, the minimum and the maximum values will be displayed to the same level of precision as the data collected. Mean and quartile values will be displayed to one level of precision greater than the data collected. Standard

deviation/standard error values will be displayed to two levels of precision greater than the data collected. All statistics should contain a maximum of three decimal places. Percentage (%): one decimal place is kept, and the second place is rounded, e.g.: 52.34% is presented as 52.3%, and 0% is directly presented as 0.

3.2 Analysis Datasets

- Full analysis set (FAS): including all subjects who are randomized according to the ITT principle. The FAS will be used for baseline and efficacy analyses.
- Safety set (SS): including all subjects who have received at least one dose of study treatment and have safety evaluation data. SS will be used for safety analysis.
- Pharmacokinetics concentration set (PKCS): including all subjects who received at least one dose of study treatment and have at least 1 drug plasma concentration measurement during the study. The PKCS will be used for the analysis of plasma concentrations. If the blood concentration of a subject prior to the first dose is greater than 5% of the first cycle C_{max} , then the subject's data

should be excluded from the PKCS. The PKCS will be used for analysis of plasma concentration.

- Immunogenicity set (IMGS): including all subjects who have received at least one dose of study treatment and have at least one post-baseline immunogenicity measurement during the study.
- Biomarker set (BS): including all patients who have received at least one dose of study treatment and have at least one biomarker during the study.

3.3 Multicenter Study

Data from all centers will be integrated for analysis, and centers will not be considered as a covariate in the statistical models.

3.4 Multiple Comparisons/Multiplicity

In the study, an interim analysis for superiority testing will be performed for the primary estimand of PFS assessed by IRC. In order to control the overall type I error rate at 0.025 (one-sided), the nominal test level of alpha for the interim analysis and final analysis will be set at one-sided $\alpha=0.0066$ and one-sided $\alpha=0.0227$ using the O'Brien-Fleming spending function, respectively. The nominal test level alpha for the interim and final analyses of PFS will be set according to the O'Brien-Fleming spending function based on the number of PFS events for interim and final analyses if the actual number of PFS events is different from the number planned.

To control the type I error, the primary estimand of PFS assessed by the IRC and the secondary estimands of objective OS and ORR will be tested sequentially (PFS→OS→ORR). An interim analysis of PFS superiority testing is planned for this study at the time of 119 PFS events assessed by IRC. If PFS was tested unsuccessfully at the interim analysis, the final analysis of PFS was performed at the time of 183 PFS events assessed by IRC. If the PFS test was successful, OS would be compared between the two groups.

An interim analysis for OS superiority testing will be performed at the final analysis of PFS or at the time of approximately 102 OS events. If OS is tested unsuccessfully at the interim analysis, the final analysis of OS is performed at the time of 184 OS events (deaths). To control the type I error in the OS test, the α for testing OS at the PFS interim analysis is set to 0.0001. The nominal test level α (total α is one-sided 0.0249) for the interim and final analyses of OS is set according to the O'Brien-Fleming spending function based on the number of OS events for interim and final analyses.

3.5 Subgroup Analyses

Subgroup analyses will be conducted in the following subgroups of the PFS, OS and ORR. A forest plot of these endpoints will be generated in the subgroups. If the number of patients in one subgroup is less than 10% of the FAS's patients (<25 patients), statistical analyses will not be performed for the subgroup, and a forest plot will not be generated.

- Age group (<65 vs ≥65)

- ECOG (0, 1)
- Prior lines of therapy: (2-3, >3), based on IRT
- Prior lines of therapy: (2-3, >3), based on EDC
- Presence of liver metastasis at baseline (Yes, No), based on IRT
- Presence of liver metastasis at baseline (Yes, No), based on EDC
- Original diagnosis TNBC (Yes, No)
- Previous treatment with PD-1 or PD-L1 inhibitors (Yes, No)
- Lymph node metastasis (Yes, No)
- Visceral metastasis (Yes, No)
- HER2 expression at enrollment (0, low expression)

Subgroup analyses will be conducted for some TEAEs by the following subgroups:

- Age group (<65 vs ≥65)
- ECOG (0, 1)

3.6 Data cut-off Specification

Multiple analyses will be conducted in this study during the process of the trial, including first-time IDMC safety data analysis, PFS interim analysis, and PFS final analysis/OS interim analysis. In the study, the data cut-off specification will be used to process the analyzed data. The details are specified in the Appendix.

4. Data Handling Rules

4.1 Derivations

4.1.1 Baseline and Changes from Baseline

The baseline is defined as the last non-missing measurement before or on the date of the first dose of study treatment.

Changes from baseline are calculated as the values of post-baseline assessment/examination minus the values of baseline.

4.1.2 Course of Disease and Time to Initial Metastasis to Randomization

Course of Disease (months)= (Date of randomization – Initial diagnosis date of TNBC+1)/ 30.4375, one decimal place is kept.

Time to Initial Metastasis to the randomization (months) = (Date of randomization – Initial metastasis date of TNBC +1)/ 30.4375, one decimal place is kept.

4.1.3 Study Day

Study Day is defined as the assessment of the efficacy/ safety/ PK/ immunogenicity/ biomarker relative to the reference date. Reference date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study treatment).

Study day is calculated as follows:

Study Day = (date of assessment/ examination – reference date + 1), if the date of the assessment/ examination is on or after the reference date.

Study Day = (date of assessment/ examination – reference date), if the date of the assessment/ examination is prior to the reference date.

4.1.4 Follow-up Time

Subjects who died before data cut-off date, the follow-up time will be censored at the death date. Otherwise, the follow-up time is calculated as follows:

Follow-up time (months) = (last follow-up date – randomization date + 1)/ 30.4375.

4.1.5 Baseline Characteristics

The classifications of original diagnosis TNBC, lymph node metastasis, visceral metastasis, previous PD-1 or PD-L1 inhibitors treatment, HER2 expression at study entry, and the number of regimens received for the unresectable locally advanced or metastatic stage are shown below:

- Original diagnosis TNBC: If HER2, PR, and ER are all negative expressions for the first diagnosis, then yes. Otherwise no.
- Lymph node metastasis: If the metastases assessed by the investigator are “lymph nodes” at the time of enrollment, then yes. Otherwise no.
- Visceral metastasis: If the target lesion or non-target lesion location assessed by the investigator at study entry is only “soft tissue” and/or “skin” and/or “lymph node” and/or “chest wall”, then yes. Otherwise no.
- Previous PD-1 or PD-L1 inhibitors treatment: If the subject has a history of prior anti-tumor therapy corresponding to the “immunotherapy” with PD-1/PD-L1 inhibitors, then yes. Otherwise no.
- HER2 expression at study entry: If the subject with HER2 test results of IHC 1+ or 2+ and negative FISH at study entry will be categorized into low expression. Otherwise, HER2 is 0.
- Number of regimens received at unresectable locally advanced or metastatic stage: If the subject has a history of prior anti-tumor therapy and the therapy stage is “unresectable locally advanced or metastatic” at study entry, it can count as 1, which can be accumulated.
- Liver metastasis: If the target lesion or non-target lesion location assessed by the investigator at study entry is “liver”, then yes. Otherwise no.

