



**AN OPEN-LABEL, RANDOMIZED, MULTICENTER
PHASE III CLINICAL TRIAL OF SHR-A1811 VERSUS
INVESTIGATOR-SELECTED CHEMOTHERAPY FOR
PLATINUM-RESISTANT RELAPSED EPITHELIAL
OVARIAN, FALLOPIAN TUBE, OR PRIMARY
PERITONEAL CANCER**

Protocol Number:

GSP 402-301 (SHR-A1811-315_Extension)

Product Name/ Code	Trastuzumab Rezetecan Injection/ SHR-A1811
Phase of Development	Phase III
Sponsor	Glenmark Specialty SA. Place du Port, CH-2000 Neuchâtel, Switzerland.
Protocol Version; Date	3.0; Date 18-Dec-2025

Confidentiality Statement

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Summary of Changes from Previous Version

PROTOCOL AMENDMENT HISTORY

Version Number	Version Date	Summary of Changes	Rationale
1.0	03-Dec-2025	Not applicable	This is the original version
2.0 (Amendment 1)	12-Dec-2025	Included clarification texts with respect to pooled analysis of data from main cohort and extension cohort; and the time of analysis of the extension cohort data.	Clarification about analysis of combined data from main cohort and extension cohort.
3.0 (Amendment 2)	18-Dec-2025	Edited texts with respect to time of analysis of extension cohort data.	Clarification regarding the time of analysis of extension cohort.

Sponsor's Signature

We have read and approved this clinical trial protocol GSP 402-301 (SHR-A1811-315_Extension), Version No.: 3.0, Version Date: 18 December 2025. The protocol reflects the Sponsor's current knowledge of trastuzumab rezetecan as applicable to this study. The protocol is designed to achieve the stated objectives while minimizing the risks from both the exposure to the products being used and the assessments. All assessments are considered appropriate, capable of validating the stated objectives of the study and provide the necessary information to ensure subject safety. The protocol is designed according to the principles of the ICH guidelines for GCP, the Declaration of Helsinki, New Drugs and Clinical Trials Rules, 2019 and/or the applicable other local/regional regulation(s). It has undergone both medical and scientific review by the Sponsor. The Sponsor is responsible for taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol compliance, integrity and validity of the data.

- Sponsor will ensure that this study is conducted in accordance with the protocol, GCP and the applicable regulatory requirements.
- Sponsor will comply with own relevant standard operating procedures (SOP) required for the conduct of this study.
- Sponsor will ensure that all associates contributing in the conduct of the study are informed regarding their obligations.

Signed on behalf of Sponsor Glenmark Specialty SA.

Kanhei Sahoo

Kanhei Sahoo

19 Dec 2025 11:18:13 IST

REASON: Reviewed By

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Investigator's Agreement

Protocol Title:

An Open-label, Randomized, Multicenter Phase III Clinical Trial of SHR-A1811 Versus Investigator-selected Chemotherapy for Platinum-resistant Relapsed Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Protocol No.: GSP 402-301 (SHR-A1811-315_Extension)

Version No.: 3.0, Date: 18 December 2025

By signing the signature page of this protocol, the investigator confirms and agrees to the following:

- I have read and am aware of the above study protocol and its appendices.
- I have fully discussed the content of this protocol with the Sponsor.
- I agree to conduct the study in accordance with this protocol, the current Good Clinical Practice (GCP), and applicable laws and regulations.
- This document contains confidential information, which will not be disclosed to anyone other than those directly involved in the study implementation or ethical/regulatory review without the written authorization from the Sponsor.
- I agree to ensure that all staff involved in this study understand their obligations in fulfilling the above commitments.

Study Site:

Address:

Principal Investigator
(Printed Name)

Principal Investigator
(Signature)

Signature Date
(MM/DD/YYYY)

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title	An Open-label, Randomized, Multicenter Phase III Clinical Trial of SHR-A1811 Versus Investigator-selected Chemotherapy for Platinum-resistant Relapsed Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Protocol No.	GSP 402-301 (SHR-A1811-315_Extension)
Version No. and Date	Version 3.0, Date 18 December 2025
Study Phase	Phase III
Study Drug	Trastuzumab Rezetecan for Injection (SHR-A1811)
Sponsor	Glenmark Specialty SA.
Participating Sites	Approximately 25 sites across India, Australia and/or other countries in the extension cohort [GSP 402-301 (SHR-A1811-315_Extension)]. Approximately 55 sites in China (Main cohort: SHR-A1811-315).
Study Objectives	Primary Objective - To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of human epidermal growth factor receptor 2 (HER2)-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by progression-free survival (PFS). - To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in patients with HER2-expressing, platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by overall survival (OS). Secondary Objectives - To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by objective response rate (ORR), duration of response (DoR), disease control rate (DCR), response rate (RR), and cancer antigen 125 (CA-125) RR. - To evaluate the safety of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. - To evaluate the pharmacokinetic (PK) profile of SHR-A1811. - To evaluate the immunogenicity of SHR-A1811.
Study Endpoints and Estimands	Primary Endpoints - PFS assessed by the Independent Review Committee (IRC) based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Estimand 1 (PFS) is characterized by the following 5 attributes: - Treatment (intervention): SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group).

	2. Population: Adult patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. 3. Variable (endpoint): PFS assessed by the IRC based on RECIST v1.1. 4. Intercurrent events and handling strategies: a) Premature discontinuation of treatment: Handled using a treatment policy strategy; tumor imaging data collected after premature discontinuation of treatment will be included in the PFS analysis. b) Initiation of new anti-tumor therapy: Handled using a hypothetical strategy; the event time will be censored at the date of the last valid tumor assessment prior to or on the day of the initiation of new anti-tumor therapy. 5. Population-level summary: Hazard ratio (HR), estimated using a stratified Cox proportional hazards model. • Overall survival (OS) Estimand 2 (OS) is characterized by the following 5 attributes: 1. Treatment (intervention): SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group). 2. Population: Adult patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. 3. Variable (endpoint): OS. 4. Intercurrent events and handling strategies: a) Premature discontinuation of treatment: Handled using a treatment policy strategy; post-discontinuation data will be included in the OS analysis; b) Initiation of new anti-tumor therapy: Handled using a treatment policy strategy; data following initiation of other anti-tumor therapy will be included in the OS analysis; 5. Population-level summary: Hazard ratio (HR), estimated using a stratified Cox proportional hazards model. <u>Other Efficacy Secondary Endpoints</u> • IRC-assessed ORR, DoR, and DCR per RECIST v1.1; • Investigator-assessed PFS, ORR, DoR, and DCR per RECIST v1.1; • CA-125 RR assessed based on Gynecologic Cancer InterGroup (GCIG) CA-125 criteria; • RR assessed based on CA-125 RR and IRC ORR. <u>Other Safety Secondary Endpoints</u> • Adverse events (AEs) and serious adverse events (SAEs), including type, incidence, severity (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 [NCI-CTCAE v6.0]), and correlation with the investigational medicinal product; • Laboratory test abnormalities, including type, incidence, and grading (per NCI-CTCAE v6.0);
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	- Vital signs, electrocardiogram (ECG), and Eastern Cooperative Oncology Group performance status (ECOG PS) score. <u>PK</u> - Serum drug concentrations of the toxin-conjugated antibody (SHR-A1811) and the free toxin SHR169265 (also known as 9106-IM-2). <u>Immunogenicity</u> - Presence of anti-SHR-A1811 antibodies (anti-drug antibodies [ADAs]) and neutralizing antibodies (NAbs).
Study Population	The study population consists of adult patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. (Platinum-resistant recurrence is defined as progressive disease [PD] occurring during platinum-based therapy or within <183 days after the last dose of a platinum-based agent.)
Study Design	This is a randomized, open-label, active-controlled, multicenter Phase 3 clinical trial. The overall study design is illustrated in Figure 1. Subjects with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer are planned to be enrolled in the study. It is planned to enrol ~350 subjects in the main (China) cohort and ~70 subjects in the extension (ex-China) cohort. Randomization will be stratified based on the following factors: 1) HER2 expression status by immunohistochemistry (IHC) (HER2 IHC 1+ vs. HER2 IHC 2+/3+); 2) prior treatment with vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitors such as bevacizumab (Yes vs. No). Subjects will be randomized in a 1:1 ratio to receive either SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group), which may include doxorubicin liposome, paclitaxel, topotecan, or gemcitabine. Detailed dosing information is provided in the dosing regimen section (Section 6.3.1). All subjects will proceed through the screening, treatment, and follow-up periods after providing written informed consent (see Table 1 and Table 2 for details): - The screening period is defined the time from the date the subject signs the informed consent form (ICF) to the date of randomization or screen failure and must not exceed 4 weeks in total. During the screening period, subjects must undergo examinations and assessments to determine eligibility before randomization. Prior to randomization, the investigator must pre-select the chemotherapy regimen that will be administered if the subject is assigned to the control group. The first dose of IMP should be administered within 3 calendar days of randomization. - During the treatment period, tumor imaging assessments will be performed every 6 weeks $\pm$ 7 days for the first 36 weeks, and every 12 weeks $\pm$ 7 days thereafter. CA-125 testing will be performed within $\pm$ 3 days of each imaging assessment. Safety assessments will be conducted prior to each administration. PK and immunogenicity blood sampling will be conducted at scheduled time points in subjects in the experimental group only. Additional data including concomitant treatments and exploratory endpoints will also be

	collected. End-of-treatment assessments must be completed accordingly. After end of treatment, subjects will enter the follow-up period (including safety follow-up and survival follow-up). During the safety follow-up (40 days [+7 days] after the last dose), information on safety, concomitant treatments, survival status, and subsequent anti-tumor therapies will be collected. After completion of the safety follow-up, survival follow-up will be conducted every 2 months ± 7 days (additional follow-up visits may be performed if necessary). Data on survival status and subsequent anti-tumor therapies will be collected. During follow-up, subjects who discontinue treatment without documented radiologic progression must continue tumor imaging assessments and CA-125 testing at protocol-specified intervals until PD is confirmed, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor. Subject enrollment in the extension cohort will continue even after early completion of enrolment in the main cohort; and efficacy and safety data of subjects in the extension cohort will continue to be collected. A separate Statistical Analysis Plan (SAP) will be developed for the extension cohort, while all other elements will remain consistent with the main cohort.
Dosing Regimen	Treatment in the experimental group SHR-A1811 will be administered via intravenous infusion on Day 1 (D1) of each treatment cycle at a dose of 4.8 mg/kg once every 3 weeks, with every 3 weeks as one treatment cycle. Treatment will continue until the occurrence of any event that meets the protocol-defined criteria for treatment discontinuation. Treatment in the control group The investigator may administer premedication prior to dosing based on the package insert or the standard of care at the site. The investigator will select one of the following treatment regimens (to be determined prior to randomization) and continue treatment until the occurrence of any event that meets the protocol-defined criteria for treatment discontinuation: - Doxorubicin liposome: Administered as intravenous (IV) infusion on D1 of each cycle at a dose of 40 mg/m², with 4 weeks as one cycle; - Paclitaxel: Administered as IV infusion on D1, D8, D15, and D22 of each cycle at a dose of 80 mg/m², with 4 weeks as one cycle; - Topotecan: Administered as IV infusion on D1, D8, and D15 of each cycle at a dose of 4 mg/m² per day, with 4 weeks as one cycle; - Gemcitabine: Administered as IV infusion on D1 and D8 of each cycle at a dose of 1,000 mg/m² per day, with 3 weeks as one cycle.
Inclusion Criteria	Subjects must meet all the following criteria to be enrolled in this study: - The patient voluntarily agrees to participate in the study and has signed the informed consent form (ICF). - Female, aged 18 to 75 years (inclusive of 18 and 75 years; age calculated as of the date of ICF signing). - Histologically or cytologically confirmed diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

	4. Documented platinum-resistant recurrence after prior platinum-based therapy (defined as PD during platinum treatment or within <183 days after the last dose of platinum-based therapy). If the subject has only received one line of platinum-based therapy, at least 4 cycles must have been administered. Platinum-resistant recurrence must be confirmed by radiologic evidence of progression. Subjects may have received no more than one line of systemic anti-tumor therapy after developing platinum resistance and must be suitable for single-agent chemotherapy in the next line of treatment. 5. Subjects known to have high folate receptor α (FRα) expression must have received prior treatment with mirvetuximab soravtansine, unless the investigator determines that the subject is intolerant of or unsuitable for mirvetuximab soravtansine treatment, or if the treatment is not approved or locally unavailable. 6. PD or intolerable toxicity (with clear supporting evidence) during or after the last line of therapy. 7. HER2 expression of IHC 1+, 2+, or 3+. The subject must provide adequate fresh or archived tumor tissue specimens to allow HER2 expression testing by the sponsor-designated or local laboratory (acceptable formats include paraffin blocks, paraffin-embedded sections, or fresh tissue sections. IHC 1+, 2+, or 3+ based on the 2016 ASCO/CAP HER2 scoring criteria for gastric and gastroesophageal junction adenocarcinoma). 8. At least one measurable lesion as defined by RECIST v1.1 (i.e., a lesion with a longest diameter ≥ 10 mm or an enlarged lymph node with a short axis ≥ 15 mm on spiral computed tomography [CT] scan). Lesions previously treated with local therapy may be selected as target lesions if there is clear evidence of significant progression after completion of local treatment. 9. ECOG PS score of 0 to 1. 10. Expected survival of ≥ 12 weeks. 11. Adequate organ function confirmed by laboratory testing within 7 days prior to randomization (use of blood products or cell growth factors within 14 days before testing is not permitted): - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$; - Platelet count $\geq 100 \times 10^9/L$; - Hemoglobin ≥ 90 g/L; - Total serum bilirubin (TBIL) $\leq 1.5 \times$ the upper limit of normal (ULN); - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN; for subjects with liver metastases, AST and ALT $\leq 5 \times$ ULN; - Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula); - Activated partial thromboplastin time (aPTT) and international normalized ratio (INR) ≤ 1.5 (Subjects receiving prophylactic anticoagulation therapy with an INR ≤ 3 are eligible for enrollment); - Serum albumin ≥ 30 g/L.
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	12. For female subjects of childbearing potential, a negative pregnancy test result must be confirmed during the screening period (subjects with a positive human chorionic gonadotropin [HCG] result may be enrolled if, in the judgment of the investigator, the result is clinically insignificant and pregnancy is excluded). Subjects must agree to use effective contraception and refrain from egg donation from the time of ICF signing until 7 months after the last dose of the IMP.
Exclusion Criteria	Subjects who meet any of the following criteria may not be enrolled in this study: 1. Histologically confirmed sarcomatous histologic subtype, or mixed tumors containing sarcomatous components. 2. Untreated or active central nervous system (CNS) metastases, or a history of or current meningeal metastases. Subjects with previously CNS metastases who have undergone adequate local therapy (surgery or radiotherapy), do not require corticosteroid therapy, have neurologically returned to baseline (excluding residual signs or symptoms related to CNS treatment), and have been clinically stable for ≥ 4 weeks may be enrolled. 3. Prior treatment with topoisomerase I inhibitors (including but not limited to irinotecan, topotecan), or treatment with antibody-drug conjugates (ADCs) containing a topoisomerase I inhibitor payload, such as Enhertu (DS-8201a) and U3-1402. 4. Receipt of systemic anti-tumor therapy within 4 weeks prior to the initiation of study treatment. For prior treatment with small molecule targeted therapies, the interval between end of treatment and the first dose of study treatment must be at least 5 half-lives of the drug or 7 days. 5. Presence of symptomatic, poorly controlled, or moderate or greater pleural effusion, pericardial effusion, or ascites. Subjects who have undergone effusion drainage (excluding diagnostic thoracentesis) and have remained clinically stable for at least 2 weeks' post-procedure may be enrolled. (Prior to ICF signing, local treatment of serosal cavity effusions per standard of care is permitted.) 6. Receipt of palliative radiotherapy within 7 days prior to the first dose of study treatment. 7. History of or concurrent other malignancies, with the exception of cured basal cell carcinoma of the skin, carcinoma in situ of the cervix, ductal carcinoma in situ of the breast, papillary thyroid cancer, or other malignancies that have been adequately treated and cured for ≥ 3 years prior to randomization and for which there is documented evidence of no recurrence or metastasis. 8. Toxicities from prior anti-tumor therapy not resolved to Grade ≤ 1 according to NCI-CTCAE v6.0 (except for lymphopenia, alopecia, fatigue, and laboratory abnormalities specified in the inclusion criteria. Chronic Grade 2 toxicities that are deemed tolerable by the investigator may be exempted). 9. History of interstitial pneumonia/interstitial lung disease or non-infectious pneumonia (e.g., radiation pneumonitis) requiring steroid therapy; current or suspected interstitial pneumonia/interstitial lung disease, non-infectious pneumonia, or other active pneumonitis.