- [REDACTED]

4.1.6 Calculation of BSA, BMI

Body surface area: $BSA (m^2) = 0.0061 \times \text{Height}(cm) + 0.0124 \times \text{Weight}(kg) - 0.0099$.

Body mass index: $BMI (kg/m^2) = \text{Weight}(kg) / (\text{Height}(m))^2$.

4.1.7 Efficacy Date Derived Rules

Multiple image examination dates will be involved in tumor assessment visits per RECIST 1.1, including imaging dates of target, non-target, and new lesions. These dates are often not on the same day. So the following rules will be pre-specified when deriving the overall response date for each visit.

- When the overall response is assessed as “PD”, the overall response date should be the earliest date among the imaging examination data used to evaluate the target, non-target and new lesions that can confirm the “PD”.
- When the overall response is not assessed as “PD”, the overall response date should be the latest date of among the imaging examination date used to evaluate target , non-target , and new lesions.

4.1.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations reported as below (and equal to) or above (and equal to) the range of detection values (i.e., $<x$, $\leq x$, $>x$, $\geq x$), will be converted to x for quantitative summaries, but will be presented as recorded by eCRF, i.e. as “ $< x$ ” , “ $\leq x$ ”, “ $> x$ ” or “ $\geq x$ ” in the listings. If clinical laboratory evaluations are missing, no imputation rule will be performed.

4.1.9 Last Known Alive Date

The last known alive date of subjects will be derived among the following dates:

- The subjects are shown alive at the date of examinations or assessments, including the laboratory or PK or biomarker sample collection date, the date of the 12-lead electrocardiogram (ECG) examination, the date of echocardiograph examination, the date of physical examination, the date of vital sign examination, the date of imaging examination, quality of life assessment date, and ECOG PS assessment date, etc.
- The start date of AE and the end date of AE.
- The end date of concomitant medications and concomitant procedures, use the start date if missing.
- The end date of subsequent anti-tumor therapy, use the start date if missing.
- The end date of radiation therapy during treatment, use the start date if missing.
- The end date of study treatment, use the start date if missing.
- Date of the last administration.
- Randomization date.
- The visit date of subjects known date for the subject alive.
- The last known alive date collected on the eCRF form “Survival Follow-up”.

4.1.10 QTcF/QTcB

- $QTcF = QT / (RR^{0.33})$, RR represents the normalized heart rate, calculated by 60 divided by the heart rate.
- $QTcB = QT / (RR^{0.5})$, RR represents the normalized heart rate, calculated by 60 divided by the heart rate.

4.2 Missing Data

Unless otherwise specified, missing data will not be imputed by any assumption values. Miss values or incomplete data will be presented as recorded by eCRF in the listings.

4.2.1 Missing/Incomplete Dates

Initial diagnosis date of TNBC or initial metastasis date of TNBC

- In the case if only the year is known, the month and day will be imputed as January 1st of the year.
- In the case if the year and month are known but the day is unknown, the day will be imputed as 1st of the month.
- In the case if the date is completely missing, no imputation will be performed.

Prior and concomitant medications date or prior and concomitant procedure date

- In the case if only the year and month are known, and equal to the corresponding year and month of the first administered date, the start date will be imputed as the first administered date (if the imputed start date is later than the end date, the start date will be imputed as the end date.). Otherwise, the day will be imputed as 1st of the month.
- In the case if only the year is known, and equal to corresponding the year of the first administered date, the start date will be imputed as the first administered date (if the imputed start date is later than the end date, the start date will be imputed as the end date). Otherwise, the month and day will be imputed as January 1st of the year.
- In the case if the end date is incomplete, the end date will be imputed as the last day of known month or the last date of known year, but no later than the earlier date of the end of study date and death date (if applicable).
- In the case if the date is completely missing, no imputation will be performed.

Subsequent anti-tumor therapy date

- In the case if only year and month are known, and equal to the corresponding year and month of the last administered date, the start date will be imputed as the last administered date (if the imputed start date is later than the end date, the start date will be imputed as the end date.). Otherwise, day will be imputed 1st of the month.
- In the case if only the year is known, and equal to the corresponding year of the last administered date, the start date will be imputed as the last administered date (if the imputed start date is later than the end date, the start date will be imputed as the end date). Otherwise, the month and day will be imputed as January 1st of the year.
- In the case if the date is completely missing, no imputation will be performed.

Adverse events date

- Completely/partially missing date for the start date of AE
 - In the case if only year and month are known, and less than the corresponding year and month of the first administered date, the day will be imputed as the last day of the known month.
 - In the case if only year and month are known, and greater than the corresponding year and the month of the first administered date, the day will be imputed as the first day of the known month.
 - In the case if only year and month are known, and equal to the corresponding year and the month of the first administered date, the start date of AE will be imputed as the first administered date.
 - In the case if only the year is known, and less than the corresponding year of the first administered date, the month and day will be imputed as December

- 31st of the year.
 - In the case if only the year is known, and equal to the corresponding year of the first administered date, the start date of AE will be imputed as the first administered date.
 - In the case if only year is known, and greater than the corresponding year of the first administered date, the month and day will be imputed as January 1st.
 - In the case if the year, month and day are missing, the start date of AE will be imputed as the first administered date.
 - In other cases, no imputation will be performed.
- Completely/partially missing date for the end date of AE
 - In the case if the year and month are known, day will be imputed as the last day of the known month.
 - In the case if only the year is known, the month and day will be imputed as December 31st.
 - If the imputed end date is earlier than the start date, the end date will be imputed as the start date.
 - For the AE leading to death, the end date of AE should be an earlier date of death date and an imputed end date.
 - In the case, if the year, month, and day are completely missing, and the outcome of AE is not ongoing, the end date will be imputed as the start date. If the outcome is ongoing, the end date will be imputed as the cut-off date.
 - In other cases, no imputation will be performed.

Death date

- In the case if only year is known, and equal to the corresponding year of the last known alive date, the death date will be imputed as the last known alive date +1. Otherwise, the month and day will be imputed as January 1st of the year.
- In the case if only year and month are known, and equal to the corresponding year and the month of the last known alive date, the death date will be imputed as the last known alive date + 1. Otherwise, the day will be imputed as the 1st of the month.
- In the case if the death date is completely missing, the death date will be imputed as the last known alive date + 1.

4.2.2 MissingRelationship between AE and Study Intervention and Missing CTCAE Grade of AE

- The missing relationship between an AE and the study intervention will not be imputed and will be considered as “Related” when AE summary was performed.
- No imputation will be performed with the missing NCI-CTCAE grade of AE.

4.3 Visit Window

All analyses except time-to-event analyses will be conducted per schedule visits

regardless of deviation from the visit window.

5. Statistical Analysis Methods

5.1 Study subjects

5.1.1 Subjects Disposition

All subjects signed ICF will be included in the analysis.

Subjects withdrawing from the study before randomization will be considered as screen failed. The total number of subjects screened, the number of subjects screened failure and the corresponding reasons will be summarized. Screen failed subjects will be excluded in subsequent analysis and the corresponding reasons will be represented in the listing.

The number and percentage of randomized subjects, randomized subjects without receiving study treatment, and subjects who received at least one dose of study treatment will be summarized by treatment groups. The number and percentage of subjects who discontinued from the study treatment, subjects who discontinued from the study, and the corresponding reasons will also be summarized. Corresponding by-subject listings will be provided.

The number and percentage of subjects in each analysis dataset and the reasons for subjects' removal from the analysis dataset will be summarized.

The distribution of each analysis dataset and reasons for exclusion from the analysis dataset will be provided in the listing.

5.1.2 Protocol Deviation

Protocol deviation will be classified as minor or major deviation.

The impact of protocol deviation on the division of the subject analysis dataset will be assessed and agreed upon by the investigator and sponsor at the data review meeting prior to the database lock.

Based on FAS, major protocol deviations will be summarized by treatment group and all protocol deviations will be provided in the listing.

5.1.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be presented based on FAS. If there is a difference between FAS and SS, these analyses will be added based on SS.

5.1.3.1 Demographics

The following demographics will be tabulated and listed by treatment group.

- Age
- Sex

- Ethnicity
- Baseline Weight
- Baseline Height
- Baseline BMI
- Baseline BSA

5.1.3.2 Baseline Characteristics

The following baseline characteristics will be tabulated and listed by treatment group.

- Disease course (months)
- The histology type of initial diagnosis
- Documented histology review of ER, PR, and HER2 status
- Original diagnosis TNBC
- Initial TNM stage
- Initial Disease stage
- HER2 test results at study entry
- HER2 low expression at study entry (yes, no)
- TNM stage at study entry
- Disease stage at study entry
- Sites of diagnosis at study entry
- Tumor status at study entry
- Time since initial metastasis to the randomization (months)
- Location of metastasis
- Number of locations of metastasis at study entry
- Lymph node metastasis
- Visceral metastasis
- The summary for prior lines of therapy (based on EDC)
- Stratification factors employed in the randomization: prior lines of therapy (2-3, >3) and liver metastasis (based on IRT)
- Actual random stratification factors: prior lines of therapy treatments (2-3,>3) and liver metastasis (based on EDC).
- BRCA mutational status
- Baseline ECOG score

- Smoking status

5.1.4 Prior Anti-tumor Therapy

Prior anti-tumor therapy will be summarized based on FAS. A listing with prior anti-tumor therapy will be provided.

Prior Anti-tumor Therapy

Prior anti-tumor therapy will be coded using the WHODrug Global 1 Mar 2022. The number and percentage of subjects receiving prior anti-tumor therapy will be summarized by ATC level 2, PN and treatment group.

In addition, the number and percentage of subjects will be summarized by treatment group based on medication categories (chemotherapy, immunotherapy, hormonotherapy, targeted therapy, PARP inhibitors, and others). Previous PD-1 or PD-L1 inhibitors treatment, previous taxanes treatment, previous anthracyclines treatment, and stages of therapy (neoadjuvant therapy, adjuvant therapy, salvage therapy, maintenance therapy, and unresectable locally advanced or metastatic stage) will be summarized by treatment group.

Prior Radiation Therapy

The number and percentages of subjects receiving prior radiation therapy will be summarized by treatment group.

Prior Anti-tumor Surgery Therapy

The number and percentage of subjects receiving prior anti-tumor surgery and the corresponding goal (radical, palliative, diagnostic and other) will be summarized by treatment group.

Prior anti-tumor surgery therapy will be coded using MedDRA 25.0 and will be summarized by SOC, PT and treatment group.

Other Anti-tumor Therapy

The number and percentage of subjects receiving prior other anti-tumor therapies will be summarized by treatment group.

5.1.5 Prior and Concomitant Medical History

Prior and concomitant medical history other than TNBC will be coded using MedDRA 25.0.

Based on FAS, the number and percentage of subjects will be summarized by SOC and PT.

A listing with prior and concomitant will be generated for all subjects by treatment group.

5.1.6 Premedication

Premedication will be coded using WHODrug Global 1 Mar 2022.

Based on SS, the reasons of premedication and drugs for pretreatment will be summarized

descriptively by treatment group. Premedication will also be summarized by ATC level 2 and PN.

A listing with premedication will be generated for all subjects by treatment group.

5.1.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHODrug Global 1 Mar 2022.

Based on FAS and SS, prior and concomitant medications will be summarized by ATC level 2 and PN.

- Prior medications are defined as medications with the end date prior to first administration of study treatment.
- Concomitant medications include medications that were taken at any time while on study treatment, including medications that were started before first administration of study therapy but ongoing at the time of first study therapy, or that were initiated on or after first administration but prior to 30 days after last administration of study therapy.

If the concomitant medication date relative to the first administered date cannot be confirmed, it will be considered as concomitant medication.

A listing will be generated for all subjects in the SS by treatment group.

5.1.8 Prior and Concomitant Procedure

Prior and concomitant non-drug therapy will be coded using MedDRA 25.0.

A listing will be generated for all subjects with prior and concomitant procedure by treatment group, based on FAS.

5.1.9 Radiation therapy During Treatment

The number and percentage of subjects received radiation therapy during treatment will be summarized by treatment group, based on SS.

A listing will be generated for all subjects with radiation therapy during treatment in the SS by treatment group.

5.1.10 Subsequent Anti-tumor Therapy

The number and percentage of subjects who received subsequent anti-tumor therapy (surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, and other) after treatment discontinuation will be summarized by treatment group, based on SS.

A listing with subsequent anti-tumor therapy will be presented by treatment group.

5.1.11 Follow-up Time

Based on FAS, median follow-up time will be estimated by Reverse Kaplan-Meier.

5.2 Efficacy Analyses

Efficacy analyses will be conducted in the FAS. In this study, one primary esitmand and three secondary esitmands have been established, aligning with the study objectives. The reference SAS codes for the primary analysis of the primary esitmand are specified in appendix 1.

5.2.1 Primary Estimand

The primary endpoint of PFS assessed by IRC based on RECIST 1.1 is defined as the time from randomization to the date of the first documented disease progression or death, whichever occurs first.

An interim analysis of PFS is planned for this study when the PFS data is approximately 119 PFS events assessed by IRC and a PFS final analysis is planed when the PFS data is approximately 183 PFS events. The following hypothesis of PFS assessed by IRC will be tested.

H₀₁: The HR between experimental group and control group is equal to 1.

H_{A1}: The HR between experimental group and control group is less than 1.

The censoring rules for PFS are presented in the table 2.