	Subjects with a history of Grade ≥ 3 interstitial pneumonia during prior immune checkpoint inhibitor therapy are also excluded. 10. Active pulmonary tuberculosis, based on the Investigator's assessment. [Subjects may be enrolled if they have completed adequate tuberculosis treatment and have discontinued anti-tuberculosis therapy for ≥ 3 months prior to randomization.] 11. Known pulmonary impairment caused by pulmonary comorbidities, including but not limited to any underlying lung disease e.g., pulmonary embolism within 3 months prior to the first dose, severe asthma, severe chronic obstructive pulmonary disease, restrictive pulmonary disease, etc. 12. Autoimmune, connective tissue, or inflammatory diseases involving the lungs (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc.), or a history of lobectomy or pneumonectomy. 13. Clinical cardiac symptoms or conditions that are not well controlled, such as: (1) heart failure classified as New York Heart Association (NYHA) Class ≥ 2 or left ventricular ejection fraction (LVEF) $< 50\%$; (2) unstable angina; (3) myocardial infarction within 1 year prior to randomization; (4) clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention; (5) corrected QT interval by Fridericia's formula (QTcF) > 470 ms; (6) hypertension not adequately controlled with medication (subjects with blood pressure controlled to $\leq 160/100$ mmHg with antihypertensive therapy may be enrolled). 14. Arterial/venous thrombotic events within 1 month prior to randomization, including but not limited to cerebrovascular accident and deep vein thrombosis. Subjects with muscular venous thrombosis or catheter-related thrombosis of infusion ports may be enrolled if deemed no risk by the investigator. 15. Gastrointestinal perforation or fistula, urethral fistula, or intra-abdominal abscess within 3 months prior to randomization. Subjects who have undergone ostomy creation or ureteral stent placement and are considered stable by the investigator may be enrolled. 16. Intestinal obstruction, symptoms or signs suggestive of intestinal obstruction, or need for parenteral nutrition within 3 months prior to the start of study treatment. Subjects who have underwent surgical intervention with complete resolution of obstruction may be screened. Subjects who have previously received enteral stent implantation and have not had the stent removed by the screening period are excluded. 17. Severe infections within 1 month prior to randomization, including but not limited to infectious complications requiring hospitalization, bacteremia, or severe pneumonia. Subjects with any active infection requiring intravenous systemic therapy, or those experiencing unexplained fever $> 38.5^{\circ}\text{C}$ during the screening period or prior to randomization, are excluded. Subjects receiving prophylactic oral antibiotic therapy are allowed to be randomized and enrolled. 18. Active hepatitis B (defined as positive hepatitis B surface antigen [HBsAg] and hepatitis B virus deoxyribonucleic acid [HBV-DNA] ≥ 500 IU/mL during screening) or active hepatitis C (defined as positive hepatitis C virus [HCV] antibody with detectable HCV ribose nucleic acid [RNA] during screening).
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	19. History of immunodeficiency, including positive human immunodeficiency virus (HIV) test, or other acquired or congenital immunodeficiency disorders, or history of organ transplantation. 20. Major surgery (excluding diagnostic procedures or biopsies) performed within 28 days prior to the first dose. Subjects who have undergone traumatic minor surgery (e.g., biopsy, endoscopy, drainage) within 7 days prior to the first dose, or those with non-healing wounds (severe, non-healing, or dehiscent wounds) are excluded. 21. Known hypersensitivity to any component of SHR-A1811, or a history of severe allergic reactions to other monoclonal antibody fusion proteins. 22. Uncontrolled psychiatric disorders, or known history of alcohol abuse, drug abuse, substance misuse, or incarceration that may interfere with the completion of the study procedures. 23. Presence of other severe comorbidities, including but not limited to acute myocardial infarction within the past 3 months, acute cerebral infarction within the past 3 months, or decompensated liver cirrhosis. 24. Any other condition that, in the opinion of the investigator, may increase the risk associated with participation in the study, interfere with study results, or render the subject unsuitable for participation.
Assessment of Efficacy	Efficacy Parameters PFS: Defined as the time from the date of randomization to the date of first documented radiologic PD or death from any cause, whichever occurs first. OS: Defined as the time from the date of randomization to death from any cause. ORR: Defined as the proportion of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR), as assessed per RECIST v1.1. For responses of CR or PR, confirmation is required at least 4 weeks (≥ 28 days) after the initial evaluation. DoR: Defined as the time from the first evaluation of CR or PR to the date of first evaluation of PD or death, whichever occurs first, in subjects who achieve confirmed CR or PR. DCR: Defined as the proportion of subjects whose BOR is CR, PR, or stable disease (SD), as assessed per RECIST v1.1. RR: Defined as the proportion of subjects achieving a response according to both RECIST v1.1 and the GCIG CA-125 criteria. CA-125 RR: Defined as the proportion of subjects achieving a response based on the GCIG CA-125 criteria. Efficacy Assessment <u>Assessment of PFS, ORR, DoR, and DCR</u> These tumor response-based endpoints will be evaluated by both the IRC and the investigator, based on radiologic assessments performed in accordance with RECIST v1.1. During the treatment period, tumor imaging assessments will be conducted every 6 weeks ± 7 days for the first 36 weeks, and every 12 weeks ± 7 days thereafter, until documented PD, initiation of other anti-

	tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor (as specified in Table 1 and Table 2). <u>OS assessment</u> During the safety follow-up period (within 40 days [+7 days] after the last dose of study treatment), data on survival status and subsequent anti-tumor therapies will be collected. After the completion of the safety follow-up, survival follow-up will be conducted every 2 months ± 7 days (additional survival follow-up may be performed as needed). Survival data and information on subsequent anti-tumor therapies will be collected until the subject dies, is lost to follow-up, withdraws informed consent and declines any form of follow-up, or the study is terminated early by the sponsor. <u>Assessment of RR and CA-125</u> CA-125 RR will only be assessed in subjects with baseline CA-125 levels $\geq 2 \times$ the ULN (as measured within 7 days prior to the initiation of treatment). A CA-125 response is defined as a $\geq 50\%$ reduction in CA-125 level from the last pre-treatment measurement, confirmed by a second assessment at least 28 days later, with the confirmatory value being $\leq 110\%$ of the previous measurement. The date of CA-125 response is defined as the date when the $\geq 50\%$ reduction is first observed. CA-125 measurements will be performed concurrently with each imaging assessment (± 3 days). Unscheduled assessments may be conducted at the discretion of the investigator. CA-125 monitoring will continue until documented PD, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.
Safety Evaluation	Safety evaluation will include the collection of AEs and SAEs, as well as laboratory tests (including routine blood test, biochemistry, urinalysis, routine stool test, coagulation, thyroid function, etc.), vital signs, ECG, and ECOG PS scores. The time points and requirements for data collection are specified in Table 1 and Table 2.
PK and Immunogenicity Evaluation	For subjects in the experimental group receiving SHR-A1811 treatment, blood samples for PK and immunogenicity analysis will be collected at the time points and under the conditions specified in Table 3. Validated methods will be used to determine the concentrations of toxin-conjugated antibody and the free toxin SHR169265. ADA and NAb analyses will also be performed.
Sample Size Determination	The primary endpoints are PFS assessed by the IRC based on RECIST v1.1 and the OS. Superiority testing will be conducted between the experimental and control groups in the main cohort. A total of approximately 350 subjects are planned for enrollment in the main cohort and approximately 70 subjects in the extension cohort. The assumptions and details for sample size determination are as follows: Subjects will be randomized 1:1, with an anticipated enrollment period of 20 months and uniform enrollment rate. As described in Section 2.1.4, for the primary endpoint PFS, it is assumed that the median PFS in the control group is 4 months, and the HR comparing the experimental group to the control group is 0.612. The annual dropout rate is assumed to be 10% for the experimental group and 20% for the control group. Type I error controlled at 0.025 (one-sided). After enrollment is completed, based on approximately 175 PFS events

	collected in the main cohort (corresponding to a sample size of 302), there is about a 90% probability of detecting a difference favoring the experimental group over the control group. For the primary endpoint OS, whether the experimental group is superior over the control group will be tested in the main cohort if the test for PFS reaches statistical significance. Based on the above assumptions for enrollment duration and sample size, as described in Section 2.1.4, it is assumed that the median OS in the control group is 13 months, and the HR comparing the experimental group to the control group is 0.67. The annual dropout rate for OS is assumed to be 5%. An interim efficacy analysis for OS will be performed in the main cohort after approximately 184 OS events have been collected, accounting for approximately 72% of the total expected OS events. With a type I error rate controlled at 0.025 (one-sided), approximately 257 OS events are expected to be collected around 26 months after the last subject is enrolled, providing approximately 89% power to demonstrate superiority of the experimental group over the control group. It is planned to enroll approximately 70 subjects in the extension cohort from India, Australia and/or other country(ies). The pooled data from the main cohort and the extension cohort will be analyzed using the same statistical method used in the main cohort analyses and the method details will be described in the SAP. It is planned to perform subgroup analyses in the extension cohort. The details of analyses will be defined in the SAP.
Interim Analysis	The main cohort plans to conduct one interim efficacy analysis for OS. This OS interim analysis will be conducted after approximately 184 OS events have been collected, accounting for approximately 72% of the total expected OS events. If the PFS analysis time point and the OS interim analysis time point are close, the two analyses may be combined; otherwise, only a descriptive analysis of OS will be performed at the PFS analysis, and the OS interim analysis will be conducted when approximately 184 OS events have been collected. If the OS interim analysis does not demonstrate superiority, a final OS analysis will be conducted when approximately 257 OS events have been collected, which is expected to occur approximately 26 months after the last subject is enrolled.
Statistical Analysis	Hypothesis Testing The primary endpoint of the study is PFS as assessed by the IRC based on RECIST v1.1. The hypothesis test for the main cohort is as follows: $H_{01}: HR_{PFS} \geq 1 \text{ vs. } H_{11}: HR_{PFS} < 1$ The hypothesis test for another primary endpoint, OS, is as follows: $H_{02}: HR_{OS} \geq 1 \text{ vs. } H_{12}: HR_{OS} < 1$ No formal hypothesis testing will be conducted for the extension cohort. Analysis Populations Intent-to-Treat (ITT) Analysis Set: All randomized subjects, analyzed according to the treatment group to which they have been randomized. Safety Analysis Set (SS): All enrolled subjects who have received at least one dose of the IMP.

	Pharmacokinetic Concentration Set (PKCS): All enrolled subjects who have received at least one dose of the IMP and have at least one evaluable PK concentration data point. Immunogenicity Analysis Set (IMS): All enrolled subjects who have received at least one dose of the IMP and have both baseline and at least one post-baseline immunogenicity assessment. Similarly, analysis sets for the extension cohort will be defined. General Analysis Unless otherwise specified, descriptive statistics will be used to summarize the data according to the following general principles: Categorical variables will be summarized using frequency counts and percentages. Continuous variables will be summarized using number of subjects, mean, standard deviation, median, maximum, and minimum. For PK concentration data, depending on the data type, summaries may include number of subjects, mean, geometric mean, standard deviation, coefficient of variation, geometric coefficient of variation, median, maximum, and minimum. Analyses for Primary Objective <u>Primary analysis of primary estimand 1 (PFS assessed by the IRC per RECIST v1.1)</u> Based on the ITT analysis set, PFS as assessed by the IRC per RECIST v1.1 will be analyzed as follows: in the extension cohort, a stratified Cox proportional hazards model will be used to estimate the HR (experimental group vs. control group) and the corresponding 95% confidence interval (CI), accounting for the randomization stratification factors. The estimated HR will be presented with the estimated HR from the main cohort. A combined analysis estimate of HR and 95% confidence interval will be calculated. The Kaplan-Meier method will be used to estimate PFS survival rates by treatment group and to generate time-PFS survival curves. PFS survival rates at specific time points (e.g., 6 months/12 months) will also be estimated, along with their 95% CIs. In addition, the 25th, 50th (median), and 75th percentiles of PFS for each treatment group will be estimated using the Kaplan-Meier method, and their 95% CIs will be calculated using the Brookmeyer-Crowley method. Descriptive statistics will be provided by treatment group, including the number and proportion of subjects with PFS events (including PD and death without PD), as well as the number and proportion of censored subjects. Reasons for censoring will be categorized and summarized. <u>Sensitivity analysis of primary estimand 1</u> Sensitivity analysis 1: An unstratified Cox proportional hazards model will be used to estimate the HR and its 95% CI. Sensitivity analysis 2: A Cox proportional hazards model will be used, incorporating the stratification factors as recorded in the electronic data capture (EDC) system, to calculate the HR, and its 95% CI. <u>Analysis of primary estimand 2 (OS)</u> OS will be analyzed based on the ITT analysis set following the same analytical approach as the primary analysis for the primary endpoint (PFS assessed by the IRC based on RECIST v1.1). <u>Sensitivity analysis of primary estimand 2</u>
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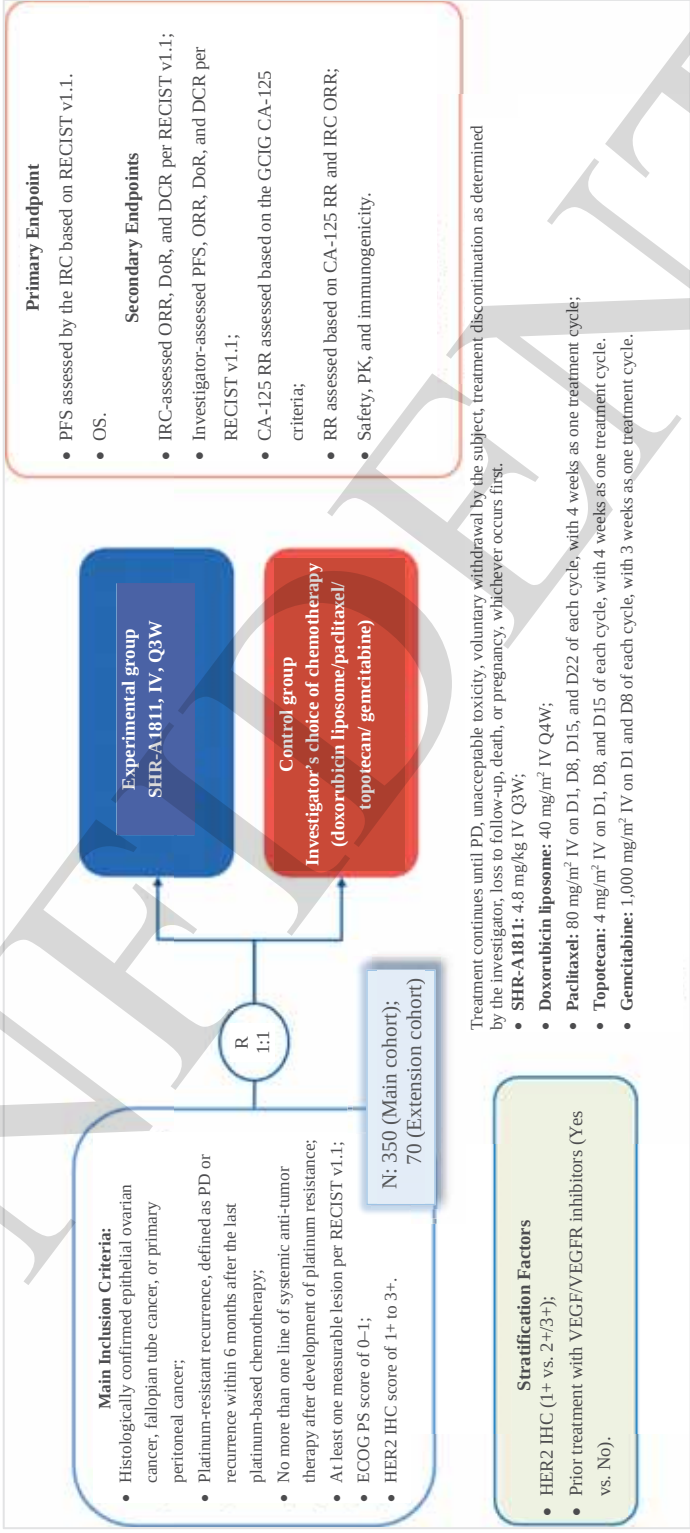
	Sensitivity analyses 1 and 2 will be performed using the same methods as for sensitivity analyses 1 and 2 of estimand 1. Sensitivity analysis 3: Considering that some subjects in the control group may receive ADCs with a topoisomerase inhibitor payload after disease recurrence, an appropriate method (e.g., two-stage method) will be applied depending on data availability, as further detailed in the Statistical Analysis Plan (SAP). <u>Supplementary analysis of primary estimand 2</u> Since OS may be influenced by subsequent anti-tumor therapies, different strategies for handling intercurrent events will be applied for these subsequent anti-tumor therapies. For example, for treatment with ADCs containing a topoisomerase inhibitor payload, a hypothetical strategy will be adopted. In this case, data will be censored at the start date of treatment with such ADCs prior to the occurrence of the event. Analyses for Secondary Objectives <u>Secondary efficacy analysis</u> For investigator-assessed PFS based on RECIST v1.1, the same analysis approach as the primary analysis for the primary endpoint (IRC-assessed PFS based on RECIST v1.1) will be applied. For DoR assessed by the IRC/investigator according to RECIST v1.1, the Kaplan-Meier method will be used to estimate survival rates for each endpoint by treatment group and to generate time-PFS survival curves. Survival rates for each endpoint at specific time points (e.g., 6 months/12 months) will also be estimated, along with their 95% CIs. In addition, the 25th, 50th (median), and 75th percentiles of each endpoint for each treatment group will be estimated using the Kaplan-Meier method, and their 95% CIs will be calculated using the Brookmeyer-Crowley method. For ORR and DCR assessed by the IRC according to RECIST v1.1, and for ORR and DCR assessed by the investigator based on RECIST v1.1, as well as RR and CA-125 RR, point estimates and two-sided 95% CIs will be calculated by treatment group based on the ITT analysis set using the Clopper-Pearson method. The Cochran-Mantel-Haenszel (CMH) method, which takes into account the randomization stratification factors, will be used to calculate the nominal <i>P</i>-values for between-group comparisons. The between-group differences (experimental group minus control group) and corresponding two-sided 95% CIs will be calculated using the normal approximation method. <u>Safety analysis</u> Based on the SS analysis set, descriptive statistics will be used to summarize AEs, laboratory tests, ECG, ECOG PS scores, and other safety parameters, including but not limited to: - Incidence and severity of AEs; - Correlation of AEs with the IMP; - AEs leading to treatment discontinuation, dose reduction, or treatment interruption; - SAEs; - AEs resulting in death; - Normal and abnormal changes from baseline in laboratory tests, ECG, and ECOG PS scores.
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	<u>PK analysis</u> Based on the PKCS analysis set, the serum concentrations of the toxin-conjugated antibody SHR-A1811 and the free toxin will be analyzed. Descriptive statistics will be used to summarize the serum drug concentrations in subjects by analyte, treatment cycle, and scheduled sampling time points. <u>Immunogenicity analysis</u> If applicable, based on the IMS analysis set, the proportion of subjects with positive immunogenicity results, time to first positive immunogenicity result, duration of positive immunogenicity, and whether neutralizing activity is present will be analyzed. To explore potential correlations between immunogenicity and serum trough drug concentrations, safety, and efficacy, the incidence and types of AEs may be further analyzed in relation to overall trough drug concentration and immunogenicity status.
Committees	An Independent Review Committee (IRC) will be established for this study to perform independent assessments of all tumor imaging data. The IRC will determine tumor response and PD based on RECIST v1.1. (When the investigator first determines that a subject has PD, the corresponding imaging data must be promptly uploaded to the independent imaging system for confirmation.) The IRC assessment results will be used to determine whether a subject should discontinue IMP treatment and for the analysis of study results. An Independent Data Monitoring Committee (IDMC) will also be established to periodically review safety data. The IDMC may provide recommendations regarding study continuation, protocol modification, or termination based on observed safety data. The composition, responsibilities, operations, and governance of the IDMC will be described in a separate IDMC charter.

1.2. Study Schematic Diagram

The overall study design is illustrated in Figure 1.

Figure 1: Study Schematic Diagram



Abbreviations: CA-125 = cancer antigen 125; D = day; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; GCIG = Gynecologic Cancer InterGroup; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IRC = Independent Review Committee; IV = intravenous; N = number of subjects; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; Q3W = once every 3 weeks; Q4W = once every 4 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RR = response rate; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

1.3. Schedule of Activities

1.3.1. Schedule of Activities (Experimental Group)

Table 1 summarizes the schedule of visits and assessments for subjects in the experimental group. All baseline assessments should be conducted prior to administration of the IMP, with the assessment closest to the time of IMP administration considered as the baseline value. To ensure subject safety and rights, the investigator may arrange unscheduled visits in addition to those listed in this table.

Table 1: Schedule of Activities (Experimental Group)

Visit Identifier	Screening Period ^[1]		Treatment Period ^a				End-of-Treatment Visit ^[2]	Follow-Up Period	
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward			Safety Follow-Up ^[3]	Survival Follow-Up ^[4]
			D1 ^b	D8, D15	D1	D8, D15 (optional)			
							±3 d		
Baseline data									
Signing of informed consent form ^[5]	X							+7 d	±7 d
Demographics ^[6]	X								
Tumor history ^[7]	X								
Medical history ^[8]	X								
Concomitant treatments ^[9]				X					
AE ^[10]				X					
Laboratory tests									
Routine blood test ^[11]		X		X (excluding C1D1)	X	X	X	X	
Biochemistry ^[12]		X		X (excluding C1D1)	X	X	X	X	

Visit Identifier	Screening Period ^[1]		Treatment Period ^a				End-of-Treatment Visit ^[2]	Follow-Up Period	
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward			Safety Follow-Up ^[3]	Survival Follow-Up ^[4]
			D1 ^b	D8, D15	D1	D8, D15 (optional)	+7 d	40 Days After the Last Dose	Once Every 2 Months
			±3 d	±1 d	±3 d	±1 d			
Urinalysis ^[13]		X	X (excluding C1D1)		X		X	X	
Routine stool test ^[14]		X		When clinically indicated			X		
Coagulation ^[15]		X	X (excluding C1D1)		X		X		
Thyroid function ^[16]	X				Once every 4 cycles		X		
Cardiac enzymes ^[17]		X			Once every 4 cycles		X		
Viral test ^[18]	X								
Pregnancy test ^[19]		X	X (excluding C1D1)		X		X		
Tumor markers ^[20]		X	From randomization, assessed concurrently with each imaging evaluation (±3 days from imaging date)						
Clinical assessments and examinations									
Vital signs ^[21]		X	X	X	X	X	X	X	
Physical examination ^[22]		X	When clinically indicated				X		
Height measurement ^[23]		X							
Weight measurement ^[24]		X	X		X		X		
ECOG PS score ^[25]		X	X (excluding C1D1)		X		X	X	
12-lead ECG ^[26]		X	X (excluding C1D1)		X		X	X	

Visit Identifier	Screening Period ^[1]		Treatment Period ^a				End-of-Treatment Visit ^[2]	Follow-Up Period	
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward			Safety Follow-Up ^[3]	Survival Follow-Up ^[4]
			D1 ^b	D8, D15	D1	D8, D15 (optional)		40 Days After the Last Dose	Once Every 2 Months
Echocardiography ^[27]	X		±3 d	±1 d	±3 d	±1 d		+7 d	±7 d
B-mode ultrasound examination of deep veins in both lower extremities ^[28]	X		When deemed necessary by the investigator						
Treatment with IMP									
Randomization ^[29]			X						
SHR-A1811 administration ^[30]			X		X				
Imaging evaluation									
Imaging examination ^[31]	X		From randomization: every 6 weeks during the first 36 weeks, then every eeks thereafter				X	Subjects who end treatment without radiologic PD should continue imaging assessments per protocol	
PRO assessment									
EQ-5D-5L and FOSI scales ^[32]			Every 2 cycles post-randomization (e.g., C1D1, C3D1, C5D1, etc.)				X	X	
Biological sample collection									
PK/immunogenicity sample collection ^[33]			Refer to Table 3 for details.						
Biomarker sample collection ^[34]	X								

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; BRCA = breast cancer susceptibility gene; C = cycle; CA-125 = cancer antigen 125; CR = complete response; CT = computed tomography; d/D = day; DNA = deoxyribonucleic acid; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; IMP = investigational medicinal product; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; PRO = patient-reported outcome; QTc = corrected QT interval; RNA = ribonucleic acid; RTSM = randomization and trial supply management.

a. The treatment cycle for the experimental group is 3 weeks.

b. From C2 onwards, the dosing window for each IMP administration is ± 3 days from the scheduled administration date. If dosing is delayed beyond the window, subsequent dosing schedules will be calculated from the actual date of the previous administration. Doses administered within the window will follow the originally planned schedule.

[1] **Screening period:** The screening period is defined as the time from the date the subject signs the informed consent form (ICF) to the date of randomization or screen failure (see Section 5.6 for the definition of “screen failure”) and must not exceed 4 weeks in total.

Re-screening is permitted for subjects who fail screening. In case of re-screening, a new ICF must be signed, and a new subject number must be assigned. Each subject may only be re-screened once. If assessments performed during the initial screening remain within the allowable window during the re-screening period, they do not need to be repeated. A single re-test of abnormal laboratory parameters identified during the screening period is permitted. If the re-test results meet protocol-defined criteria, the subject may be enrolled. This scenario is not considered re-screening.

[2] **End-of-treatment visit:** This visit must be performed on the day treatment is discontinued or within 7 days thereafter. If safety assessments were performed within 7 days before end of treatment, they do not need to be repeated at this visit. Subjects with radiologically confirmed PD do not require tumor imaging or CA-125 testing at the end-of-treatment visit. For subjects discontinuing treatment for other reasons, if more than 4 weeks have elapsed since the last imaging assessment, tumor imaging and CA-125 testing must be performed at the end-of-treatment visit.

[3] **Safety follow-up:** 40 days (+7 days) after the last dose of IMP, regardless of whether the subject has initiated a new anti-tumor therapy, the subject is required to return to the site for a safety follow-up visit. If the subject is unable to resume IMP due to an AE, the date of last administration is considered the date of last dose. If this date is more than 40 days from the decision to terminate treatment, it is not considered a protocol deviation. However, it is recommended that the subject return to the site for safety follow-up as soon as possible. Information on AEs, concomitant treatments, survival status, and subsequent anti-tumor therapies must be collected during this visit.

[4] **Survival follow-up:** After the completion of the safety follow-up, survival follow-up will be conducted every 2 months ± 7 days (additional survival follow-up may be performed as needed). Survival data and information on subsequent anti-tumor therapies will be collected until the subject dies, is lost to follow-up, withdraws informed consent and declines any form of follow-up, or the study is terminated early by the sponsor.

[5] **Signing of ICF:** Subjects must sign the ICF before undergoing any screening procedures specified in this study. Assessments performed at the site prior to ICF signing may be used for screening evaluation if they meet protocol requirements. The informed consent process is described in Section 10.3.

[6] **Demographics:** Includes sex, date of birth, and age.

[7] **Tumor history:** Includes clinical diagnosis of the tumor, pathological diagnosis, clinical stage, molecular diagnostics (including but not limited to BRCA gene mutation status), and treatment history (e.g., surgery, radiotherapy, local or systemic therapies).

[8] **Medical history:** Includes diagnosis and treatment history of concomitant diseases, prior malignancies excluding treatment with the IMP, history of allergies, alcohol use, and smoking history.

[9] **Concomitant treatments:** All concomitant medications and non-medication concomitant therapies (excluding drug solvents) administered within 28 days prior to randomization and during the treatment period will be recorded, until the end of the safety follow-up or initiation of new anti-tumor therapy, whichever occurs first. After this time point, only concomitant treatments related to reported AEs need to be recorded.

- [10] **AE:** AEs will be recorded from the time the subject signs the ICF until the end of the safety follow-up period. For further details, refer to Section 8.4.2.
- [11] **Routine blood test:** Includes white blood cell count, absolute neutrophil count, absolute lymphocyte count, red blood cell count, hemoglobin, and platelet count. The routine blood test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. For subjects receiving SHR-A1811, additional testing will be performed on D8 and D15 during the first 4 cycles. From C5 onward, additional testing will be done on D8 (D15 testing may be added at the investigator's discretion and, if performed, will follow the same procedures as D8).
- [12] **Biochemistry:** Includes serum albumin, serum total protein, serum alkaline phosphatase, serum ALT, serum AST, serum TBIL, serum γ -glutamyl transferase, serum direct bilirubin, serum triglycerides, serum total cholesterol, BUN/serum urea (serum urea preferred), serum creatinine, uric acid, serum potassium, serum sodium, serum chloride, serum total calcium, serum magnesium, serum inorganic phosphate, serum lactate dehydrogenase, and fasting plasma glucose. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. For subjects receiving SHR-A1811, additional testing will be performed on D8 and D15 during the first 4 cycles. From C5 onward, additional testing will be done on D8 (D15 testing may be added at the investigator's discretion and, if performed, will follow the same procedures as D8). Serum lipase or serum amylase: The test will be performed within 7 days prior to randomization and as clinically indicated during treatment if the subject develops symptoms suggestive of pancreatitis (e.g., abdominal pain, bloating).
- [13] **Urinalysis:** Includes urine white blood cells, urine protein, urine red blood cells, and urine occult blood. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. If urine protein is detected at $\geq 2+$ in two consecutive visits, 24-hour urine protein quantification must be performed.
- [14] **Routine stool test:** If fecal occult blood is positive during the screening period, retesting is required (except for weakly positive results deemed clinically insignificant by the investigator). If the retest remains positive, the investigator will determine whether gastrointestinal endoscopy is required. During treatment, if fecal occult blood is positive, the investigator will determine clinical significance and may order gastroscopy if necessary. Testing should be performed within 7 days prior to randomization and at the end-of-treatment visit (if not performed within the previous 7 days). Additional testing during treatment may be performed as deemed necessary by the investigator based on the subject's symptoms.
- [15] **Coagulation:** Includes prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, and at the end-of-treatment visit (if not performed within the previous 7 days).
- [16] **Thyroid function:** Includes free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). Testing will be performed once within 28 days prior to randomization, and once every 4 cycles starting from C5. A final test will be conducted at the end-of-treatment/withdrawal visit (if no test has been performed within the past 14 days).
- [17] **Cardiac enzymes:** Includes serum creatine kinase (CK), creatine kinase-MB (CK-MB), troponin I or troponin T, and N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP). Testing will be performed once within 7 days prior to randomization, and once every 4 cycles starting from C5. A final test will be conducted at the end-of-treatment/withdrawal visit (if no test has been performed within the past 14 days).
- [18] **Viral test:** Includes hepatitis B serology panel (if HBsAg is positive, quantitative HBV-DNA testing is required), HCV antibody (if positive, HCV-RNA testing is required), and HIV antibody (as per Investigator's discretion). Testing must be performed once within 28 days prior to randomization.
- [19] **Pregnancy test:** Female subjects of childbearing potential will undergo serum HCG testing once within 7 days prior to randomization, before dosing on D1 of each cycle from C2 onward, and at the end-of-treatment visit (if not performed within the previous 7 days). Additional testing may be conducted during the study as deemed necessary by the investigator based on the subject's condition.

- [20] **Tumor markers:** CA-125 testing will be performed once within 7 days prior to randomization, and thereafter at each scheduled imaging assessment (± 3 days from the imaging date; the earliest imaging within a given imaging cycle will be used for reference). Unscheduled testing may be conducted at the investigator's discretion. Testing will continue until documented PD, initiation of new anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.
- [21] **Vital signs:** Includes body temperature, respiratory rate, pulse, and blood pressure. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. For subjects receiving SHR-A1811, additional testing will be performed on D8 and D15 during the first 4 cycles. From C5 onward, additional testing will be done on D8 (D15 testing may be added at the investigator's discretion and, if performed, will follow the same procedures as D8).
- [22] **Physical examination:** Includes general condition, head and face, skin, lymph nodes, eyes (scleras and pupils), ears, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive-urinary system (when clinically indicated), musculoskeletal system, nervous system, and mental condition. Physical examination will be performed within 7 days prior to randomization and at the end-of-treatment visit. (Apart from the screening and end-of-treatment visits, full physical examination results do not need to be recorded in the eCRF during the treatment period; only abnormalities should be reported.) Targeted physical examinations should be performed during treatment if clinically indicated.
- [23] **Height measurement:** Height will be measured once within 7 days prior to randomization.
- [24] **Weight measurement:** Weight will be measured once within 7 days prior to randomization, before dosing on D1 of each cycle, and at the end-of-treatment visit. The weight measurement prior to D1 dosing in each cycle may be used to adjust the dosing.
- [25] **ECOG PS score:** ECOG PS will be assessed once within 7 days prior to randomization, before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit, and at 40 days (+7 days) after the last dose.
- [26] **12-lead ECG:** Includes heart rate, QT interval, QTc, and PR interval. ECG assessments will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. If QTc > 470 ms is observed during screening, two additional ECGs must be performed (on the same day) at intervals of no less than 10 min. The average of the three QTc values must meet the enrollment criteria. During treatment, if new clinically significant ECG abnormalities are detected, the investigator will determine whether additional ECGs are required.
- [27] **Echocardiography:** Includes left ventricular ejection fraction (LVEF). Echocardiography will be performed once within 28 days prior to randomization, and once every 4 cycles starting from C5. One final echocardiogram will be performed at the end-of-treatment/withdrawal visit (if no assessment has been performed within the previous 14 days).
- [28] **B-mode ultrasound examination of deep veins in both lower extremities:** It will be performed once within 28 days prior to randomization. Additional assessments may be conducted as deemed necessary by the investigator.
- [29] **Randomization:** Subjects who meet all eligibility criteria will be randomized through the RTSM system. The first dose (C1D1) must be administered within 3 calendar days after randomization.
- [30] **SHR-A1811 administration:** SHR-A1811 will be administered via intravenous infusion on D1 of each cycle. The first infusion should be administered over 90 ± 10 min. If no infusion-related reactions occur after the first dose, subsequent infusions may be shortened to approximately 30 min (minimum 20 min, maximum 60 min). The dosing regimen is 4.8 mg/kg once every 3 weeks. Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1). If the subject's body weight at follow-up remains within $\pm 5\%$ of the baseline value (C1D1), excluding the $\pm 5\%$ boundary, recalculation of the theoretical dose is not required. If the body weight change at that follow-up is $\geq 5\%$ or $\leq -5\%$ compared to baseline value, the theoretical dose should be recalculated, and the weight set as the new baseline weight. Only dose reductions are permitted (first reduction: 4.0 mg/kg; second reduction: 3.2 mg/kg); dose re-escalation is not allowed.
- [31] **Imaging examination:** Imaging examinations required during the **screening period** include contrast-enhanced CT or MRI of the chest, abdomen, pelvis, and any other sites clinically suspected of disease. (If the subject is allergic to CT contrast agents, a non-contrast CT of the chest and contrast-enhanced MRI of the abdomen and pelvis should be performed.) For subjects with known or suspected brain metastases, contrast-enhanced MRI or CT of the brain is required. For subjects with known or suspected

bone metastases, a bone scan is required. (If abnormal bone lesions are identified, additional local bone CT or MRI should be performed as appropriate.) Bone scans performed within 42 days prior to randomization are acceptable. Baseline tumor assessments during the screening period may be completed up to 4 weeks prior to randomization. CT/MRI results obtained prior to signing the ICF may be used for screening tumor assessments if they meet protocol requirements.

During the treatment period, all imaging examinations must be performed under the same conditions as baseline (e.g., slice thickness, contrast agent use). Imaging examinations should be performed every 6 weeks during the first 36 weeks post-randomization, and every 12 weeks thereafter. Examined regions should include the chest, abdomen, pelvis, and any other sites with baseline lesions. For subjects with known bone metastases, bone scans will be repeated when bone progression is suspected or to confirm CR. Additional imaging should be performed as needed if new lesions are suspected.

If PD is suspected during treatment (e.g., due to worsening symptoms), unscheduled imaging examinations may be performed. Bone scan examination is required when bone metastases are clinically suspected. If abnormal bone metastases are found, further local bone CT or MRI examination is required according to the site; enhanced MRI or enhanced CT of the brain must be performed for patients suspected of brain metastases.

Confirmation must be performed no less than 4 weeks after the first PR/CR. The window period allowed by the imaging examination schedule is ± 7 days, and the imaging examination time is not affected by drug interruption.

Except for subjects who discontinue treatment due to radiologically confirmed PD, subjects who terminate treatment for other reasons must undergo imaging assessment at the end-of-treatment visit if no imaging was performed within the previous 4 weeks. Post-treatment, subjects must continue imaging assessments according to the protocol-defined frequency (based on the date of the last imaging) until documentation of PD, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.

[32] **EQ-5D-5L and FOSI scales:** Subjects will complete the scales on D1 of every two cycles (e.g., C1D1, C3D1, C5D1, and so on), at the end-of-treatment visit, and at 40 days (+7 days) after the last dose. The scales must be independently completed by the subject prior to any other assessments or treatment administration at each visit.

[33] **PK/immunogenicity blood collection:** Refer to Table 3 for the specific blood collection time points and requirements.

[34] **Biomarker sample collection:** Subjects should provide a tumor tissue sample. The sample should be either fresh or the most recently archived tumor tissue. Tumor tissue samples will be used for HER2 immunohistochemistry (IHC) and FISH testing at the sponsor-designated or local laboratory. See the laboratory manual for the collection and disposal of tumor samples.

1.3.2. Schedule of Activities (Control Group)

Table 2 summarizes the schedule of visits and assessments for subjects in the control group. All baseline assessments should be conducted prior to administration of the IMP, with the assessment closest to the time of IMP administration considered as the baseline value. To ensure subject safety and rights, the investigator may arrange unscheduled visits in addition to those listed in this table.