Table 2 Censoring rules for PFS

Situation	Outcome	Date of Progression or Censoring
No baseline/no post-baseline and no death occurred before the second scheduled tumor assessment visit from randomization.	censored	date of randomization
No baseline/no post-baseline and death occurred before the second scheduled tumor assessment visit from randomization.	event	date of death
No event (PD or death) and no new anti-tumor therapy	censored	date of last evaluable tumor assessment
No event (PD or death) but start new anti-tumor therapy	censored	date of last evaluable tumor assessment before new anti-tumor therapy
PD berfore new anti-tumor therapy	event	date of first documented PD
Event (PD or death) after new anti-tumor therapy	censored	date of last evaluable tumor assessment before new anti-tumor therapy
Event (PD or death) after 2 or more consecutive missed tumor assessments*	censored	date of last evaluable tumor assessment before 2 or more consecutive missed tumor assessments

*: Efficacy will be assessed by imaging examinations every 6 weeks (± 1 week) from the start of the first dose of study treatment until disease progression, or every 12 weeks (± 1 week) if the patient has not progressed after receiving 12 months of study drug. Within 12 months after the first dose, 2 or more consecutive missed tumor assessments is defined as the time between 2 evaluable tumor assessment is greater than 98 days. Beyond 12 months after the first dose, 2 or more consecutive missed tumor assessments is defined as the time between 2 evaluable tumor assessment is greater than 182 days. If one of 2 consecutive missed tumor assessments is within 12 months after the first dose and the other one is beyond 12 months after the first dose, then 2 or more consecutive missed tumor assessments is defined as the time between 2 evaluable tumor assessment is greater than 140 days.

5.2.1.1 Primary Analyses

Median PFS will be estimated using the Kaplan-Meier method and the corresponding 95% CI will be calculated by the Brookmeyer-Crowley method^[1]. The Kaplan-Meier method will also be used to estimate the PFS rate and the associated 95% CIs using Greenwood's method^[2] will be reported at specified time points (e.g., every 3 months). Kaplan-Meier curve of PFS will be plotted.

The PFS between the two treatment groups will be compared using the stratified log-rank test. The hazard ratios along with the 95% CI will be estimated using stratified Cox's Proportional Hazard model. The stratified log-rank test and the stratified Cox model will be based on the randomization strata as captured via IRT. The Efron method^[5] will be used to handle ties in that different subjects have the same PFS value.

The ICEs will be summarized by treatment group for all subjects in the FAS. The categories of the PFS event/censor, date, ICEs, and strategies for addressing ICEs for all subjects in the FAS will be presented in the listing.

5.2.1.2 Sensitivity Analyses

Sensitivity analysis 1: The analysis outlined for PFS is similar to the primary analysis except that it will be performed to use the date of PD or death when PD or death is documented after 2 or more consecutive missed assessments.

Sensitivity analysis 2: The analysis outlined for PFS is similar to the primary analysis except that it will be performed to use PFS assessed by the investigator.

Sensitivity analysis 3: The analysis outlined for PFS is similar to the primary analysis except that it will be performed to use randomization strata as captured via EDC.

5.2.1.3 Supplementary Analyses

Supplementary analysis 1: All ICEs will be addressed by treatment policy strategy. That is, it will be performed to use all actual collected data and the new anti-tumor therapy should be discarded.

Supplementary analysis 2: The analysis outlined for PFS is similar to the primary analysis except that the unstratified log-rank test and unstratified Cox model will be performed to compare the PFS between the two groups.

Supplementary analysis 3: The analysis outlined for PFS is similar to the primary analysis except that the subjects who do not meet any of the inclusion or exclusion criteria (inclusion criteria 2,3; exclusion criteria: 1,2) will be excluded from the analysis set.

Supplementary analysis 4: The analysis outlined for PFS is similar to the primary analysis except that subjects whose treatment delay is more than 3 weeks (more than 5 weeks since the last dose) or treatment discontinuation due to COVID-19 will be censored at the date of last evaluable tumor assessment before treatment delay or treatment discontinuation.

5.2.1.4 Subgroup Analyses

The subgroup analyses outlined for PFS are similar to the primary analyses. The detailed subgroup variables are specified in section 3.5 and the PFS assessed by IRC and investigator will be analyzed based on these subgroups, respectively. The HR and its corresponding 95% CI overall and by subgroups will be presented in a forest plot.

5.2.2 Secondary Estimand

5.2.2.1 ORR Assessed by IRC and Investigator

ORR is defined as the proportion of subjects with a BOR of CR or PR. The following hypothesis of ORR assessed by IRC will be tested.

$$H_{02}: \text{ORR}_{(\text{control group})} \geq \text{ORR}_{(\text{experiment group})}$$

$$H_{A2}: \text{ORR}_{(\text{control group})} < \text{ORR}_{(\text{experiment group})}$$

Primary analysis: The BOR (CR, PR, SD, PD, and NE) assessed by IRC will be summarized in terms of the number of subjects and percentage. The ORR between the two groups will be compared using a Cochran-Mantel-Haenszel method^[6] stratified by randomization strata and the difference along with 95% CI (Sato method^[7]) in ORR will be provided. The Clopper-Person method will be used for calculating 95% CI of ORR. In addition, the following sensitivity analyses and supplementary analyses for ORR assessed by IRC will be performed.

Sensitivity analysis 1: The analysis outlined for ORR is similar to the primary analysis except that the BOR is assessed by investigator.

Supplementary analysis 1: The analysis is similar to the primary analysis except that subjects whose treatment delay is more than 3 weeks (more than 5 weeks since the last dose) or treatment discontinuation due to COVID-19 will be excluded from the analysis set.

Supplementary analysis 2: The analysis is similar to the primary analysis except that subjects whose target lesions can not be measured by IRC at baseline are not included in the analysis set.

The BOR (including response and non-response) assessed by IRC and investigator will be respectively summarized in crosstable by treatment group to assess the consistency of BOR between IRC and investigator. Based on the assessed ORR by IRC and investigator, respectively, The waterfall plot will be provided for percentage change from baseline in the sum of the diameters assessed by IRC and investigator.

The subgroup analyses outlined are similar to the primary analysis. The detailed subgroup variables are specified in section 3.5 and the ORR assessed by IRC and investigator will be analyzed based on these subgroups, respectively. The difference along with 95% CI in ORR between the two treatment groups overall and by subgroups will be presented in a forest plot.

5.2.2.2 DCR Assessed by IRC and Investigator

DCR is defined as the proportion of subjects with a BOR of CR, PR, or SD. The primary analyses, sensitivity analyses, and supplementary analyses performed for DCR assessed by IRC and investigator are the same as ORR.

5.2.2.3 OS

OS is defined as the time from randomization to the date of death due to any cause. The OS will be censored at the cut-off date if subjects survive to pass the cut-off date. The OS will be censored at the randomization date if the survival data of subjects are not found at the post-baseline. If subjects die but the death date is missing, the death date will be imputed based on the specified rules in section 4.2.1.

An interim analysis of OS will be conducted at the final analysis of PFS or approximately 102 OS events have been observed. If the hypothesis test for OS has not shown statistically significant at the interim analysis, the final analysis of OS will be conducted when approximately 184 OS events have been observed. The following hypothesis of OS will be tested.