Table 2: Schedule of Activities (Control Group)

Visit Identifier	Screening Period ^[1]		Treatment Period ^a					End-of-Treatment Visit ^[2]	Follow-Up Period	
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward				Safety Follow-Up ^[3]	Survival Follow-Up ^[4]
			D1 ^{b,c,d,e,f}	D8, D15 ^{c,d,e}	D22 ^d	D1 ^{b,c,d,e,f}	D8, D15 ^{c,d,e}	D22 ^d		
			±3 d	±1 d	±1 d	±3 d	±1 d	±1 d	40 Days After the Last Dose	Once Every 2 Months
									+7 d	±7 d
Baseline data										
Signing of informed consent form ^[5]	X									
Demographics ^[6]	X									
Tumor history ^[7]	X									
Medical history ^[8]	X									
Concomitant treatments ^[9]					X					
AE ^[10]					X					
Laboratory tests										
Routine blood test ^[11]		X	X (excluding C1D1)	X	X	X	X	X	X	
Biochemistry ^[12]		X	X (excluding C1D1)	X	X	X	X	X	X	

Visit Identifier	Screening Period ^[1]		Treatment Period ^a					End-of-Treatment Visit ^[2]	Follow-Up Period		
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1-C4		C5 and Onward				Safety Follow-Up ^[3]	Survival Follow-Up ^[4]	
			D1 _{b,c,d,e,f}	D8, D15 _{c,d,e}	D22 ^d	D1 _{b,c,d,e,f}	D8, D15 _{c,d,e}	D22 ^d			
Urinalysis ^[13]		X	±3d	±1d	±1d	±3d	±1d	±1d	+7 d	±7 d	
			X (excluding C1D1)			X			X		
Routine stool test ^[14]		X	When clinically indicated								
Coagulation ^[15]		X	X (excluding C1D1)			X			X		
Thyroid function ^[16]	X					Once every 4 cycles			X		
Cardiac enzymes ^[17]		X				Once every 4 cycles			X		
Viral test ^[18]	X										
Pregnancy test ^[19]		X	X (excluding C1D1)			X			X		
Tumor markers ^[20]		X	From randomization, assessed concurrently with each imaging evaluation (±3 days from imaging date)								
Clinical assessments and examinations											
Vital signs ^[21]		X	X	X	X	X	X	X	X	X	
Physical examination ^[22]		X	When clinically indicated								X
Height measurement ^[23]		X									

Visit Identifier	Screening Period ^[1]		Treatment Period ^a					End-of-Treatment Visit ^[2]	Follow-Up Period	
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward				Safety Follow-Up ^[3]	Survival Follow-Up ^[4]
			D1 _{b,c,d,e,f}	D8, D15 _{c,d,e}	D22 ^d	D1 _{b,c,d,e,f}	D8, D15 _{c,d,e}	D22 ^d		
			±3d	±1d	±1d	±3d	±1d		40 Days After the Last Dose	±7d
Weight measurement ^[24]		X	X			X		X		
ECOG PS score ^[25]		X	X (excluding C1D1)			X		X	X	
12-lead ECG ^[26]		X	X (excluding C1D1)			X		X	X	
Echocardiography ^[27]	X					Once every 4 cycles		X		
B-mode ultrasound examination of deep veins in both lower extremities ^[28]	X					When deemed necessary by the investigator				
Treatment with IMP										
Randomization ^[29]			X							
Doxorubicin liposome administration ^[30]			X			X				
Paclitaxel administration ^[31]			X	X	X	X	X	X		
Topotecan administration ^[32]			X	X		X	X			

Visit Identifier	Screening Period ^[1]		Treatment Period ^a				End-of-Treatment Visit ^[2]	Follow-Up Period		
	Within 28 Days Prior to Randomization	Within 7 Days Prior to Randomization	C1–C4		C5 and Onward			Safety Follow-Up ^[3]	Survival Follow-Up ^[4]	
Gemcitabine administration ^[33]			D1 ^{b,c,d,e,f}	D8, D15 ^{c,d,e}	D22 ^d	D1 ^{b,c,d,e,f}	D8, D15 ^{c,d,e}	D22 ^d	40 Days After the Last Dose	Once Every 2 Months
			±3 d	±1 d	±1 d	±3 d	±1 d	±1 d		
			X	X (D8 only)		X	X (D8 only)		+7 d	±7 d
Imaging evaluation										
Imaging examination ^[34]	X		From randomization: every 6 weeks during the first 36 weeks, then every 12 weeks thereafter				X	Subjects who end treatment without radiologic PD should continue imaging assessments per protocol		
PRO assessment										
EQ-5D-5L and FOSI scales ^[35]			Every 2 cycles post-randomization (e.g., C1D1, C3D1, C5D1, etc.)				X	X		
Biological sample collection										
Biomarker sample collection ^[36]	X									

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; BRCA = breast cancer susceptibility gene; C = cycle; CA-125 = cancer antigen 125; CR = complete response; CT = computed tomography; d/D = day; DNA = deoxyribonucleic acid; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; FISH = fluorescence in situ hybridization; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor 2; HIV = human immunodeficiency virus; IMP = investigational medicinal product; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PR = partial response; PRO = patient-reported outcome; QTc = corrected QT interval; RNA = ribonucleic acid; RTSM = randomization and trial supply management.

- The treatment cycle for subjects receiving gemcitabine in the control group is 3 weeks; for all other regimens, the treatment cycle is 4 weeks.
- From C2 onwards, the dosing window for each IMP administration is ±3 days from the scheduled administration date. If dosing is delayed beyond the window, subsequent dosing schedules will be calculated from the actual date of the previous administration. Doses administered within the window will follow the originally planned schedule.

- c. Applicable to subjects receiving topotecan (administered on D1, D8, and D15 of each treatment cycle. D22 visit is at the discretion of the investigator. If conducted, the visit should include routine blood test, biochemistry, and vital sign assessments; no IMP will be administered).
- d. Applicable to subjects receiving paclitaxel (administered on D1, D8, D15, and D22 of each treatment cycle).
- e. Applicable to subjects receiving gemcitabine (administered on D1 and D8 of each treatment cycle. D15 visit is at the discretion of the investigator. If conducted, the visit should include routine blood test, biochemistry, and vital sign assessments; no IMP will be administered).
- f. Applicable to subjects receiving doxorubicin liposome (administered on D1 of each treatment cycle. D8/D15/D22 visits are at the discretion of the investigator. If conducted, the visits should include routine blood test, biochemistry, and vital sign assessments; no IMP will be administered).

[1] **Screening period:** The screening period is defined as the time from the date the subject signs the informed consent form (ICF) to the date of randomization or screen failure (see Section 5.6 for the definition of “screen failure”) and must not exceed 4 weeks in total.

Re-screening is permitted for subjects who fail screening. In case of re-screening, a new ICF must be signed, and a new subject number must be assigned. Each subject may only be re-screened once. If assessments performed during the initial screening remain within the allowable window during the re-screening period, they do not need to be repeated. A single re-test of abnormal laboratory parameters identified during the screening period is permitted. If the re-test results meet protocol-defined criteria, the subject may be enrolled. This scenario is not considered re-screening.

[2] **End-of-treatment visit:** This visit must be performed on the day treatment is discontinued or within 7 days thereafter. If safety assessments were performed within 7 days before end of treatment, they do not need to be repeated at this visit. Subjects with radiologically confirmed PD do not require tumor imaging or CA-125 testing at the end-of-treatment visit. For subjects discontinuing treatment for other reasons, if more than 4 weeks have elapsed since the last imaging assessment, tumor imaging and CA-125 testing must be performed at the end-of-treatment visit.

[3] **Safety follow-up:** 40 days (+7 days) after the last dose of IMP, regardless of whether the subject has initiated a new anti-tumor therapy, the subject is required to return to the site for a safety follow-up visit. If the subject is unable to resume IMP due to an AE, the date of last administration is considered the date of last dose. If this date is more than 40 days from the decision to terminate treatment, it is not considered a protocol deviation. However, it is recommended that the subject return to the site for safety follow-up as soon as possible. Information on AEs, concomitant treatments, survival status, and subsequent anti-tumor therapies must be collected during this visit.

[4] **Survival follow-up:** After the completion of the safety follow-up, survival follow-up will be conducted every 2 months $\pm$ 7 days (additional survival follow-up may be performed as needed). Survival data and information on subsequent anti-tumor therapies will be collected until the subject dies, is lost to follow-up, withdraws informed consent and declines any form of follow-up, or the study is terminated early by the sponsor.

[5] **Signing of ICF:** Subjects must sign the ICF before undergoing any screening procedures specified in this study. Assessments performed at the site prior to ICF signing may be used for screening evaluation if they meet protocol requirements. The informed consent process is described in Section 10.3.

[6] **Demographics:** Includes sex, date of birth, and age.

[7] **Tumor history:** Includes clinical diagnosis of the tumor, pathological diagnosis, clinical stage, molecular diagnostics (including but not limited to BRCA gene mutation status), and treatment history (e.g., surgery, radiotherapy, local or systemic therapies).

[8] **Medical history:** Includes diagnosis and treatment history of concomitant diseases, prior malignancies excluding treatment with the IMP, history of allergies, alcohol use, and smoking history.

[9] **Concomitant treatments:** All concomitant medications and non-medication concomitant therapies (excluding drug solvents) administered within 28 days prior to randomization and during the treatment period will be recorded, until the end of the safety follow-up or initiation of new anti-tumor therapy, whichever occurs first. After this time point, only concomitant treatments related to reported AEs need to be recorded.

[10] **AE:** AEs will be recorded from the time the subject signs the ICF until the end of the safety follow-up period. For further details, refer to Section 8.4.2.

[11] **Routine blood test:** Includes white blood cell count, absolute neutrophil count, absolute lymphocyte count, red blood cell count, hemoglobin, and platelet count. The routine blood test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. Subjects receiving paclitaxel must also undergo this test within 1 day prior to dosing on D8, D15, and D22 of each cycle. Subjects receiving topotecan must undergo testing within 1 day prior to dosing on D8 and D15 of each cycle. Subjects receiving gemcitabine must undergo testing within 1 day prior to dosing on D8 of each cycle. If the investigator determines that D8, D15, or D22 visits should be conducted, the routine blood test must also be performed at those visits.

[12] **Biochemistry:** Includes serum albumin, serum total protein, serum alkaline phosphatase, serum ALT, serum AST, serum TBIL, serum γ -glutamyl transferase, serum direct bilirubin, serum triglycerides, serum total cholesterol, BUN/serum urea (serum urea preferred), serum creatinine, uric acid, serum potassium, serum sodium, serum chloride, serum total calcium, serum magnesium, serum inorganic phosphate, serum lactate dehydrogenase, and fasting plasma glucose. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. Subjects receiving paclitaxel must also undergo this test within 1 day prior to dosing on D8, D15, and D22 of each cycle. Subjects receiving topotecan must undergo testing within 1 day prior to dosing on D8 and D15 of each cycle. Subjects receiving gemcitabine must undergo testing within 1 day prior to dosing on D8 of each cycle. If the investigator determines that D8, D15, or D22 visits should be conducted, the biochemistry test must also be performed at those visits.

Serum lipase or serum amylase: The test will be performed within 7 days prior to randomization and as clinically indicated during treatment if the subject develops symptoms suggestive of pancreatitis (e.g., abdominal pain, bloating).

[13] **Urinalysis:** Includes urine white blood cells, urine protein, urine red blood cells, and urine occult blood. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (+7 days) after the last dose. If urine protein is detected at $\geq 2+$ in two consecutive visits, 24-hour urine protein quantification must be performed.

[14] **Routine stool test:** If fecal occult blood is positive during the screening period, retesting is required (except for weakly positive results deemed clinically insignificant by the investigator). If the retest remains positive, the investigator will determine whether gastrointestinal endoscopy is required. During treatment, if fecal occult blood is positive, the investigator will determine clinical significance and may order gastroscopy if necessary. Testing should be performed within 7 days prior to randomization and at the end-of-treatment visit (if not performed within the previous 7 days). Additional testing during treatment may be performed as deemed necessary by the investigator based on the subject's symptoms.

[15] **Coagulation:** Includes prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, and at the end-of-treatment visit (if not performed within the previous 7 days).

[16] **Thyroid function:** Includes free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH). Testing will be performed once within 28 days prior to randomization, and once every 4 cycles starting from C5. A final test will be conducted at the end-of-treatment/withdrawal visit (if no test has been performed within the past 14 days).

[17] **Cardiac enzymes:** Includes serum creatine kinase (CK), creatine kinase-MB (CK-MB), troponin I or troponin T, and N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP). Testing will be performed once within 7 days prior to randomization, and once every 4 cycles starting from C5. A final test will be conducted at the end-of-treatment/withdrawal visit (if no test has been performed within the past 14 days).

[18] **Viral test:** Includes hepatitis B serology panel (if HBsAg is positive, quantitative HBV-DNA testing is required), HCV antibody (if positive, HCV-RNA testing is required), and HIV antibody (as per Investigator's discretion). Testing must be performed once within 28 days prior to randomization.

[19] **Pregnancy test:** Female subjects of childbearing potential will undergo serum HCG testing once within 7 days prior to randomization, before dosing on D1 of each cycle from C2 onward, and at the end-of-treatment visit (if not performed within the previous 7 days). Additional testing may be conducted during the study as deemed necessary by the investigator based on the subject's condition.

- [20] **Tumor markers:** CA-125 testing will be performed once within 7 days prior to randomization, and thereafter at each scheduled imaging assessment (± 3 days from the imaging date). Unscheduled testing may be conducted at the investigator's discretion. Testing will continue until documented PD, initiation of new anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.
- [21] **Vital signs:** Includes body temperature, respiratory rate, pulse, and blood pressure. The test will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (± 7 days) after the last dose. Subjects receiving paclitaxel must also undergo this test within 1 day prior to dosing on D8, D15, and D22 of each cycle. Subjects receiving topotecan must undergo testing within 1 day prior to dosing on D8 and D15 of each cycle. Subjects receiving gemcitabine must undergo testing within 1 day prior to dosing on D8 of each cycle. If the investigator determines that D8, D15, or D22 visits should be conducted, the vital signs measurement must also be performed at those visits.
- [22] **Physical examination:** Includes general condition, head and face, skin, lymph nodes, eyes (scleras and pupils), ears, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive-urinary system (when clinically indicated), musculoskeletal system, nervous system, and mental condition. Physical examination will be performed within 7 days prior to randomization and at the end-of-treatment visit. (Apart from the screening and end-of-treatment visits, full physical examination results do not need to be recorded in the eCRF during the treatment period; only abnormalities should be reported.) Targeted physical examinations should be performed during treatment if clinically indicated.
- [23] **Height measurement:** Height will be measured once within 7 days prior to randomization.
- [24] **Weight measurement:** Weight will be measured once within 7 days prior to randomization, before dosing on D1 of each cycle, and at the end-of-treatment visit. The weight measurement prior to D1 dosing in each cycle may be used to adjust the dosing.
- [25] **ECOG PS score:** ECOG PS will be assessed once within 7 days prior to randomization, before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit, and at 40 days (± 7 days) after the last dose.
- [26] **12-lead ECG:** Includes heart rate, QT interval, QTc, and PR interval. ECG assessments will be conducted once within 7 days prior to randomization, once before dosing on D1 of each cycle from C2 onward, at the end-of-treatment visit (if not performed within the previous 7 days), and at 40 days (± 7 days) after the last dose. If QTc > 470 ms is observed during screening, two additional ECGs must be performed (on the same day) at intervals of no less than 10 min. The average of the three QTc values must meet the enrollment criteria. During treatment, if new clinically significant ECG abnormalities are detected, the investigator will determine whether additional ECGs are required.
- [27] **Echocardiography:** Includes left ventricular ejection fraction (LVEF). Echocardiography will be performed once within 28 days prior to randomization, and once every 4 cycles starting from C5. One final echocardiogram will be performed at the end-of-treatment/withdrawal visit (if no assessment has been performed within the previous 14 days).
- [28] **B-mode ultrasound examination of deep veins in both lower extremities:** It will be performed once within 28 days prior to randomization. Additional assessments may be conducted as deemed necessary by the investigator.
- [29] **Randomization:** Subjects who meet all eligibility criteria will be randomized through the RTSM system. The first dose (C1D1) must be administered within 3 calendar days after randomization.
- [30] **Doxorubicin liposome administration:** It is administered via intravenous infusion on D1 of each cycle at a dose of 40 mg/m². Each treatment cycle lasts 4 weeks. Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1).
- [31] **Paclitaxel administration:** It is administered via intravenous infusion on D1, D8, D15, and D22 of each cycle at a dose of 80 mg/m². Each treatment cycle lasts 4 weeks. Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1).
- [32] **Topotecan administration:** It is administered via intravenous infusion on D1, D8, and D15 of each cycle at a dose of 4 mg/m² per day. Each treatment cycle lasts 4 weeks. Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1).
- [33] **Gemcitabine administration:** It is administered via intravenous infusion on D1 and D8 of each cycle at a dose of 1,000 mg/m² per day. Each treatment cycle lasts 3 weeks. Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1).

[34] **Imaging examination:** Imaging examinations required during the **screening period** include contrast-enhanced CT or MRI of the chest, abdomen, pelvis, and any other sites clinically suspected of disease. (If the subject is allergic to CT contrast agents, a non-contrast CT of the chest and contrast-enhanced MRI of the abdomen and pelvis should be performed.) For subjects with known or suspected brain metastases, contrast-enhanced MRI or CT of the brain is required. For subjects with known or suspected bone metastases, a bone scan is required. (If abnormal bone lesions are identified, additional local bone CT or MRI should be performed as appropriate.) Bone scans performed within 42 days prior to randomization are acceptable. Baseline tumor assessments during the screening period may be completed up to 4 weeks prior to randomization. CT/MRI results obtained prior to signing the ICF may be used for screening tumor assessments if they meet protocol requirements.

During the treatment period, all imaging examinations must be performed under the same conditions as baseline (e.g., slice thickness, contrast agent use). Imaging examinations should be performed every 6 weeks during the first 36 weeks' post-randomization, and every 12 weeks thereafter. Examined regions should include the chest, abdomen, pelvis, and any other sites with baseline lesions. For subjects with known bone metastases, bone scans will be repeated when bone progression is suspected or to confirm CR. Additional imaging should be performed as needed if new lesions are suspected.

If PD is suspected during treatment (e.g., due to worsening symptoms), unscheduled imaging examinations may be performed. Bone scan examination is required when bone metastases are clinically suspected. If abnormal bone metastases are found, further local bone CT or MRI examination is required according to the site; enhanced MRI or enhanced CT of the brain must be performed for patients suspected of brain metastases.

Confirmation must be performed no less than 4 weeks after the first PR/CR. The window period allowed by the imaging examination schedule is ± 7 days, and the imaging examination time is not affected by drug interruption.

Except for subjects who discontinue treatment due to radiologically confirmed PD, subjects who terminate treatment for other reasons must undergo imaging assessment at the end-of-treatment visit if no imaging was performed within the previous 4 weeks. Post-treatment, subjects must continue imaging assessments according to the protocol-defined frequency (based on the date of the last imaging) until documentation of PD, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.

[35] **EQ-5D-5L and FOSI scales:** Subjects will complete the scales on D1 of every two cycles (e.g., C1D1, C3D1, C5D1, and so on), at the end-of-treatment visit, and at 40 days (+7 days) after the last dose. The scales must be independently completed by the subject prior to any other assessments or treatment administration at each visit.

[36] **Biomarker sample collection:** Subjects should provide a tumor tissue sample. The sample should be either fresh or the most recently archived tumor tissue. Tumor tissue samples will be used for HER2 immunohistochemistry (IHC) and FISH testing at the sponsor-designated or local laboratory. See the laboratory manual for the collection and disposal of tumor samples.

1.3.3. Pharmacokinetic/Immunogenicity Sampling Schedule

For subjects in the experimental group receiving SHR-A1811 treatment, blood samples for PK and immunogenicity analysis will be collected at the time points and under the conditions specified in Table 3.

Table 3: Pharmacokinetic/Immunogenicity Sampling Schedule

Cycle	C1/2		C6	Every 9 Cycles from C15 Onward (Inclusive)	End-of- Treatment Visit	Follow-Up Period
Day	D1		D1 ± 3 d	D1 ± 3 d		40 days (+7 d) after last dose
Time window	Within 2 h prior to administration	Within 5 min after completion of administration	Within 2 h prior to administration	Within 2 h prior to administration	±7 d	
SHR-A1811 PK ^[1]	X		X	X	X	
SHR169265 PK ^[2]	X	X	X	X	X	
Immunogenicity of SHR-A1811 ^[3]	X (C1D1 only)		X	X	X	X

Abbreviations: ADA = anti-drug antibody, PK = pharmacokinetics, C = cycle, D/d = day, NAb = neutralizing antibody.

- [1] **SHR-A1811 (toxin-conjugated antibody) PK blood collection time points:** Blood samples should be collected on C1D1, C2D1, and C6D1 within 2 h prior to SHR-A1811 administration; thereafter, sampling will be performed once every 9 cycles within 2 h prior to SHR-A1811 dosing; and at end of treatment with SHR-A1811/withdrawal. Approximately 3 mL of blood will be collected at each time point for the determination of toxin-conjugated antibody concentrations.
- [2] **SHR169265 (free toxin) PK blood collection time points:** Blood samples should be collected on C1D1 and C2D1 both within 2 h prior to SHR-A1811 administration and within 5 min after completion of administration (flushing included); on C6D1 within 2 h prior to SHR-A1811 dosing; thereafter, once every 9 cycles within 2 h prior to dosing; and at end of treatment with SHR-A1811/withdrawal. Approximately 2 mL of blood will be collected at each time point for determination of free toxin SHR169265 concentrations.
- [3] **SHR-A1811 immunogenicity blood collection time points:** Blood samples should be collected on C1D1, C6D1, and every 9 cycles thereafter within 2 h prior to SHR-A1811 dosing; at end of treatment with SHR-A1811/withdrawal; and at 40 days (+7 days) after the last dose of SHR-A1811. Approximately 4 mL of blood will be collected at each time point for anti-SHR-A1811 antibody (ADA) and NAb analysis.

If the time windows for the end-of-treatment/withdrawal visit and the 40-day (+7 days) post-last-dose follow-up visit overlap, a single blood sample may be collected for both PK and immunogenicity assessments. The time for post-dose blood collection should be calculated from the completion of the flushing. Blood samples collected within 5 min after administration (flushing included) must not be drawn from the same arm used for SHR-A1811 infusion.

2. INTRODUCTION

2.1. Study Background

2.1.1. Disease Background

Ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) is one of the most common malignant tumors of the female reproductive system. It ranks third in incidence (324,603 cases) among gynecologic malignancies, but second in mortality (206,956 cases) in the world^[1]. According to the GLOBOCAN statistical data, in 2022, the age standardized incidence rate (ASR) of ovarian cancer is 6.7 per 100,000 in the world that varies according to geographical region, with ASR of 5.3 in Africa, 5.7 in Latin America and the Caribbean, 6.2 in Asia, 7.5 in North America, 7.8 in Australia and 9.3 in Europe; with age standardized mortality rates of 4, 3.6, 4, 3.7, 3.8, 3.9 and 5, respectively^[1]. Ovarian cancer is one of the most common cancer mortality in women, and occurs predominantly in older women. The most common type at diagnosis is advanced stage/high grade disease with an overall 5-year survival rate of 20-43% and a relapse rate of 70% within 3 years of treatment initiation^[2].

Ovarian cancer includes various pathological types, with epithelial ovarian cancer being the most common, accounting for approximately 80% of all ovarian malignancies. More than 70% of patients are diagnosed at an advanced stage (FIGO stage III/IV). Current initial standard treatment consists of surgery combined with platinum-based chemotherapy. Although initial treatment often yields favorable responses, at least 70% of patients with advanced disease will experience recurrence within 3 years. In patients with platinum-sensitive relapse, secondary cytoreductive surgery may be considered if optimal resection is achievable, followed by 2nd-line platinum-based chemotherapy and maintenance therapy with targeted agents. However, with each subsequent recurrence, the PFS achieved with platinum-based chemotherapy becomes progressively shorter, ultimately leading to platinum-resistant relapse^[3].

According to the 2024 guidelines of the U.S. National Comprehensive Cancer Network (NCCN) and other guidelines, the main treatment strategy for platinum-resistant recurrent ovarian cancer is non-platinum single-agent chemotherapy, with or without bevacizumab. However, the efficacy of these regimens remains limited. Therefore, there is an urgent clinical need for the development of novel, low-toxicity, and effective therapies specifically targeting platinum-resistant ovarian cancer.

2.1.2. Introduction to SHR-A1811

SHR-A1811 for injection (hereafter referred to as SHR-A1811) is an antibody-drug conjugate (ADC) targeting the HER2 protein, and is being developed for the treatment of various type of tumors expressing HER2. SHR-A1811 is composed of a recombinant humanized anti-HER2 IgG1 monoclonal antibody (SHR-1805) conjugated with a small molecular component, SHR169106.

SHR-A1811 can specifically bind to HER2 on the surface of tumor cells. Subsequently, the conjugate is internalized into the cells and transported to lysosomes. Through tissue protease hydrolysis, it releases the free toxin SHR169265, which can inhibit the activity of DNA topoisomerase I and induce apoptosis of tumor cells. Due to its high membrane permeability, SHR169265 also exhibits a bystander killing effect, wherein it can diffuse into adjacent cells

after being released in the tumor cells and can also have a killing effect on HER2-negative cells.

2.1.3. Nonclinical Experience

Pharmacology studies have demonstrated that SHR-A1811 significantly inhibits the growth of subcutaneous xenograft tumors derived from HER2-expressing human gastric or breast cancer in nude mice, resulting in tumor regression. Its antitumor efficacy was significantly superior to equimolar doses of the naked antibody SHR-1805 (the anti-HER2 antibody) or the free toxin SHR169265 (also known as 9106-IM-2, a DNA topoisomerase I inhibitor), without a notable increase in toxicity.

Animal pharmacokinetic (PK) studies showed that in cynomolgus monkeys, the systemic exposure (AUC_{0-t}) of SHR-A1811 increased more than dose-proportionally, while the serum clearance decreased with increasing dose, indicating a nonlinear PK profile. The half-life of total antibody ranged from 1.96 to 5.96 days, comparable to that of trastuzumab reported in literature, supporting a clinical dosing regimen of once every 3 weeks (Q3W). Following a single intravenous administration of ^{125}I -labeled SHR-A1811 in NCI-N87 tumor-bearing mice, the compound was primarily distributed in serum and, to a lesser extent, in tumor tissue. The parent drug was not detected in urine. SHR-A1811 was stable in plasma from humans, cynomolgus monkeys, and rats, with only trace amounts of toxin release observed. In rats, following a single intravenous dose of SHR-A1811 at 200 mg/kg, cumulative excretion of SHR169265 over 0–336 h accounted for 38.0% of the administered dose in feces and 5.23% in urine, with a combined total of 43.3%. In bile duct-cannulated rats, the cumulative biliary excretion of SHR169265 within 48 h accounted for 15.8% of the administered dose.

Toxicology studies (single dose, repeat dose studies up to 13-week, genotoxicity, safety pharmacology incl hERG assay, local tolerance, tissue cross reactivity, in vitro hemolysis, in vitro phototoxicity, embryofetal developmental toxicity) required to support the Biologics License Application (BLA) have been conducted.

Repeat-dose studies (intravenous) of SHR-A1811 and SHR169265 were performed in cynomolgus monkeys, and of SHR169265 in Sprague-Dawley rats. Cynomolgus monkeys are considered the relevant species for assessing the risk of SHR-A1811 in humans because it binds HER2 in both monkeys and humans, but not in rodents. In single- and 6-week repeat-dose toxicity studies in cynomolgus monkeys, the toxicities observed with SHR-A1811 were consistent with those of SHR169265, primarily manifesting as alterations in the immune and hematopoietic systems, indicating that toxicity was mainly attributable to the toxin. In the 6-week and 13-week repeat-dose toxicity studies in cynomolgus monkeys, the highest non-severely toxic dose was 40 mg/kg in both the studies. The toxin SHR169265 is a DNA topoisomerase I inhibitor and in vitro studies showed that it did not induce gene mutations in *Salmonella typhimurium*, but it did induce structural chromosomal aberrations in Chinese-hamster lung (CHL) cells which is considered related to the mechanism of action of the DNA topoisomerase I inhibition. In a 4-week repeat-dose (intravenous) study in SD rats, SHR169265 caused bone marrow suppression but did not result in chromosomal structural damage or segregation abnormalities in bone marrow cells.

Embryofetal development study in rats with SHR169265 at 0.25, 0.5 and 1 mg/kg, IV, and with SHR-A1811 at 20, 60 and 200 mg/kg, IV showed maternal and fetal findings at the lowest tested doses. Pregnant women are excluded from clinical study; and effective

contraception and refraining from egg donation for women of child-bearing potential participating in the study.

No irritation to the blood vessels or surrounding tissues was noted at the injection sites in monkeys with SHR-A1811 repeat administration up to 10 mg/mL concentration, and no hemolysis or aggregation was noticed in rabbit erythrocytes up to 5 mg/mL concentration. SHR169265 was found non-phototoxic in a rat study at a dose of 0.6 mg/kg, IV.

2.1.4. Clinical Experience

To date, a total of 25 clinical trials of SHR-A1811 have been initiated, including one international multicenter study (SHR-A1811-I-101; N=396) conducted in USA, Australia, China and other Asian countries and the remaining studies in China. The trials are covering a range of tumor types such as gynecologic malignancies (including ovarian cancer), breast cancer, gastric cancer or gastroesophageal junction adenocarcinoma, colorectal cancer, biliary tract cancer and non-small cell lung cancer.

Clinical Pharmacology

As of February 29, 2024, preliminary PK results from the SHR-A1811-I-101 study indicate that within the dose range of 1.0–8.0 mg/kg, exposure to both the total antibody and the ADC was similar and increased with dose following single-dose administration. Across 6 dose groups, the mean terminal elimination half-life of SHR-A1811 after a single dose ranged from approximately 2.8 to 7.8 days and increased with dose. Exposure to free SHR169265 following a single dose of SHR-A1811 was low. At the highest dose level of 8.0 mg/kg, the geometric mean C_{max} of free SHR169265 was 3.89 ng/mL, and the mean terminal half-life ranged from approximately 3.3 to 5.8 days following a single dose. When administered Q3W via multiple intravenous infusions, mild accumulation of both total antibody and ADC was observed, whereas no accumulation of free SHR169265 was detected.

Clinical Safety

A total of 2971 subjects^[i] have received SHR-A1811 either as monotherapy or in combination with other agents in the various clinical trials of SHR-A1811 program. The most frequently reported SHR-A1811-related adverse events (AEs) were hematological toxicities and gastrointestinal reactions. SHR-A1811-related AEs with an incidence of $\geq 10\%$ included: neutrophil count decreased (78.0%), anaemia (74.5%), white blood cell count decreased (72.2%), nausea (61.8%), vomiting (42.4%), platelet count decreased (41.0%), decreased appetite (40.3%), alopecia (38.6%), AST increased (37.1%), ALT increased (34.0%), hypoalbuminaemia (27.4%), weight decreased (23.8%), lymphocyte count decreased (22.3%), gamma-glutamyltransferase increased (22.3%), hypertriglyceridaemia (20.4%), proteinuria (20.3%), diarrhoea (19.8%), blood alkaline phosphatase increased (19.7%), blood lactate dehydrogenase increased (17.2%), fatigue (16.8%), hyperglycaemia (16.4%), hyponatraemia (16.3%), hypokalaemia (15.0%), urinary tract infection (15.0%), hyperuricaemia (13.6%), asthenia (12.5%), constipation (12.2%), stomatitis (11.5%), hypocalcaemia (10.5%), and blood bilirubin increased (10.2%).

Based on a comprehensive evaluation by the sponsor, the most common serious adverse reactions in clinical trials of SHR-A1811 included hematological toxicities (platelet count

i Excluding 8 ongoing pivotal randomized controlled Phase III trials, the pooled safety analysis was performed on the remaining 17 SHR-A1811 clinical studies. The data were sourced from the sponsor's electronic data capture (EDC) system as of May 13, 2025.

decreased/neutrophil count decreased/white blood cell count decreased, and anaemia), gastrointestinal reactions (vomiting/nausea), and pulmonary toxicities (pneumonia/interstitial lung disease), as detailed in [Table 4](#).

Table 4: Incidence of Expected Serious Adverse Reactions of SHR-A1811

System Organ Class Preferred Term	Estimated Number of Subjects Exposed to SHR-A1811 (N = 2971)	
	Frequency	All Serious Adverse Reactions n (%)
Investigations		
Platelet count decreased	Common	193 (6.5)
Neutrophil count decreased*	Common	156 (5.3)
White blood cell count decreased	Common	142 (4.8)
Lymphocyte count decreased	Uncommon	4 (0.1)
Alanine aminotransferase increased	Uncommon	18 (0.6)
Aspartate aminotransferase increased		13 (0.4)
Gamma-glutamyltransferase increased		5 (0.2)
Blood and lymphatic system disorders		
Anaemia	Common	117 (3.9)
Febrile neutropenia	Common	75 (2.5)
Myelosuppression	Uncommon	8 (0.3)
Gastrointestinal disorders		
Vomiting	Common	54 (1.8)
Nausea	Uncommon	30 (1.0)
Diarrhoea	Uncommon	9 (0.3)
Functional gastrointestinal disorder	Uncommon	4 (0.1)
Respiratory, thoracic and mediastinal disorders		
Interstitial lung disease	Common	33 (1.1)
Pneumonitis	Uncommon	5 (0.2)
Epistaxis	Uncommon	3 (0.1)
General disorders and administration site conditions		
Asthenia	Uncommon	20 (0.7)
Infections and infestations		
Pneumonia	Common	46 (1.6)
Gastroenteritis	Uncommon	5 (0.2)
Hepatobiliary disorders		

System Organ Class Preferred Term	Estimated Number of Subjects Exposed to SHR-A1811 (N = 2971)	
	Frequency	All Serious Adverse Reactions n (%)
Hepatic function abnormal	Uncommon	6 (0.2)
Metabolism and nutrition disorders		
Decreased appetite	Uncommon	19 (0.6)
Hypokalaemia	Uncommon	11 (0.4)
Hyponatraemia	Uncommon	6 (0.2)
Injury, poisoning and procedural complications		
Infusion related reaction	Uncommon	4 (0.1)
Immune system disorders		
Hypersensitivity	Rare	2 (0.07)

Abbreviations: MedDRA v27.0 = Medical Dictionary for Regulatory Activities Version 27.0

This table is based on data from the safety database as of May 13, 2025. AEs are listed and reported by cumulative incidence according to MedDRA v27.0 System Organ Class (SOC) and Preferred Term (PT).

Frequency categories are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), and very rare ($< 1/10,000$).

*Includes neutrophil count decreased and neutropenia.

Clinical Efficacy

(1) Overview of previous studies: Among the conducted clinical trials of SHR-A1811, two studies SHR-A1811-I-101 and SHR-A1811-209 included subjects with platinum-resistant ovarian cancer. As of October 12, 2024 (or May 13, 2024 for study 101), a total of 48 subjects with platinum-resistant ovarian cancer were enrolled and treated with SHR-A1811 monotherapy. Of these, 10 subjects were enrolled in the 6.4 mg/kg dose group and 38 subjects in the 4.8 mg/kg dose group. A total of 24 subjects (50.0%) discontinued treatment, with reasons including: radiographic disease progression in 20 subjects (41.7%), voluntary withdrawal in 2 subjects (4.2%), and clinical progression in 2 subjects (4.2%). As of the data cut-off date, 24 subjects (50.0%) remained on treatment with the investigational medicinal product (IMP).

(2) Baseline characteristics: In the RP2D 4.8 mg/kg dose group, the median age of subjects was 53.5 years (range: 20–74 years). ECOG Performance Status (PS) score was 0 in 11 subjects (28.9%) and 1 in 27 subjects (71.1%). The primary tumor site was the ovary in 37 subjects (97.4%) and the fallopian tube in 1 subject (2.6%). A total of 20 subjects (52.6%) had primary platinum-resistant ovarian cancer, and 5 subjects (13.2%) had platinum-refractory recurrent ovarian cancer (defined as a platinum-free interval [PFI] < 4 weeks after last-line platinum-based therapy). Prior exposure to VEGF/VEGFR inhibitors and PARP inhibitors was reported in 27 subjects (71.1%) and 17 subjects (44.7%), respectively.

(3) Efficacy summary: The median follow-up duration for the 48 subjects with platinum-resistant recurrent ovarian cancer was 7.6 months (range: 1.8–16.7 months). All 48 subjects underwent at least one post-baseline imaging assessment (see [Table 5](#)). Best overall response (BOR) included 2 complete responses (CR), 24 partial responses (PR), 17 stable disease (SD), and 5 progressive disease (PD). The objective response rate (ORR) was 54.2% (95%

CI: 39.2–68.6), and the disease control rate (DCR) was 89.6% (95% CI: 79.3–96.5). All CRs and PRs were confirmed.

Among subjects in the 4.8 mg/kg (RP2D) dose group, all received at least one imaging assessment. The best responses were 2 CRs and 21 PRs (all confirmed), 11 SDs, and 4 PDs. The ORR was 60.5% (95% CI: 43.4–76.0), and the DCR was 89.5% (95% CI: 75.2–97.1). The majority of subjects (86.8%) experienced some degree of target lesion reduction in sum of diameters (SOD) from baseline after treatment initiation.

Among the 26 subjects who achieved tumor response, the median follow-up was 7.8 months (range: 5.4–12.6 months). Ten subjects (38.5%) experienced PD or withdrawal, while 16 subjects (61.5%) remained in ongoing response; the longest duration of response (DoR) reached 11.2 months. In the 4.8 mg/kg dose group, among 23 subjects with objective response, 8 (34.8%) experienced PD. The median DoR was 8.1 months (95% CI: 5.8–NR), with a 6-month DoR rate of 72.3% (95% CI: 44.1–87.9). A total of 15 subjects (65.2%) with objective responses remained on treatment and in ongoing response. Preliminary results demonstrate that SHR-A1811 monotherapy induces high-quality and durable responses in platinum-resistant ovarian cancer.

In addition, only 7 subjects experienced death events, and median overall survival (OS) has not yet been reached or matured in either dose group.

In conclusion, SHR-A1811 monotherapy at the RP2D dose (4.8 mg/kg) achieved an ORR of 60.5%, median progression-free survival (mPFS) of 8.5 months, and median duration of response (mDoR) of 8.1 months in subjects with platinum-resistant ovarian cancer. These results are notably superior to historical data for single-agent chemotherapy. (e.g., in the Phase 3 MIRASOL study of the folate receptor alpha-targeted ADC mirvetuximab soravtansine^[4], mPFS was 3.98 months with a PFS hazard ratio [HR] of 0.65 for the experimental group vs. control group; mDoR was not reported, and mOS was 12.75 months. In the Phase 3 SCORES study of suvemcitug^[5], mPFS was 2.73 months with a PFS HR of 0.46 for the experimental group vs. control group; mDoR was 6.05 months, and mOS was 14.88 months.)