H₀₃: The HR between the experimental group and the control group is equal to 1.

H_{A3}: The HR between the experimental group and the control group is less than 1.

The primary analyses for OS are the same as the primary endpoints of PFS.

Sensitivity analyses 1: The analysis is similar to the primary analysis except that it will be performed to use randomization strata as captured via EDC.

Supplementary analysis 1: The analysis is similar to the primary analysis except that the unstratified log-rank test and unstratified Cox model will be performed to compare OS between the two groups.

Supplementary analysis 2: The analysis is similar to the primary analysis except that the subjects who do not meet any of the inclusion or exclusion criteria (inclusion criteria 2,3; exclusion criteria: 1,2) will be excluded from the analysis set.

Supplementary analysis 3: The analysis is similar to the primary analysis except that subjects whose treatment delay is more than 3 weeks (more than 5 weeks since the last dose) or whose treatment discontinuation due to COVID-19 will be censored at the date of last known alive before treatment delay or treatment discontinuation.

Supplementary analysis 4: The analysis is similar to the primary analysis except that the OS will be censored at the starting the new anti-tumor therapy date if subjects receive other new ADC drugs.

The subgroup analysis is similar to the primary analysis. The detailed subgroup variables are specified in section 3.5. The HR and its corresponding 95% CI overall and by subgroups will be presented in a forest plot.

A listing that includes the types of OS event or censored, time, and subsequent anti-tumor therapy will be provided by the treatment group.

5.2.3 The Other Secondary Efficacy Endpoints

5.2.3.1 DOR assessed by IRC and investigator

DOR is defined as the time from the date of the first response to progression or death, whichever occurs first. DOR will only be calculated based on the subjects with a BOR of CR or PR.

The censoring rules for DOR are presented in table 3.

Table 3 Censoring rules for DOR

Situation	Outcome	Date of Progression or Censoring
No event (PD or death) and no new anti-tumor therapy	censored	date of last evaluable tumor assessment
No event (PD or death) but start new anti-tumor therapy	censored	date of last evaluable tumor assessment before new anti-tumor therapy
PD before new anti-tumor therapy	event	date of first documented PD
Event (PD or death) after new anti-tumor therapy	censored	date of last evaluable tumor assessment before new anti-tumor therapy
Event (PD or death) after 2 or more consecutive missed tumor assessments*	censored	date of last evaluable tumor assessment before 2 or more consecutive missed tumor assessments

*:Within 12 months after the first dose, 2 or more consecutive missed tumor assessments is defined as the time between 2 evaluable tumor assessments is greater than 98 days. Beyond 12 months after the first dose, 2 or more consecutive missed tumor assessments are defined as the time between 2 evaluable tumor assessments is greater than 182 days. If one of 2 consecutive missed tumor assessments is within 12 months after the first dose and the other one is beyond 12 months after the first dose, then 2 or more consecutive missed tumor assessments are defined as the time between 2 evaluable tumor assessments greater than 140 days.

The analysis methods for DOR assessed by IRC and investigator are similar to the primary analyses of PFS. The swim lane plot will be provided to present the tumor status of subjects assessed by IRC and investigator, respectively.

5.2.3.2 Time to response (TTR)

TTR is defined as the time from randomization to the first response (CR/PR). TTR will only be calculated based on the subjects with a BOR of CR or PR.

The subjects whose BOR is CR or PR assessed by IRC and investigator will be summarized respectively in terms of the number of subjects, median, minimum, and maximum.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.3.1 PK Concentration Analyses

The serum concentration of SKB264-ADC, SKB264-TAB, and the plasma concentration of free KL610023 will be summarized in the table and presented in a listing by nominal sampling time, respectively. The number of subjects, the number of subjects with BQL, mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient of variation will be calculated.

The BQL data will be reported as “BQL” when the PK concentration data is presented in the listing. Handling of BQL samples for serum/plasma PK will be as follows: 1). BQL data will be imputed with zero and included in the descriptive statistics; 2). The number of total PK sample data and the lower limit of quantification (LLOQ) sample will be summarized by timepoints; 3). The geometric mean will not be reported if a timepoint has at least one PK data with BQL; 4). When more than 50% of the samples for a timepoint are BQLs, the mean and median will be reported as 0 and the standard deviation and coefficient variation will not be reported and minimum and maximum will be reported as observed values.

The concentration-time summary curve (including mean and standard deviation) for the serum SKB264-ADC, the serum SKB264-TAB, and the plasma free KL610023 will be generated respectively by using linear scale and semi-logarithmic scale. The statistics and curve will be presented at scheduled timepoint. Handling rules for serum/plasma PK will be as follows: 1). All BQL data will be plotted as zero in linear scale graph; 2). All BQL data will not be plotted in a semi-logarithmic scale graph; 3). Samples collected outside of the collection window or protocol deviation will not be included in the concentration-time curve; 4). When more than 50% of the samples for a timepoint are BQLs, the mean will be reported as BQL and will be plotted as 0 in linear scale and will not be plotted in the semi-logarithmic scale graph. In addition, the boxplot for the serum SKB264-ADC, the serum SKB264-TAB, and the plasma free KL610023 concentration time data before and drug administration will be generated, respectively.

5.3.2 PK Parameters Analyses

The serum concentration of SKB264-ADC, SKB264-TAB, and the plasma concentration of free KL610023 will be analyzed based on PKCS. $C_{\max}$ is defined as the concentration at 0.5 hours after the end of drug administration; $C_{\min}$ is defined as the concentration before drug administration. $R_{ac_C_{\max}}$ will be summarized and presented if data is applicable. $R_{ac_C_{\max}}$ is defined as accumulation ratio, which is the concentration at 0.5 hours after the end of the first drug administration of cycle 3 divided by the concentration at 0.5 hour after the end of the first drug administration of cycle 1.

The PK parameters for SKB264-ADC, SKB264-TAB, and the plasma concentration of free KL610023 will be summarized respectively in terms of the number of subjects, mean, standard deviation, median, minimum, maximum, geometric mean, and coefficient variation.

[REDACTED]

[REDACTED]

5.5 Safety Analyses

Safety analyses will be conducted based on the SS.

5.5.1 Exposure of Study Drugs

The total cycles of exposure, categorized total cycles of exposure (≥ 1 , ≥ 2 , ≥ 3 , ≥ 4 , ≥ 5 , ≥ 6) and the total number of drug administration (expect Capecitabine) will be summarized descriptively by treatment group in terms of mean, median, standard deviation, minimum and maximum. Number of subjects not dosed will be summarized by treatment group and reasons. Number of subjects with dose delayed, reason for dose delayed, number of dose delayed per subject (1, 2, >2), dose delayed time, and categorized dose delayed time (≤ 7 , 7-17, >14) will be summarized descriptively. Number of dose delayed and dose delayed time due to AE will be summarized. Number of subjects with dose level adjusted, reason for dose level adjusted, number of times of dose level adjusted (1, 2) per subject and time to the first dose level adjusted will be summarized. Dose delayed time and time to the first dose level adjusted will be calculated as follows.