Table 5: Efficacy of SHR-A1811 Monotherapy in Subjects with Platinum-Resistant Ovarian Cancer

	4.8 mg/kg (N = 38)	6.4 mg/kg (N = 10)
BOR, n (%)		
CR	2 (5.3)	0
PR	21 (55.3)	3 (30.0)
SD	11 (28.9)	6 (60.0)
PD	4 (10.5)	1 (10.0)
NE	0	0
ORR, % (95% CI)	60.5 (43.4, 76.0)	30.0 (6.7, 65.2)
DCR, % (95% CI)	89.5 (75.2, 97.1)	90.0 (55.5, 99.7)
Median PFS, months (95% CI)	8.5 (5.7–NR)	7.6 (5.7–NR)

	4.8 mg/kg (N = 38)	6.4 mg/kg (N = 10)
Median DoR, months (95% CI)	8.1 (5.8–NR)	6.4 (4.3–NR)

Abbreviations: BOR = best overall response; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PD = progressive disease; PR = partial response; SD = stable disease; CR = complete response; NE = not evaluable; ORR = objective response rate; DCR = disease control rate; PFS = progression-free survival; DoR = duration of response.

Data cut-off dates: Study 209: October 12, 2024; Study 101: May 13, 2024.

2.2. Summary of Benefits and Risks

2.2.1. Summary of Benefits

Based on the available nonclinical and clinical data (see Section 2.1.3 and Section 2.1.4), participation in this clinical trial and treatment with SHR-A1811 may provide a meaningful therapeutic opportunity for patients with poor prognosis under existing standard treatment. SHR-A1811 has the potential to offer a novel therapeutic option and clinical benefit for patients with HER2-expressing platinum-resistant recurrent ovarian cancer (including fallopian tube cancer and primary peritoneal cancer).

2.2.2. Summary of Risk and Risk Management

SHR-A1811 has been studied in clinical trials across multiple tumor types, including gynecologic malignancies, breast cancer, gastric cancer, colorectal cancer, and non-small cell lung cancer. Data from early-phase trials indicate that the overall safety profile of SHR-A1811 is manageable.

- In tumor-bearing subjects receiving SHR-A1811 monotherapy, commonly reported (incidence $\geq 10\%$) SHR-A1811-related adverse reactions, some of which may also be serious, included the following:
 - Hematological system: Neutrophil count decreased, anaemia, white blood cell count decreased, platelet count decreased, lymphocyte count decreased;
 - Gastrointestinal system: Nausea, vomiting, diarrhoea, stomatitis, constipation;
 - Liver function: Aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased, blood bilirubin increased;
 - Metabolism and nutrition: Decreased appetite, hypoalbuminaemia, weight decreased, hypertriglyceridaemia, hyperglycaemia, hyponatraemia, hyperuricaemia, hypokalaemia, hypocalcemia;
 - Others: alopecia, proteinuria, fatigue, blood lactate dehydrogenase increased, urinary tract infection, asthenia.

Among the above adverse reactions, Grade ≥ 3 adverse reactions with an incidence of $\geq 10\%$ included: neutrophil count decreased, white blood cell count decreased, anaemia, and platelet count decreased, and most of the remaining cases were Grade 1–2. Most of the adverse reactions could be controlled with or without medical intervention.

- In addition to the above adverse reactions, other serious adverse events (SAEs) with lower incidence have been observed in subjects treated with SHR-A1811. Suspected

SAEs reported in ≥ 2 subjects included: interstitial lung disease, pneumonitis, myelosuppression, febrile neutropenia, pneumonia, gastroenteritis, functional gastrointestinal disorder, epistaxis, infusion related reaction, and allergic reaction.

- During treatment with SHR-A1811, particular attention should be paid to hematological toxicities (especially neutropenia, with serious cases of infection due to neutropenia already reported), gastrointestinal toxicities, interstitial lung disease/noninfectious pneumonitis (which may present as dry cough, shortness of breath, dyspnea, or systemic symptoms such as fatigue and fever, with serious cases of interstitial lung disease already reported), and left ventricular dysfunction (primarily decreased left ventricular ejection fraction [LVEF]). These adverse reactions are typically detectable through routine clinical monitoring and follow-up.
- According to the mechanism of action of SHR-A1811 itself and the adverse reactions of same-class drugs, the following adverse reactions must also be paid attention to throughout participation in the study: abdominal pain, abdominal distension, organizing pneumonia, electrocardiogram QT prolonged, pain in joint, musculoskeletal pain, hot flashes, headache, numbness, dry eyes, dry skin, allergic reaction, etc. See SHR-A1811 Investigator's Brochure for details.

According to the package insert for doxorubicin liposome hydrochloride injection, commonly reported adverse reactions include bone marrow suppression (the most frequently observed), white blood cell count decreased (most common), anaemia, platelet count decreased, alkaline phosphatase increased, aspartate aminotransferase increased, blood bilirubin increased, nausea, asthenia, alopecia, pyrexia, diarrhoea, acute infusion-related reactions (the primary manifestations of infusion reactions include flushing, dyspnea, facial edema, headache, chills, back pain, tightness in the chest and throat, and hypotension), stomatitis, and respiratory disorders. Other less common adverse reactions (incidence $< 5\%$) include palmar-plantar erythrodysesthesia syndrome, oral candidiasis, nausea, vomiting, weight decreased, rash, oral ulceration, dyspnea, abdominal pain, and hypersensitivity reactions including hypersensitivity, vasodilation, dizziness, anorexia, glossitis, constipation, paresthesia, retinitis, and confusion. Congestive heart failure has been reported at a high incidence with conventional doxorubicin formulations. In rare cases, radiation recall reactions have been observed in patients previously treated with radiotherapy during treatment with doxorubicin liposome hydrochloride.

According to the package insert of paclitaxel injection, the common adverse reactions in 812 patients with solid tumors who received monotherapy with this product include bone marrow (neutrophils reduced, white blood cell count decreased, platelets decreased, anaemia, infection, bleeding), allergic reaction, cardiovascular disorders (vital sign changes, hypotension, bradycardia, significant cardiovascular events), abnormal ECG, peripheral neuropathy, muscle pain/arthralgia, gastrointestinal disorders (nausea, vomiting, diarrhoea, mucositis), alopecia, liver disorders (increased bilirubin, alkaline phosphatase increased, aspartate aminotransferase increase), and injection site reactions.

According to the package insert of topotecan hydrochloride for injection, the common adverse reactions include hematological system (white blood cell count decreased, platelets decreased, anaemia, and other reactions; bone marrow suppression (primarily neutropenia) is the dose-limiting toxicity of this drug), digestive system disorders (nausea, vomiting, diarrhoea, constipation, intestinal obstruction, abdominal pain, stomatitis, anorexia), skin and appendage disorders (alopecia, occasional severe dermatitis and pruritus), neuromuscular

disorders (headache, joint pain, muscle pain, pantalgia, paresthesia), respiratory system disorders (dyspnea), liver disorders (hepatic function abnormal, transaminases increased), generalized disorders (asthenia, fever, discomfort), local disorders (drug leakage outside the blood vessels may lead to local irritation, redness and swelling), allergic reaction (rare anaphylaxis and angioedema).

According to the package insert of gemcitabine hydrochloride for injection, the most commonly reported treatment-related adverse reactions include: nausea (reported by approximately 60% of patients, with or without vomiting); elevated hepatic transaminases (AST/ALT) and alkaline phosphatase increased; proteinuria and hematuria (reported in approximately 50% of patients); and dyspnea (reported in 10%–40% of patients, with the highest incidence observed in lung cancer patients). Approximately 25% of patients reported allergic rash, and pruritus was present in roughly 10% of these cases. The dose-limiting toxicities include platelet count decreased, white blood cell count decreased, and neutrophil count decreased. In clinical studies, very common and common adverse reactions included: blood and lymphatic system disorders: leukopenia (including neutropenia; Grade 3 incidence: 19.3%, Grade 4 incidence: 6%. Bone marrow suppression is generally mild to moderate and most often affects neutrophil counts), platelet count decreased, anaemia, febrile neutropenia; metabolism and nutrition disorders: anorexia; nervous system disorders: headache, insomnia, somnolence; respiratory, thoracic and mediastinal disorders: dyspnea (typically mild and self-limiting without treatment), cough, rhinitis; gastrointestinal disorders: nausea, vomiting, diarrhea, stomatitis, oral ulceration, constipation; hepatobiliary disorders: transaminases increased (AST/ALT), alkaline phosphatase increased, blood bilirubin increased; skin and subcutaneous tissue disorders: allergic rash (often associated with pruritus), alopecia, pruritus, hyperhidrosis; musculoskeletal and connective tissue disorders: back pain, myalgia; renal and urinary disorders: proteinuria (mild), hematuria; general disorders and administration site conditions: flu-like symptoms (most commonly including pyrexia, headache, chills, myalgia, fatigue, and anorexia; other reported symptoms included cough, rhinitis, malaise, hyperhidrosis, and sleep disorder), edema/peripheral edema (including facial edema, which is usually reversible after discontinuation), pyrexia, fatigue, and chills.

Management measures for the above risks include: 1) strict screening of subjects at enrollment in accordance with inclusion and exclusion criteria to ensure that individuals with pre-existing relevant abnormalities or high-risk conditions are not enrolled; 2) Establishment of dose adjustment criteria and guidelines for the management of common adverse reactions; 3) Routine monitoring during the study period, including relevant clinical assessments to detect and manage AEs in a timely manner, continuous follow-up of AEs, and systematic collection and reporting of safety information.

2.2.3. Overall Benefit-Risk Conclusion

SHR-A1811 is currently ongoing clinical development for treatment of various tumor types. Additionally, SHR-A1811 has been approved by NMPA in China (conditional approval in May'2025 basis pivotal Phase 2 data) for the treatment of unresectable advanced/metastatic HER2 mutated NSCLC. The observed adverse reaction profile is consistent with that of other agents in its class, without evidence of increased treatment-related risk. Most adverse reactions are manageable through treatment discontinuation or medical intervention. Treatment with SHR-A1811 may offer survival benefits and improve the quality of life for patients with HER2-expressing platinum-resistant recurrent ovarian cancer (including fallopian tube cancer and primary peritoneal cancer).

3. STUDY OBJECTIVES, ENDPOINTS AND ESTIMANDS

3.1. Study Objectives and Endpoints

Study objectives and endpoints are presented in [Table 6](#).

Table 6: Study Objectives and Endpoints

Primary Objective	Primary Endpoints
To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of human epidermal growth factor receptor 2 (HER2)-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by progression-free survival (PFS).	PFS assessed by the IRC based on RECIST v1.1.
To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in patients with HER2-expressing, platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by overall survival (OS);	OS.
Secondary Objectives	Secondary Endpoints
To evaluate the efficacy of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, as measured by ORR, DoR, DCR, RR, and CA-125 RR.	- IRC-assessed ORR, DoR, and DCR per RECIST v1.1; - Investigator-assessed PFS, ORR, DoR, and DCR per RECIST v1.1; - CA-125 RR assessed based on GCIG CA-125 criteria; - RR assessed based on CA-125 RR and IRC ORR.
To evaluate the safety of SHR-A1811 versus investigator's choice of chemotherapy in the treatment of HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.	- AEs and SAEs, including type, incidence, severity (graded according to the NCI-CTCAE v6.0), and correlation with the IMP; - Laboratory test abnormalities, including type, incidence, and grading (per NCI-CTCAE v6.0); - Vital signs, electrocardiogram (ECG), and ECOG PS score.
To evaluate the PK profile of SHR-A1811.	Serum drug concentrations of the toxin-conjugated antibody (SHR-A1811) and the free toxin SHR169265.
To evaluate the immunogenicity of SHR-A1811.	Presence of anti-SHR-A1811 antibodies (ADAs) and neutralizing antibodies (NABs).
Exploratory Objectives	Exploratory Endpoints
To explore the correlation between biomarkers (HER2 IHC and H-score expression levels) and efficacy.	Correlation between HER2 expression level in tumor tissue (IHC and H-score) and efficacy endpoints (including but not limited to PFS, OS, ORR, and DoR).
To evaluate health-related quality of life in patients treated with SHR-A1811 versus investigator's choice of chemotherapy in the treatment of HER2-expressing platinum-resistant recurrent epithelial ovarian cancer,	Change from baseline in EQ-5D-5L and FOSI scores.

Primary Objective	Primary Endpoints
fallopian tube cancer, or primary peritoneal cancer.	
To evaluate time to second disease progression/death (PFS2) in patients treated with SHR-A1811 versus investigator's choice of chemotherapy for HER2-expressing, platinum-resistant, recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.	PFS2.

Abbreviations: ADA = anti-drug antibody; AE = adverse event; CA-125 = cancer antigen 125; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; EQ-5D-5L = EuroQol 5-Dimension 5-Level Questionnaire; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; GCIG = Gynecologic Cancer InterGroup; HER2 = human epidermal growth factor receptor 2; H-score = histochemical score; IHC = immunohistochemistry; IMP = investigational medicinal product; IRC = Independent Radiological Review Committee; NAb = neutralizing antibody; NCI-CTCAE v6.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; RR = response rate; SAE = serious adverse event.

3.2. Estimands

3.2.1. Primary Estimands

Primary Estimand 1 corresponds to the primary endpoint (PFS assessed by IRC per RECIST v1.1), and includes the following five attributes:

1. Treatment (intervention): SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group).
2. Population: Patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
3. Variable (endpoint): PFS assessed by the IRC based on RECIST v1.1.
4. Intercurrent events and handling strategies:
 - a. Premature discontinuation of treatment: Handled using a treatment policy strategy; tumor imaging data collected after premature discontinuation of treatment will be included in the PFS analysis.
 - b. Initiation of new anti-tumor therapy: Handled using a hypothetical strategy; the event time will be censored at the date of the last valid tumor assessment prior to or on the day of the initiation of new anti-tumor therapy.
5. Population-level summary: Hazard ratio (HR), estimated using a stratified Cox proportional hazards model.

Primary Estimand 2 corresponds to the primary endpoint (OS), and includes the following five attributes:

1. Treatment (intervention): SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group).
2. Population: Patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

3. Variable (endpoint): OS.
4. Intercurrent events and handling strategies:
 - a. Premature discontinuation of treatment: Handled using a treatment policy strategy; post-discontinuation follow-up data (survival or death) will be included in the OS analysis;
 - b. Initiation of new anti-tumor therapy: Handled using a treatment policy strategy; follow-up data (survival or death) from subjects receiving other subsequent anticancer therapies will be included in the OS analysis.
5. Population-level summary: Hazard ratio (HR), estimated using a stratified Cox proportional hazards model.

4. STUDY DESIGN

4.1. Description of Study Design

This is a randomized, open-label, active-controlled, multicenter Phase 3 clinical trial. The overall study design is illustrated in [Figure 1](#). The study has a Main (China) cohort (SHR-A1811-315) with sites in China and an Extension cohort (GSP 402-301 [SHR-A1811-315_Extension]) with sites in India, Australia and/or other country.

Subjects with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer are planned to be enrolled in the study. It is planned to enrol approximately 350 subjects in the main cohort and approximately 70 subjects in the extension cohort. Randomization will be stratified based on the following factors: 1) HER2 expression status by immunohistochemistry (IHC) (HER2 IHC 1+ vs. HER2 IHC 2+/3+); 2) prior treatment with VEGF/VEGFR inhibitors such as bevacizumab (Yes vs. No). Subjects will be randomized in a 1:1 ratio to receive either SHR-A1811 (experimental group) or investigator's choice of chemotherapy (control group), which may include doxorubicin liposome, paclitaxel, topotecan, or gemcitabine. Detailed dosing information is provided in [Section 6.3](#).

[After enrollment in the main cohort is completed, subjects in the extension cohort will continue to be enrolled, and efficacy and safety data of subjects in the extension cohort will continue to be collected. A separate Statistical Analysis Plan (SAP) will be developed for the extension cohort, while all other elements will remain consistent with the main cohort.]

All subjects will proceed through the screening, treatment, and follow-up periods after providing written informed consent (see [Table 1](#) and [Table 2](#) for details):

- The screening period lasts 28 days following the signing of the informed consent form. During the screening period, subjects must undergo examinations and assessments to determine eligibility before randomization. Prior to randomization, the investigator must pre-select the chemotherapy regimen that will be administered if the subject is assigned to the control group. The first dose of IMP should be administered within 3 calendar days of randomization.
- During the treatment period, tumor imaging assessments will be performed every 6 weeks ± 7 days for the first 36 weeks, and every 12 weeks ± 7 days thereafter. CA-125 testing will be performed within ± 3 days of each imaging assessment. Safety assessments will be conducted prior to each administration. PK and immunogenicity blood sampling will be conducted at scheduled time points in subjects in the experimental group only. Additional data including concomitant treatments and exploratory endpoints will also be collected. End-of-treatment assessments must be completed accordingly.
- After end of treatment, subjects will enter the follow-up period (including safety follow-up and survival follow-up). During the safety follow-up (40 days [+7 days] after the last dose), information on safety, concomitant treatments, survival status, and subsequent anti-tumor therapies will be collected. After completion of the safety follow-up, survival follow-up will be conducted every 2 months ± 7 days (additional follow-up visits may be performed if necessary). Data on survival status and

subsequent anti-tumor therapies will be collected. During follow-up, subjects who discontinue treatment without documented radiologic progression must continue tumor imaging assessments and CA-125 testing at protocol-specified intervals until PD is confirmed, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.

4.2. Rationale for Study Design

4.2.1. Rationale for Control Group Selection

According to the 2024 NCCN and other treatment guidelines, the standard treatment for platinum-resistant recurrent ovarian cancer is non-platinum single-agent chemotherapy with or without bevacizumab. Based on the subject's prior-line treatment regimens, performance status, and other clinical factors, the investigator may select one of the following four chemotherapy agents as the control group treatment:

- Doxorubicin liposome;
- Paclitaxel;
- Topotecan;
- Gemcitabine.

4.2.2. Rationale for Open-Label Design

In this study, the treatment cycles differ between the experimental and control groups (3-week cycles in the experimental group vs. 3- or 4-week cycles in the control group), making the implementation of a single- or double-blind design impractical. Therefore, the study will adopt an open-label design.

Given that treatment allocation is known to relevant personnel in an open-label study, there may be a degree of trial bias. To minimize such bias, the following measures will be implemented:

- Subjects will be randomized using a stratified randomization method (seeSection 6.6.2) to ensure balance in baseline characteristics between treatment arms, thereby reducing selection bias and confounding bias;
- An IRC will be established to independently review all tumor imaging (seeSection 10.2.1), and PFS assessed by IRC will be used as the primary efficacy endpoint to minimize assessment bias;
- Prior to database lock, partial blinding of sponsor personnel will be performed according to the blinding plan, and unplanned inter-group analyses or comparisons will be avoided during the study (seeSection 6.6.3), in order to reduce information bias and selection bias.

4.3. Access to Study Intervention After Study Completion

The study intervention (as defined inSection 6.1) will be provided to subjects only during the conduct of this study. It will not be provided after the study ends.

4.4. Definition of Study Start and Completion

The start of the study is defined as the first subject's first visit (FSFV), i.e., the date on which the first subject signs the informed consent form.

The end of the study is defined as the last subject's last visit (LSLV), i.e., the date on which the last enrolled subject completes the final study visit per the Schedule of Activities or discontinues from the study for any reason (see [Section 7.2](#)).

5. STUDY POPULATION

5.1. Study Population Selection

The study population consists of adult patients with HER2-expressing platinum-resistant recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. (Platinum-resistant recurrence is defined as PD occurring during platinum-based therapy or within <183 days after the last dose of a platinum-based agent.); subjects must have received no more than one line of systemic anti-cancer therapy following the development of platinum resistance.

5.2. Rationale for Study Population Selection

Currently, clinical treatment options for patients with platinum-resistant recurrent ovarian cancer (including fallopian tube cancer and primary peritoneal cancer) are limited, typically involving non-platinum single-agent chemotherapy. However, these treatments are associated with poor prognosis, indicating a significant unmet medical need.

As SHR-A1811 targets HER2, this study will enroll patients whose tumors express HER2 (defined as HER2 IHC 1+ to 3+, based on the 2016 ASCO/CAP HER2 scoring criteria for gastric and gastroesophageal junction adenocarcinoma), to minimize unnecessary treatment in non-target populations.

This study will exclude children and adults without the capacity to provide informed consent, and populations who may have altered responses to the study intervention (e.g., subjects with hepatic or renal impairment or those who are immunocompromised).

5.3. Inclusion Criteria

Subjects must meet all the following criteria to be enrolled in this study:

1. The patient voluntarily agrees to participate in the study and has signed the informed consent form (ICF).
2. Female, aged 18 to 75 years (inclusive of 18 and 75 years; age calculated as on the date of ICF signing).
3. Histologically or cytologically confirmed diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.
4. Documented platinum-resistant recurrence after prior platinum-based therapy (defined as PD during platinum treatment or within <183 days after the last dose of platinum-based therapy). If the subject has only received one line of platinum-based therapy, at least 4 cycles must have been administered. Platinum-resistant recurrence must be confirmed by radiologic evidence of progression. Subjects may have received no more than one line of systemic anti-tumor therapy after developing platinum resistance and must be suitable for single-agent chemotherapy in the next line of treatment.
5. Subjects known to have high folate receptor α (FRA) expression must have received prior treatment with mirvetuximab soravtansine, unless the investigator determines that the subject is intolerant of or unsuitable for mirvetuximab soravtansine treatment, or if the treatment is not approved or locally unavailable.

6. PD or intolerable toxicity (with clear supporting evidence) during or after the last line of therapy.
7. HER2 expression of IHC 1+, 2+, or 3+.

The subject must provide adequate fresh or archived tumor tissue specimens to allow HER2 expression testing by the sponsor-designated or local laboratory (acceptable formats include paraffin blocks, paraffin-embedded sections, or fresh tissue sections. IHC 1+, 2+, or 3+ based on the 2016 ASCO/CAP HER2 scoring criteria for gastric and gastroesophageal junction adenocarcinoma).
8. At least one measurable lesion as defined by RECIST v1.1 (i.e., a lesion with a longest diameter ≥ 10 mm or an enlarged lymph node with a short axis ≥ 15 mm on spiral CT scan). Lesions previously treated with local therapy may be selected as target lesions if there is clear evidence of significant progression after completion of local treatment.
9. ECOG PS score of 0 to 1.
10. Expected survival of ≥ 12 weeks.
11. Adequate organ function confirmed by laboratory testing within 7 days prior to randomization (use of blood products or cell growth factors within 14 days before testing is not permitted):
 - a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$;
 - b. Platelet count $\geq 100 \times 10^9/L$;
 - c. Hemoglobin ≥ 90 g/L;
 - d. Serum total bilirubin (TBIL) $\leq 1.5 \times$ upper limit of normal (ULN);
 - e. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN; for subjects with liver metastases, AST and ALT $\leq 5 \times$ ULN;
 - f. Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula);
 - g. Activated partial thromboplastin time (aPTT) and international normalized ratio (INR) ≤ 1.5 (Subjects receiving prophylactic anticoagulation therapy with an INR ≤ 3 are eligible for enrollment);
 - h. Serum albumin ≥ 30 g/L.
12. For female subjects of childbearing potential, a negative pregnancy test result must be confirmed during the screening period (subjects with a positive HCG result may be enrolled if, in the judgment of the investigator, the result is clinically insignificant and pregnancy is excluded). Subjects must agree to use effective contraception and refrain from egg donation from the time of ICF signing until 7 months after the last dose of the IMP (see Section 13.1 for details).

5.4. Exclusion Criteria

Subjects who meet any of the following criteria shall not be enrolled in this study:

1. Histologically confirmed sarcomatous histologic subtype, or mixed tumors containing sarcomatous components.
2. Untreated or active CNS metastases, or a history of or current meningeal metastases. Subjects with previously CNS metastases who have undergone adequate local therapy (surgery or radiotherapy), do not require corticosteroid therapy, have neurologically

- returned to baseline (excluding residual signs or symptoms related to CNS treatment), and have been clinically stable for ≥ 4 weeks may be enrolled.
3. Prior treatment with topoisomerase I inhibitors (including but not limited to irinotecan, topotecan), or treatment with antibody-drug conjugates (ADCs) containing a topoisomerase I inhibitor payload, such as Enhertu (DS-8201a) and U3-1402.
 4. Receipt of systemic anti-tumor therapy within 4 weeks prior to the initiation of study treatment. For prior treatment with small molecule targeted therapies, the interval between end of treatment and the first dose of study treatment must be at least 5 half-lives of the drug or 7 days.
 5. Presence of symptomatic, poorly controlled, or moderate or greater pleural effusion, pericardial effusion, or ascites. Subjects who have undergone effusion drainage (excluding diagnostic thoracentesis) and have remained clinically stable for at least 2 weeks' post-procedure may be enrolled. (Prior to ICF signing, local treatment of serosal cavity effusions per standard of care is permitted.)
 6. Receipt of palliative radiotherapy within 7 days prior to the first dose of study treatment.
 7. History of or concurrent other malignancies, with the exception of cured basal cell carcinoma of the skin, carcinoma in situ of the cervix, ductal carcinoma in situ of the breast, papillary thyroid cancer, or other malignancies that have been adequately treated and cured for ≥ 3 years prior to randomization and for which there is documented evidence of no recurrence or metastasis.
 8. Toxicities from prior anti-tumor therapy not resolved to Grade ≤ 1 according to NCI-CTCAE v6.0 (except for lymphopenia, alopecia, fatigue, and laboratory abnormalities specified in the inclusion criteria. Chronic Grade 2 toxicities that are deemed tolerable by the investigator may be exempted).
 9. History of interstitial pneumonia/interstitial lung disease or non-infectious pneumonia (e.g., radiation pneumonitis) requiring steroid therapy; current or suspected interstitial pneumonia/interstitial lung disease, non-infectious pneumonia, or other active pneumonitis. Subjects with a history of Grade ≥ 3 interstitial pneumonia during prior immune checkpoint inhibitor therapy are also excluded.
 10. Active pulmonary tuberculosis, based on the Investigator's assessment. [Subjects may be enrolled if they have completed adequate tuberculosis treatment and have discontinued anti-tuberculosis therapy for ≥ 3 months prior to randomization.]
 11. Known pulmonary impairment caused by pulmonary comorbidities, including but not limited to any underlying lung disease e.g., pulmonary embolism within 3 months prior to the first dose, severe asthma, severe chronic obstructive pulmonary disease, restrictive pulmonary disease, etc.
 12. Autoimmune, connective tissue, or inflammatory diseases involving the lungs (e.g., rheumatoid arthritis, Sjögren's syndrome, sarcoidosis, etc.), or a history of lobectomy or pneumonectomy.
 13. Clinical cardiac symptoms or conditions that are not well controlled, such as: (1) heart failure classified as NYHA Class ≥ 2 or LVEF $< 50\%$; (2) unstable angina; (3) myocardial infarction within 1 year prior to randomization; (4) clinically significant supraventricular or ventricular arrhythmias requiring treatment or intervention; (5)

- QTcF >470 ms; (6) hypertension not adequately controlled with medication (subjects with blood pressure controlled to $\leq 160/100$ mmHg with antihypertensive therapy may be enrolled).
14. Arterial/venous thrombotic events within 1 month prior to randomization, including but not limited to cerebrovascular accident and deep vein thrombosis. Subjects with muscular venous thrombosis or catheter-related thrombosis of infusion ports may be enrolled if deemed no risk by the investigator.
 15. Gastrointestinal perforation or fistula, urethral fistula, or intra-abdominal abscess within 3 months prior to randomization. Subjects who have undergone ostomy creation or ureteral stent placement and are considered stable by the investigator may be enrolled.
 16. Intestinal obstruction, symptoms or signs suggestive of intestinal obstruction, or need for parenteral nutrition within 3 months prior to the start of study treatment. Subjects who have underwent surgical intervention with complete resolution of obstruction may be screened. Subjects who have previously received enteral stent implantation and have not had the stent removed by the screening period are excluded.
 17. Severe infections within 1 month prior to randomization, including but not limited to infectious complications requiring hospitalization, bacteremia, or severe pneumonia. Subjects with any active infection requiring intravenous systemic therapy, or those experiencing unexplained fever $>38.5^{\circ}\text{C}$ during the screening period or prior to randomization, are excluded. Subjects receiving prophylactic oral antibiotic therapy are allowed to be randomized and enrolled.
 18. Active hepatitis B (defined as positive HBsAg and HBV-DNA ≥ 500 IU/mL during screening) or active hepatitis C (defined as positive HCV antibody with detectable HCV RNA during screening).
 19. History of immunodeficiency, including positive HIV test, or other acquired or congenital immunodeficiency disorders, or history of organ transplantation.
 20. Major surgery (excluding diagnostic procedures or biopsies) performed within 28 days prior to the first dose. Subjects who have underwent traumatic minor surgery (e.g., biopsy, endoscopy, drainage) within 7 days prior to the first dose, or those with non-healing wounds (severe, non-healing, or dehiscent wounds) are excluded.
 21. Known hypersensitivity to any component of SHR-A1811, or a history of severe allergic reactions to other monoclonal antibody fusion proteins.
 22. Uncontrolled psychiatric disorders, or known history of alcohol abuse, drug abuse, substance misuse, or incarceration that may interfere with the completion of the study procedures.
 23. Presence of other severe comorbidities, including but not limited to acute myocardial infarction within the past 3 months, acute cerebral infarction within the past 3 months, or decompensated liver cirrhosis.
 24. Any other condition that, in the opinion of the investigator, may increase the risk associated with participation in the study, interfere with study results, or render the subject unsuitable for participation.

5.5. Lifestyle Requirements

5.5.1. Contraception Requirements

Female subjects of childbearing potential must agree to use effective contraception and refrain from egg donation from the time of signing the ICF until 7 months after the last administration of the IMP (see Section 13.1 for details).

5.5.2. Diet and Daily Activities

Once enrolled, subjects should avoid concomitant use of medications, herbal supplements, or foods that are strong inhibitors or inducers of cytochrome P450 (CYP) 3A4. Additionally, subjects should avoid consumption of food products known to inhibit CYP3A4, such as grapefruit, pomelo, bitter orange, and related fruit or derivatives.

Subjects should refrain from smoking and alcohol consumption during the treatment period.

5.6. Screen Failure

Screen failure is defined as a subject who consents to participate in the clinical study but is subsequently not randomized or not successfully enrolled. The necessary screening failure information must be recorded to ensure the transparency of the report, meet the requirements released in the Consolidated Standards of Reporting Trials (CONSORT), and respond to queries from regulatory authorities. The information includes the demographics, informed consent, reason for screening failure, inclusion criteria, and any SAE.

Re-screening of screen failure subjects is permitted in this study (see Table 1 and Table 2 for specific provisions).

6. STUDY INTERVENTION AND CONCOMITANT TREATMENT

6.1. Information on Study Intervention

All study interventions in this trial are investigational medicinal products (IMPs); no non-investigational medicinal products (NIMPs) or auxiliary medicinal products (AxMPs) are involved.

The IMPs in this study include SHR-A1811 (investigational drug) and investigator's choice of chemotherapy (liposomal doxorubicin, paclitaxel, topotecan, or gemcitabine; control drugs). All IMPs will be provided by the sponsor, consistently labeled, and qualified for use following quality testing. Detailed information is provided in [Table 7](#).

Table 7: Study Investigational Medicinal Product Information

IMP	SHR-A1811	Doxorubicin Hydrochloride Liposome Injection	Paclitaxel Injection	Topotecan Hydrochloride for Injection	Gemcitabine Hydrochloride for Injection
Type	Experimental drug	Control drug	Control drug	Control drug	Control drug
Dosage form	Injection (lyophilized powder)	Injection	Injection	Injection	Injection (powder)
Strength	0.1 g/vial	10 mL: 20 mg	5 mL: 30 mg	2 mg/vial	1.0 g/vial
Dosing regimen	4.8 mg/kg IV Q3W	40 mg/m ² IV Q4W	80 mg/m ² IV on D1, D8, D15, and D22 of each cycle, with 4 weeks as one treatment cycle	4 mg/m ² IV on D1, D8, and D15 of each cycle, with 4 weeks as one treatment cycle	1,000 mg/m ² IV on D1 and D8 of each cycle, with 3 weeks as one treatment cycle
Storage Conditions	2–8°C, protected from light, avoid freezing and shaking	Sealed, protected from light	Sealed, protected from light	Sealed, protected from light	Stored at room temperature (15–30°C)
Packaging	Neutral borosilicate tubular glass injection vial	Vial	Vial	Vial	Neutral borosilicate tubular glass injection vial
Shelf life	24 months	24 months	24 months	24 months	24 months

Abbreviations: D = Day; IMP = investigational medicinal product; IV = intravenous; Q3W = once every 3 weeks; Q4W = once every 4 weeks.

6.2. Rationale for Selection of Study Intervention

The early-phase SHR-A1811-I-101 study demonstrated preliminary antitumor activity of SHR-A1811 in patients with HER2-expressing gynecologic malignancies. In terms of safety, all subjects in the 8.0 mg/kg Q3W dose group experienced Grade ≥ 3 treatment-emergent adverse events (TEAEs), and this dose was not considered suitable as the recommended Phase 2 dose (RP2D). In contrast, subjects in the 4.8 mg/kg Q3W and 6.4 mg/kg Q3W dose groups showed good tolerability. Based on the overall benefit-risk profile, the subsequent Phase 2 study SHR-A1811-209 (a trial evaluating SHR-A1811 in HER2-expressing gynecologic malignancies) initiated efficacy exploration at a dose of 6.4 mg/kg Q3W.

As of September 15, 2023, in the SHR-A1811-209 trial, all 7 subjects in the 6.4 mg/kg Q3W dose group experienced Grade ≥ 3 hematologic adverse events within the first two treatment cycles, resulting in dose reductions or treatment interruptions. Considering the overall benefit-risk profile, the RP2D was adjusted to 4.8 mg/kg Q3W.

As of August 15, 2024, a total of 88 subjects had been enrolled in the 4.8 mg/kg Q3W dose group of the SHR-A1811-209 trial. No adverse events leading to treatment discontinuation or death were reported. The proportions of subjects who required dose reductions or treatment interruptions due to treatment-related adverse events (TRAEs) were 22.7% and 36.4%, respectively. Overall tolerability was favorable. The main observed toxicities were hematologic toxicities and gastrointestinal reactions, most of which resolved spontaneously or with symptomatic treatment. The safety profile was considered manageable, supporting further clinical investigation at this dose level.

Exposure–response analysis showed no statistically significant correlation between PFS and ADC exposure level (Cavg_ADC) during treatment in ovarian cancer subjects ($P > 0.05$). Furthermore, confirmed ORR was also not significantly correlated with Cavg_ADC, with a relatively flat logistic regression curve. Exposure–safety analysis indicated that the incidence of Grade ≥ 3 treatment-related adverse events, Grade ≥ 3 treatment-related hematologic adverse events, and TRAEs leading to dose reductions were significantly associated with the average ADC or free toxin exposure from first dose to event onset ($P < 0.05$).

Therefore, the dose of SHR-A1811 selected for this study is 4.8 mg/kg Q3W.

6.3. Dosage and Administration

6.3.1. Dosing Regimen

Treatment in the experimental group

SHR-A1811 will be administered via intravenous infusion on D1 of each cycle. The first infusion should be administered over 90 ± 10 min. If no infusion-related reaction occur after the first dose, subsequent infusions may be shortened to approximately 30 min (minimum 20 min, maximum 60 min). The dosing regimen is 4.8 mg/kg once every 3 weeks (Q3W). Treatment will continue until the occurrence of any event that meets the protocol-defined treatment discontinuation criteria (see Section 7.1.1). If the subject's body weight at follow-up remains within $\pm 5\%$ of the baseline value (C1D1), excluding the $\pm 5\%$ boundary, recalculation of the theoretical dose is not required. If the body weight change at that follow-up is $\geq 5\%$ or $\leq -5\%$ compared to baseline value, the theoretical dose should be recalculated, and the weight set as the new baseline weight at each administration. The deviation between the actual total dose and the theoretical total dose must not exceed 5%.

Treatment in the control group

The investigator may administer premedication prior to dosing based on the package insert or the standard of care at the site. The investigator will select one of the following treatment regimens (to be determined prior to randomization) and continue treatment until the occurrence of any event that meets the protocol-defined criteria for treatment discontinuation (see Section 7.1.1):

- Doxorubicin liposome: Administered via intravenous infusion on D1 of each cycle at a dose of 40 mg/m², with every 4 weeks as one treatment cycle. Body weight must be re-measured before dosing on D1 of each cycle to calculate body surface area:
- Paclitaxel: Administered via intravenous infusion on D1, D8, D15, and D22 of each cycle at a dose of 80 mg/m², with every 4 weeks as one treatment cycle.
- Topotecan: Administered via intravenous infusion on D1, D8, and D15 of each cycle at a dose of 4 mg/m² per day, with every 4 weeks as one treatment cycle.
- Gemcitabine: Administered via intravenous infusion on D1 and D8 of each cycle at a dose of 1,000 mg/m² per day, with every 3 weeks as one treatment cycle.

Body Surface Area Formula

Body surface area (m²) = 0.0061 × height (cm) + 0.0128 × weight (kg) – 0.1529

Note: Body weight must be measured prior to D1 of each cycle to calculate the total dose.

6.3.2. Dose Adjustment

6.3.2.1. Dose Adjustment of SHR-A1811

For subjects experiencing Grade ≥3 AEs related to SHR-A1811 (as graded per NCI-CTCAE v6.0), treatment interruption is recommended. The interval between two consecutive administrations must not be less than 18 days. Specific guidelines for treatment interruption and dose modification are provided in Table 8. If, during clinical practice, the investigator determines based on the individual subject's benefit-risk profile that the approach outlined in Table 8 (e.g., dose modification levels) is not appropriate, or an unlisted scenario arises, the investigator should manage the case based on clinical judgment and in consultation with the sponsor. Recommendations for the monitoring and management of infusion-related reactions/hypersensitivity, pulmonary toxicity, cardiac toxicity, and corresponding SHR-A1811 treatment interruption/dose modification are provided in Section 8.4.10 .