- Dose delayed time
 - Only include subjects with dose delayed
 - Dose delayed time is defined as the time from the latest date within scheduled dosing window to the actual dose delayed date. If a subject has multiple dose delayed time, the longest delay will be selected.
- Time to the first dose level adjusted
 - Only include subjects with dose level adjusted
 - Time to the first dose level adjusted is defined as the time from the randomization date to the first dose level adjusted date.

The actual cumulative total dose administered, duration of exposure, categorized of duration of exposure (≥ 3 , ≥ 6 , ≥ 9 , ≥ 12), actual dose intensity, relative dose intensity and categorized of relative dose intensity ($<80\%$, $80\%-120\%$, $>120\%$) will be summarized descriptively by treatment group. The method of treatment allocation of the study is as follows.

Table 4 method of treatment administration

Treatment groups	Drug	Dosage	Route of administration	Dose Regimen
------------------	------	--------	-------------------------	--------------

Experimental group	SKB264	5 (mg/kg)	IV infusion	Days 1 and 15 of a 28-day cycle
Control group	Eribulin	1.4 (mg/m ²)	IV push	Days 1 and 8 of a 21-day cycle
	Capecitabine	1000-1250 (mg/m ²)	Orally	Twice daily on Days 1-14 of a 21-day cycle
	Gemcitabine	1000 (mg/m ²)	IV infusion	Days 1 and 8 of a 21-day cycle
	Vinorelbine	25 (mg/m ²)	IV infusion	Days 1 and 8 of a 21-day cycle (Note: patients with Grade 2 neuropathy should not be prescribed vinorelbine)

The total cycles of exposure, the actual cumulative total dose administered, duration of exposure, actual dose intensity and relative dose intensity will be calculated as follows.

- The total cycles of exposure are defined as the number of cycles receiving study treatment per subject. The cycle will be accumulated if a subject received at least one dose of study treatment in a cycle.
- The actual cumulative total dose administered (mg/kg or mg/m²)
 - SKB264: The sum of all the total dosages that the subject received during an exposure period (received dosage (mg) divided by weight (kg) at each time of infusion).
 - Eribulin/Gemcitabine/Vinorelbine: The sum of all the total dosages that the subject received during an exposure period (received dosage (mg) divided by BSA (m²) at each time of infusion).
 - Capecitabine: The sum of all the total dosages that the subject received during an exposure period (received dosage (mg) divided by BSA (m²) at each time of infusion). If a subject experiences vomiting within 30 minutes of dosing and does not take a new one, the actual dose administered of the subject on the same day is set to 0 mg. If the subject experiences vomiting within 30 minutes of dosing and takes a new one, the actual dose administered is unchanged on the same day.

Note: Compared to the pre-infusion weight on C1D1, if the weight change is within $\pm 10\%$ range, the dose of SKB264 will be calculated based on the weight on C1D1; if weight change is out of the range of $\pm 10\%$ from that before the first dose, the dose will be recalculated, and the weight at the time of recalculation will serve as the new calculated baseline. Subjects in the control group who received Capecitabine had a body weight examination before the first dose in each cycle, and the dose administered was adjusted according to the change in weight as described before.

- Duration of exposure (wk)
 - SKB264: (date of the last dosing – date of the first dosing + 14)/7
 - Eribulin/Gemcitabine/Vinorelbine/Capecitabine: (date of the last dosing – date of the first dosing + interval between the date of last dosing and the date of next dosing)/7
- Duration of exposure (month)

- SKB264: (date of the last dosing – date of the first dosing + 14)/30.4375
- Eribulin/Gemcitabine/Vinorelbine/Capecitabine: (date of the last dosing – date of the first dosing + interval between the date of last dosing and the date of next dosing)/30.4375
- Actual dose intensity (mg/kg/wk or mg/m²/wk)= The actual cumulative total dose administered (mg/kg or mg/m²) / duration of exposure (wk)
- Planned dose intensity (mg/kg/wk or mg/m²/wk)
 - SKB264: 2.5mg/kg/wk
 - Eribulin: 0.93 mg/m²/wk
 - Capecitabine: 10500 mg/m²/wk
 - Gemcitabine: 666.67 mg/m²/wk
 - Vinorelbine : 16.67 mg/m²/wk
- Relative dose intensity (%)= actual dose intensity (mg/kg/wk or mg/m²/wk)/ planned dose intensity (mg/kg/wk or mg/m²/wk)× 100.

All dosing data will be listed by treatment group.

5.5.2 Adverse Events (AEs)

All adverse events will be coded using the MedDRA 25.0.

Treatment emergent adverse events (TEAEs) are defined as any AEs that occur or worsen after study treatment and within 30 days after the last dose of study treatment or a new anti-tumor therapy is initiated, whichever is earlier.

Treatment-related TEAEs (TRAEs) are defined as any TEAEs with a drug-event relationship documented as “definite related”, “probable related” and “possible related” are considered as “related” to the study treatment. TEAEs with a missing relationship to study treatment or not to be judged will be regarded as related to study treatment.

Infusion-related reactions/hypersensitivity reactions are defined as any TRAEs occurring on the same day of infusion (during the infusion or after infusion) or occurring on the second day of infusion, including the following Preferred Terms: Infusion-related reaction, Infusion-related hypersensitivity reaction, Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Hypersensitivity, Type I hypersensitivity, Drug hypersensitivity.

Adverse events of special interest (AESIs) are defined as any TRAEs of scientific and medical interest specific to the sponsor’s product or project. The adverse event of special interest which can be a serious adverse event or non-serious adverse event, is required further study to understand product characteristics and will be finalized by a medical monitor prior to EDC lock.



[illegible]

5.5.2.1 Overview of TEAEs

The overall summary of TEAEs table will be provided to summarize the number and incidence of the below categories by treatment group.

- TEAEs
- TRAEs
- NCI-CTCAE grade 3 or higher TEAEs
- NCI-CTCAE grade 3 or higher TRAEs
- TEAEs leading to dose reduction
- TRAEs leading to dose reduction
- TEAEs leading to study treatment interruption
- TRAEs leading to study treatment interruption
- TEAEs leading to study treatment discontinuation permanently
- TRAEs leading to study treatment discontinuation permanently
- Serious TEAEs
- Serious TRAEs
- TEAEs leading to death
- TRAEs leading to death

5.5.2.2 Summary of TEAEs by SOC and PT

The number and incidence of subjects will be presented by SOC, PT and treatment group as below categories.

- TEAEs
- TEAEs reported by $\geq 10\%$ of subjects in any treatment group by preferred term
- TRAEs
- TRAEs reported by $\geq 10\%$ of subjects in any treatment group by preferred term
- NCI-CTCAE grade 3 or higher TEAE

- NCI-CTCAE grade 3 or higher TEAEs reported by $\geq 1\%$ of subjects in any treatment group by preferred term
- NCI-CTCAE grade 3 or higher TRAE
- NCI-CTCAE grade 3 or higher TRAEs reported by $\geq 1\%$ of subjects in any treatment group by preferred term
- TEAEs leading to dose reduction
- TRAEs leading to dose reduction
- TEAEs leading to study treatment interruption
- TRAEs leading to study treatment interruption
- TEAEs leading to study treatment discontinuation permanently
- TRAEs leading to study treatment discontinuation permanently
- Serious TEAEs
- Serious TRAEs
- TEAEs leading to death
- TRAEs leading to death

5.5.2.3 Summary of TEAEs by SOC, PT and NCI-CTCAE

The number and incidence of subjects will be presented by SOC, PT, NCI-CTCAE and treatment group as below categories.

- TEAEs
- TRAEs
- NCI-CTCAE grade 3 or higher TEAEs
- NCI-CTCAE grade 3 or higher TRAEs

5.5.2.4 Analyses of deaths, AESIs, infusion-related reactions/hypersensitivity reactions

5.5.2.4.1 Deaths

The time of death and the reasons for death (including disease progression, SAE, others, unknown) are summarized by treatment group.

- Deaths
- Treatment-emergent deaths are defined as any deaths from the first administered date up to 30 days after the last administered date.
- Deaths during follow-up are defined as any deaths that occurred 30 days after the last administered date.

A data listing with TEAEs leading to death will be presented by the treatment group.

5.5.2.4.2 Infusion-related reactions/hypersensitivity reactions

The number and incidence of subjects will be provided by SOC, PT and treatment group as below categories.

- Infusion-related reactions/hypersensitivity reactions
- NCI-CTCAE grade 3 or higher infusion-related reactions/hypersensitivity reactions

A listing with infusion-related reactions/hypersensitivity reactions will be presented by the treatment group.

5.5.2.4.3 AESIs

The number and incidence of subjects will be provided by treatment group and below categories.

- AESIs
- NCI-CTCAE grade 3 or higher AESIs
- AESIs leading to dose reduction
- AESIs leading to study treatment interruption
- AESIs leading to study treatment discontinuation permanently
- Serious AESIs
- AESIs leading to death

The number and incidence of subjects will be presented by PT and treatment group as below categories.

- AESIs

In addition, the following information will be summarized and plotted for AESIs.

- [REDACTED]

████████████████████

[illegible]

Gender	Age Group	Percentage
Men	18-24	95%
	25-34	95%
	35-44	95%
	45-54	95%
Women	18-24	95%
	25-34	95%
	35-44	95%
	45-54	95%
Total	18-24	95%
	25-34	95%
	35-44	95%
	45-54	95%

[REDACTED]

A listing with AESIs will be presented by the treatment group.

5.5.2.5 Subgroup analyses

The detail subgroup variables are specified in section 3.5. The summary table of TEAEs will be summarized by treatment group with using these variables.

5.5.3 Clinical Laboratory Tests

Laboratory tests include hematology, serum chemistry, urinalysis, HbA1c/ fasting blood glucose, coagulation function, serum/urine pregnancy test, and viral serology test (HBV, HCV, HIV).

Descriptive statistics of observed values and corresponding changes from baseline will be summarized for each of the laboratory test parameters, overtime by scheduled visits. The laboratory test results will be categorized using the NCI-CTCAE v5.0. Shift tables of baseline grade to worst post-baseline grade will be tabulated. In addition, the number and percentage of subjects with an increase in post-baseline NCI-CTCAE grade, an increase to grade 2 or above, and an increase to grade 3 or 4 will also be summarized respectively by treatment group and laboratory test parameters.

The number and percentage of subjects with baseline alanine transaminase (ALT), aspartate transferase (AST), ALT or AST, total bilirubin (TBIL), and alkaline phosphate (ALP) above the upper limit of the normal range will be summarized by treatment group. The number and percentage of subjects meeting the following preset criteria for abnormal liver function at post-baseline, and at any timepoint (including unscheduled visits) will be summarized by treatment group:

- ALT
 - $\geq 3 \times \text{ULN}$
 - $\geq 5 \times \text{ULN}$
 - $\geq 10 \times \text{ULN}$
 - $\geq 20 \times \text{ULN}$
- AST
 - $\geq 3 \times \text{ULN}$
 - $\geq 5 \times \text{ULN}$
 - $\geq 10 \times \text{ULN}$
 - $\geq 20 \times \text{ULN}$
- ALT or AST
 - $\geq 3 \times \text{ULN}$

- $\geq 5 \times \text{ULN}$
- $\geq 10 \times \text{ULN}$
- $\geq 20 \times \text{ULN}$
- TBIL
 - $\geq 2 \times \text{ULN}$
- ALP
 - $\geq 1.5 \times \text{ULN}$
- ALT or AST and TBIL
 - ALT/AST $\geq 3 \times \text{ULN}$ and TBIL $\geq 1.5 \times \text{ULN}$
 - ALT/AST $\geq 3 \times \text{ULN}$ and TBIL $\geq 2 \times \text{ULN}$
- ALT or AST and TBIL and ALP (Hy's Law)
 - ALT/AST $\geq 3 \times \text{ULN}$ and TBIL $\geq 2 \times \text{ULN}$ and ALP $< 2 \times \text{ULN}$

All laboratory test results will be displayed in the listing. Listings of abnormal clinically significant will also be provided.

5.5.4 Vital Signs

Measured (observed) values including changes from baseline will be summarized by scheduled visits and by vital sign parameters.

A listing with all vital sign measurements will be presented by the treatment group.

5.5.5 ECOG

The ECOG shift table of baseline to the end of the treatment visit, and the worst score will be summarized by treatment group.

A listing with ECOG PS will be provided by the treatment group.

5.5.6 12-lead ECG

Descriptive statistics for absolute values and changes from baseline will be summarized by scheduled visit and by treatment group for the ECG parameters, including ventricular rate, QT, PR, QRS, QTcB and QTcF corrections. For the triplicate ECG at screening (baseline), the average of the non-missing triplicate results will be included in the summary.

The ECG will be evaluated by the Investigator as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS'. A shift table will be used to summarize the baseline category versus the category at the end of the treatment visit, and the worst post-baseline category. In addition, the number and percentage of subjects with the following categories post-baseline at any timepoint (including unscheduled visits) will be summarized for QTcF, QTcB, and QT, respectively.

- >450 ms (baseline $\leq$ 450 ms)
- >480 ms (baseline $\leq$ 480 ms)
- >500 ms (baseline $\leq$ 500 ms)
- With an increase of >30 ms from baseline
- With an increase of >60 ms from baseline

A listing with 12-lead ECG will be provided and a listing of clinically significant abnormal results will also be provided by the treatment group.

5.5.7 Physical Examination

All physical examination results will be displayed in the listing and any clinically significant abnormal findings will also be presented by the treatment group.

5.5.8 Echocardiograph

A listing with an echocardiograph will be provided and any clinically significant abnormal results will also be provided by the treatment group.

5.5.9 Other Safety Tests

HbA1c, fasting blood glucose, serum/urine pregnancy test, and viral serology test results will be presented in listings by treatment group, respectively.

5.6 Immunogenicity

5.6.1 Immunogenicity Analyses

In this study, immunogenic samples will be only collected in the experimental group. Immunogenicity analyses will be based on IMGS. A summary for the following categories of the ADA test results will be provided:

- The number and percentage of subjects with positive ADA test results at baseline:
 - The number and percentage of subjects with negative ADA test results at any time after the first dose.
 - The number and percentage of subjects with at least one positive ADA test results at any time after the first dose.
 - The number and percentage of subjects with treatment-boosted ADA test results. (positive ADA at baseline, positive ADA at post-baseline and the ADA titer is equal to or greater than 25 times than the baseline titer.).
- The number and percentage of subjects with negative ADA test results at baseline:

- The number and percentage of subjects with negative ADA test results at any time after the first dose.
- The number and percentage of subjects with treatment-induced positive ADA test results. (negative ADA at baseline, positive ADA at post-baseline);
- The number and percentage of subjects with transient positive ADA test results. (treatment-induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.
- The number and percentage of subjects with persistent ADA-positive (treatment-induced ADA detected at two or more sampling time points during the treatment, where the first and last ADA-positive samples are separated by a period of 16 weeks or longer or treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample).
- The number and percentage with at least one positive ADA test result at any time point before or after the first dose.
- The number and percentage with at least one positive ADA test result at any time point after the first dose. (regardless of ADA test results at baseline).

ADA test results (positive, negative) will be summarized for the number and percentage of subjects by visit. Titer values of ADA and Nab test results (positive, negative) will be summarized descriptively if applicable.

A listing with immunogenicity test results will be provided.

5.6.2 Analyses The Relationship between Immunogenicity and Efficacy and Safety

The positive ADA is defined as at least one positive ADA test result detected before or after the first dose. The negative ADA is defined as all negative ADA test results detected before or after the first dose. The subjects will be divided into two groups based on ADA level (positive, negative) to compare the ORR, PFS (assessed by IRC), OS, respectively. In addition, the number and percentage of subjects according to ADA (positive, negative) will be summarized based on the TEAE summary table.

5.6.3 Analyses The Relationship between Immunogenicity and PK

Subjects will be divided into different groups according to ADA and/or Nab. Scatter plots and/or box plots of the C_{max} and C_{min} of SKB264-ADC, SKB264-TAB, and KL610023 by visit will be provided, respectively. Average blood concentration – time summary curve (including linear and semilog coordinates) will also be plotted for SKB264-ADC, SKB264-TAB, and KL610023, respectively. In addition, descriptive summaries will be provided to analyze the C_{max} and C_{min} of SKB264-ADC, SKB264-TAB, and KL610023 according to ADA and Nab levels by visit, respectively.

6. Pre-specified Analyses

6.1 IDMC Responsibilities and Analysis Scope

In this study, an independent data monitoring committee (IDMC) will be established to review AE and efficacy and provide recommendations.

The following data will be reviewed at the IDMC security conference:

- Subject disposition
- Protocol deviations
- Demographics and baseline characteristics
- Prior anti-tumor therapy
- Prior and concomitant medical history
- Prior and concomitant medications
- Prior and concomitant procedures
- Radiotherapy during treatment
- Subsequent anti-tumor therapy
- Follow-up time
- Treatment exposure
- AE (TEAE, TRAE, NCI-CTCAE Grade 3 or higher, SAE, death)
- Clinical laboratory tests

In the PFS interim analysis, the following efficacy data (including assessed by IRC and investigator) will be analyzed. Only hypothesis tests for PFS will be performed, and primary analyses, sensitivity analyses, supplementary analyses, and subgroup analyses will be provided.

- PFS
- ORR
- DOR
- DCR
- OS

6.2 Interim Analysis

An interim analysis of PFS is planned for this study when approximately 119 PFS events occur as assessed by IRC. We will conclude that PFS result is significant if the P-value is less than 0.0066 (one-sided) at the PFS interim analysis. If the actual PFS events differ from the planned ones, the nominal alpha at the interim and final analysis of PFS will use O'Brien-Fleming boundaries based on spending function.

An interim efficacy of OS analysis will be conducted when approximately 183 PFS events assessed by IRC or approximately 102 OS events have been observed. We will conclude that OS result is significant if the P-value is less than 0.0037 (one-sided) at OS interim analysis. If the actual OS events differ from the planned ones the nominal alpha at the interim and final analysis of OS will use O'Brien-Fleming boundaries based on spending function.

The statistical decision criteria for the PFS and OS analysis are shown in table 6 as below:

Table 6 The statistical decision criteria for the PFS and OS analysis

Type of analysis	Time (months)	No. of Events	Nominal alpha level	Stopping boundary in HR
PFS (one-sided $\alpha=0.025$)				
Interim analysis	11	119	0.0066	0.6339
Final analysis	16	183	0.0227	0.7436
OS (one-sided $\alpha=0.0249$)				
Interim analysis	16	102	0.0037	0.5870
Final analysis	30	184	0.0235	0.7460

6.3 Final Analysis

The final analysis for PFS will be performed after approximately 183 PFS events assessed by IRC have been observed. If the hypothesis test for OS has not shown statistical significance in the interim analysis, the final analysis of OS will be conducted when approximately 184 OS events have been observed.

7. Changes to Protocol-Planned Analysis

The investigator-assessed PFS was initially designated as the secondary estimand in the protocol, but in the actual analysis, it serves as a sensitivity to the PFS assessed by IRC.

In the protocol, PKCS is defined as “including all subjects who received at least one dose of study treatment and at least one drug plasma concentration measurement during the study.” In the actual analysis, PKCS is defined as “including all subjects who receive at least one dose of study treatment and at least one drug plasma concentration measurement during the study. If the blood concentration of a subject prior to the first dose is greater than 5% of the first cycle C_{max} , then the subject's data should be excluded from the PKCS.”

8. Statistical Analysis Tables/Listings/Figures

The study includes a separate document that contains the template for the tables, listings and figures.

9. References

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Appendix 1 Example SAS code

/*1. Reference SAS code for the primary analysis of PFS and OS */

```
proc lifetest data=adtte ;  
time aval * cnsr(1);  
strata strata1 strata2/ group=trtpn;  
run;
```

```
proc phreg data = adtte;  
model aval * cnsr(1) = trtpn / alpha = 0.05 rl ties= efron;  
strata strata1 strata2;  
run ;
```

/*2. Reference SAS code for the primary analysis of ORR and DCR*/

```
proc freq data = adef;  
tables success/binomial( cl=exact level=1) alpha=0.05 ;  
run ;
```

```
proc freq data = adef;  
tables strata1*strata2*trtpn*aval/cmh riskdiff(common);  
run ;
```