Table 8: SHR-A1811 Dose Interruption and Modification Guidelines

SHR-A1811-Related AE	Severity	Dose Interruption/Modification Guidelines
Hematology		
Neutrophil count decreased/white blood cell count decreased	Grade 3-4	Interrupt SHR-A1811 until resolution to Grade ≤2; then resume at the original dose and initiate secondary prophylaxis with long-acting G-CSF in the next cycle (if long-acting G-CSF is contraindicated, reduce by one dose level). If Grade 3 neutrophil count decreased/white blood cell count decreased recurs after secondary prophylaxis, reduce by one dose level.
Febrile neutropenia	Grade 3-4	Interrupt SHR-A1811 until recovery; then resume at the original dose and initiate secondary prophylaxis with long-acting G-CSF in the

SHR-A1811-Related AE	Severity	Dose Interruption/Modification Guidelines
		next cycle (if long-acting G-CSF is contraindicated, reduce by one dose level). If Grade 3 neutrophil count decreased/white blood cell count decreased recurs after secondary prophylaxis, reduce by one dose level.
Anaemia	Grade 3	Interrupt SHR-A1811 until resolution to Grade ≤ 2 ; then resume at the original dose.
	Grade 4	Interrupt SHR-A1811 until resolution to Grade ≤ 2 ; then reduce by one dose level.
Platelet count decreased	Grade 3	Interrupt SHR-A1811 until resolution to Grade ≤ 1 : if recovery occurs within ≤ 7 days from onset, resume at the original dose and consider secondary prophylaxis as per clinical practice guidelines in the next cycle. If recovery occurs >7 days from onset, the original dose may be maintained, and secondary prophylaxis is recommended in the next cycle. If Grade ≥ 3 platelet count decreased recurs after secondary prophylaxis, reduce by one dose level.
	Grade 4	Interrupt SHR-A1811 until resolution to Grade ≤ 1 ; consider secondary prophylaxis as per clinical practice guidelines in the next cycle. A dose reduction by one dose level or continuation of the original dose may be applied.
Lymphocyte count decreased	Grade 4	Interrupt SHR-A1811 until resolution to Grade ≤ 2 : If recovery occurs within ≤ 14 days from onset, resume at the original dose; If recovery occurs >14 days from onset, reduce by one dose level.
Hepatotoxicity		
ALT or AST elevation with TBIL elevation (ALT/AST $\geq 3.0 \times \text{ULN}$ and TBIL $>2.0 \times \text{ULN}$)		Interrupt SHR-A1811 until drug-induced liver injury is ruled out; If drug-induced liver injury is ruled out, the subject should receive appropriate treatment. Resumption of study treatment should be discussed between the investigator and sponsor based on subject's recovery; If drug-induced liver injury cannot be ruled out by diagnostic testing, permanently discontinue study drug; Monitor ALT/AST and TBIL twice weekly until recovery or return to baseline.
Gastrointestinal toxicities		
Diarrhoea/colitis	Grade 3	Interrupt SHR-A1811 until resolution to Grade ≤ 1 or baseline: If recovery occurs within ≤ 3 days from onset, resume at original dose; If recovery occurs >3 days from onset, reduce by one dose level.
	Grade 4	Permanently discontinue treatment.
Other non-hematological toxicities	Grade 3	Interrupt SHR-A1811 until resolution to Grade ≤ 1 or baseline: If recovery occurs within ≤ 7 days from onset, resume at original dose; If recovery occurs >7 days from onset, reduce by one dose level.
	Grade 4	Reduce by one dose level or permanently discontinue treatment.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; TBIL = total bilirubin; ULN = upper limit of normal.

Dose reduction should follow a unidirectional downward adjustment approach, i.e., once a subject's dose has been reduced, it must not be re-escalated to the original or a higher dose. In principle, no more than two dose reductions are allowed per subject. The sequential dose reduction levels are: 4.0 mg/kg and 3.2 mg/kg. If, based on a comprehensive benefit-risk assessment, the investigator determines that a more aggressive dose reduction is required to manage the AE, or if a third dose reduction is being considered, the dose level or further reduction should be determined in consultation with the sponsor.

Permanent discontinuation of SHR-A1811 is required if a subject experiences any of the following SHR-A1811-related AEs:

- Grade ≥ 2 non-infectious pneumonia and interstitial lung disease;
- LVEF of 40%–45% with a 10%–20% decrease from baseline, and failure to recover to within 10% of baseline within 3 weeks despite symptomatic treatment and/or treatment interruption; LVEF $< 40\%$ or $> 20\%$ decrease from baseline, confirmed by repeat assessment within 3 weeks despite symptomatic treatment and/or treatment interruption; symptomatic congestive heart failure;
- Grade ≥ 3 infusion related reaction;
- Grade 4 diarrhoea or colitis;
- Treatment-related AE resulting in SHR-A1811 interruption for more than 42 days (for dose interruption due to Grade 1 interstitial lung disease/noninfectious pneumonitis, refer to Table 14. If the interruption is due to reasons unrelated to toxicity [e.g., elective surgery], resumption of treatment should be discussed with the sponsor).

6.3.2.2. Dose Modification for Investigator's Choice of Chemotherapy

Dose modifications and treatment delays for investigator's choice of chemotherapy agents used in the control group should follow the respective package insert or site clinical practice standards.

Recommended dose reduction levels for control drugs are provided in Table 9.

Table 9: Recommended Dose Reduction Levels for Control Drugs

	Doxorubicin Liposome	Paclitaxel	Topotecan	Gemcitabine
First dose adjustment	Reduce to 30 mg/m ²	Reduce to 70 mg/m ²	Reduce to 3.5 mg/m ²	Reduce to 750 mg/m ²
Second dose adjustment	Reduce to 20 mg/m ²	Reduce to 60 mg/m ²	Reduce to 3 mg/m ²	Reduce to 500 mg/m ²
Third dose adjustment	Discontinue	Discontinue	Discontinue	Discontinue

Recommended guidelines for delayed dosing in the control group: If dosing is delayed beyond the predefined window in the control group, the date of the next administration should be recalculated based on the actual date of the current administration. If paclitaxel administration on D8, D15, or D22 is delayed by > 3 days, if topotecan administration on D8

is delayed by > 3 days or on D15 by > 7 days, or gemcitabine administration on D8 is delayed by > 7 days, then the missed dose should be skipped, and dosing should resume at the next scheduled administration date.

6.4. Management of Overdose

“Overdose” is defined in Section 12.1.1. If overdose is suspected, the drug should be discontinued immediately and the subject should be closely observed, and appropriate supportive treatment can be given if necessary.

6.5. Preparation, Handling, Storage, and Accountability of Investigational Medicinal Products

6.5.1. Preparation of Investigational Medicinal Products

All IMPs will be prepared by qualified site personnel in accordance with the Investigator’s Brochure and/or Pharmacy manual and dispensed to subjects.

6.5.2. Handling and Storage of Investigational Medicinal Products

IMPs must be stored in their original containers and under the storage conditions specified on the product label. They must be stored and transported in its original packaging at 2–8°C, protected from light, and must not be frozen or shaken. Storage requirements for control drugs should follow the package insert or other applicable documentation.

In cases where the storage conditions indicated on the product label differ from those described in the Investigator’s Brochure, the conditions on the product label shall prevail.

Study site systems must be capable of measuring and recording (e.g., via a log) the daily minimum and maximum temperatures at all storage locations within the site (including, as applicable, frozen, refrigerated, and/or room temperature products). This data must be collected continuously from the time of IMP receipt through the duration of the trial. Even if a continuous monitoring system is used, there must be a log or site procedure in place to ensure proactive review of deviations. This is achieved by recording and inspecting the minimum and maximum temperatures for each working day to confirm that no deviation occurred since the last assessment, and to ensure that after returning to normal operation, the site is able to capture or access the minimum/maximum temperatures for all non-working days. Temperature monitoring equipment and storage devices (e.g., refrigerators) should be checked regularly for operation (if applicable) to ensure they are in proper working condition.

Any deviation from the storage conditions of the product label shall be reported in a timely manner upon discovery. The study site should actively take measures to place the product in the storage conditions stated on the label as soon as possible, and report the temperature excursion and the action taken to the sponsor.

IMPs that are affected by temperature excursion must be temporarily isolated in an environment that meets the drug storage conditions and cannot be used until permission is obtained from the sponsor. If the sponsor permits continued use of the IMPs after a temperature excursion, this excursion is not considered a protocol deviation. However, using the IMPs before receiving such permission from the sponsor is considered a protocol deviation. The sponsor will provide the study site with specific steps to report temperature excursions.

6.5.3. Investigational Medicinal Product management

The management, dispensing, and return of IMPs in this study should be the responsibility of designated personnel. The investigator must ensure that all IMPs are used exclusively for subjects participating in this clinical study and are administered strictly in accordance with the protocol. Any unused IMP must be returned to the sponsor and must not be provided to any individual not participating in the study.

The sponsor or its designee will provide instructions to the site on the destruction of unused or returned IMPs. If the site is authorized to destroy IMPs, the investigator must ensure that destruction is performed in compliance with applicable environmental regulations, institutional policies, and other relevant requirements, and must provide documentation of the destruction process. Records must be maintained for all destroyed IMPs.

6.6. Subject Assignment, Randomization, and Blinding

6.6.1. Subject Assignment

Following the signing of the ICF, the sponsor will assign a subject identification number. In the case of rescreening, the subject must sign a new ICF and be re-registered to obtain a new subject number. The subject number will be used on all electronic case report form (eCRF) pages and other trial-related documents and systems.

The screening period lasts 28 days following the signing of the informed consent form. Subjects who meet all eligibility criteria will proceed to randomization and receive a unique randomization number. Once randomization is complete, the correspondence between the subject number and the randomization number will be established.

The investigator's knowledge of the treatment assignment must not influence the enrollment decision for individual subjects or the order in which subjects are enrolled.

6.6.2. Randomization

This study will adopt a stratified randomization method. Stratification factors include: 1) HER2 expression status by immunohistochemistry (IHC) (HER2 IHC 1+ vs. HER2 IHC 2+/3+); 2) prior treatment with VEGF/VEGFR inhibitors such as bevacizumab (Yes vs. No). Subjects will be randomized in a 1:1 ratio to the experimental group (SHR-A1811) or the control group (investigator's choice of chemotherapy).

Randomization will be managed via the Interactive Response Technology (IRT) system. Based on the randomization scheme, a designated randomization specialist will generate the randomization schedule using SAS software (version 9.4 or higher) and upload it into the IRT. The IRT system will assign eligible subjects to treatment groups and provide the corresponding study medication accordingly.

6.6.3. Blinding and Unblinding

This is an open-label study. Neither investigators nor subjects will be blinded to treatment allocation. However, certain sponsor personnel will remain blinded to treatment assignments prior to database lock, in accordance with the blinding plan.

Special attention should be paid to avoid any unplanned inter-group analyses or comparisons during the course of the study.

6.7. Compliance with Study Intervention

During the recruitment and screening phase, subjects will be fully informed of the study objectives, basic information about the IMP, study procedures, dosing regimen (including dose, route, and duration), frequency and procedures of clinical assessments and biospecimen collection, potential risks, compensation, and indemnification, to ensure voluntary participation and enhance compliance with treatment. Throughout the study, the investigator should remind the subjects to comply with the protocol to ensure subject compliance.

All IMPs will be administered by appropriate study personnel designated by the study site. The study site will complete all drug preparations and records in accordance with the pharmacy manual. The site's documentation system must record all relevant information related to dose preparation and administration.

6.8. Concomitant Treatments

Concomitant treatment refers to any medicinal or non-medicinal therapy administered at the investigator's discretion in the interest of the subject. All concomitant medications, blood products, and non-drug interventions administered from the screening period through the end of study visits must be documented in the eCRF.

6.8.1. Prohibited Concomitant Treatments

The use of any anti-tumor therapy other than the IMP specified in this protocol is prohibited. This includes, but is not limited to, chemotherapy, targeted therapy, immunotherapy, ovarian function suppression, endocrine therapy, biologic therapy, traditional alternative medicines (e.g., homeopathy, Ayurvedic, traditional Chinese medicine or Chinese patent medicine) with anti-tumor indications, or participation in other clinical trials involving anti-tumor drugs/medical devices.

Any local treatment targeted at the index lesion (e.g., surgery, localized radiotherapy) is prohibited. The investigator must clearly state that such local treatment is not administered due to PD. IMP administration must be interrupted during the period of local palliative treatment and may resume only after the recovery period is complete.

Other prohibited concomitant treatments are outlined in Section 5.4.

6.8.2. Concomitant Treatments to Be Used with Caution

In vitro studies have shown that the toxin SHR169265 is primarily metabolized by CYP3A4 and CYP2D6 and is a substrate of P-glycoprotein (P-gp). Therefore, it may be affected by inhibitors or inducers of these enzymes and transporters. The use of strong inhibitors or inducers of CYP3A4 and CYP2D6, as well as P-gp inhibitors and inducers, should be approached with caution during the study. These include but are not limited to:

- Strong inhibitors of CYP3A4: ceritinib, clarithromycin, cobicistat, boceprevir, elvitegravir + ritonavir, idelalisib, indinavir + ritonavir, itraconazole, ketoconazole, lopinavir + ritonavir, nefazodone, nelfinavir, paritaprevir + ritonavir + ombitasvir/dasabuvir, posaconazole, ritonavir, saquinavir + ritonavir, telithromycin, tipranavir + ritonavir, voriconazole;
- Strong inducers of CYP3A4: apalutamide, carbamazepine, enzalutamide, ivacaftor, lumacaftor + ivacaftor, mitotane, phenytoin, rifampin, St. John's wort;

- Strong inhibitors of CYP2D6: bupropion, fluoxetine, paroxetine, quinidine, terbinafine;
- P-gp inhibitors: amiodarone, clarithromycin, cobicistat, cyclosporine, dronedarone, erythromycin, itraconazole, ketoconazole, lapatinib, lopinavir + ritonavir, propafenone, quinidine, ranolazine, saquinavir + ritonavir, sofosbuvir + velpatasvir + voxilaprevir, verapamil.

6.8.3. Permitted Concomitant Treatments

Palliative and supportive treatment for disease-related symptoms may be administered based on the investigator's judgment and relevant guidelines (such as the "American Society of Clinical Oncology Guidelines").

During the treatment period, subjects can be given the best supportive care. Clinical comorbidities and various adverse reactions should be actively treated and managed. Recommendations for the prevention/management of common adverse reactions are provided in Section 8.4.10.

The use of bisphosphonates or denosumab to manage bone-related events due to bone metastases is permitted.

Anti-inflammatory or anesthetic analgesics could be given if it had no known or predictable drug-drug interaction and was not included in the concomitant treatment (Section 6.8).

7. DISCONTINUATION OF STUDY INTERVENTION OR WITHDRAWAL FROM THE STUDY

7.1. Discontinuation of Study Intervention

7.1.1. Discontinuation of Study Intervention

Discontinuation of study intervention does not constitute withdrawal from the study. Subjects who discontinue study intervention are required to complete the remaining study visits as specified in the protocol. Reasons for discontinuation of study intervention may include:

- Subject's request for discontinuation;
- Progressive disease (PD);
- AE, abnormal laboratory test, or other medical condition rendering continued treatment non-beneficial to the subject;
- General deterioration in health status precluding further participation;
- Lost to follow-up;
- Death of the subject;
- Pregnancy;
- Major protocol deviations, e.g., the subject no longer meets the criteria to continue in the study after enrollment;
- Early study termination by the sponsor;
- Other reasons determined by the investigator to preclude further study intervention.

Every effort should be made to complete the end of treatment (EOT) visit as specified in the schedule of activities and to conduct safety and survival follow-up. The investigator may recommend or provide new or alternative treatment methods to subjects based on their actual condition.

7.1.2. Temporary Interruption and Re-challenge of Study Intervention

Subjects may temporarily interrupt IMP treatment due to safety events. After evaluation by the investigator and confirmation of safety, IMP treatment may be re-initiated. Dose modification requirements are outlined in Section 6.3.2.

7.2. Withdrawal from the Study

Possible reasons for subject withdrawal from the trial include but are not limited to:

- AEs;
- Subject's request to withdraw;
- Lost to follow-up;
- Death of the subject;
- Early study termination by the sponsor;

- Other reasons determined by the investigator to preclude further participation.

If a subject fails to return to the site for scheduled visits, all reasonable efforts should be made to contact the subject and document the outcome. The investigator should inquire about the reason for withdrawal and request the subject to complete the final visit per the Schedule of Activities, including follow-up of any unresolved AEs.

If a subject refuse further visits to the study site, efforts should still be made to continue tracking and collecting survival data or study related information, unless the subject refuses to disclose further information or be contacted further. In this case, no more study evaluation should be conducted, and no more data should be collected.

For subjects who are lost to follow-up or have died, the steps for study withdrawal will no longer be applicable.

7.3. Lost to Follow-up

If a subject misses scheduled visits at the study site more than three times and the study site is unable to establish contact with them, they are considered lost to follow-up.

If a subject fails to return to the study site for necessary study visits, the following actions should be taken:

- The study site should make efforts to contact the subject, reschedule any missed visits promptly, provide counseling to the subject about the importance of attending visits on time, and determine whether the subject wishes to and/or should continue with the study.
- Before considering a subject as lost to follow-up, the investigator or designated personnel shall make every possible effort to contact the subject (e.g., attempting to contact the subject at least three times by phone and, if necessary, sending emails to their email address, and using social media tools to establish communication). All attempts made to contact the subject should be documented in the medical documents.
- If the subject still cannot be reached in spite of such efforts, the subject is considered to have withdrawn from the study, with the primary reason for withdrawal being loss to follow-up.

7.4. Specific Discontinuation Criteria

This section is not applicable.

8. TRIAL EVALUATION AND PROCEDURES

The tests and procedures required by the protocol should be ensured as much as possible in accordance with the plan. However, unplanned circumstances may occur from time to time, which is beyond the investigator's control, making testing difficult. Under such circumstances, the investigator must take all necessary measures to protect the safety and interests of the subjects. When the procedure required by the protocol cannot be performed, the investigator must record the reason. In addition, the study team must be notified by the investigator of unexpected situations in a timely manner.

This clinical trial should be conducted in accordance with the study protocol, the current Good Clinical Practice (GCP) and relevant laws and regulations.

8.1. Screening/Baseline Assessments and Procedures

Subjects must sign the ICF prior to undergoing any subsequent screening procedures. Detailed screening/baseline assessments and procedures are provided in [Table 1](#) and [Table 2](#).

8.2. Efficacy Evaluation and Procedures

8.2.1. Efficacy Parameters

PFS: Defined as the time from the date of randomization to the date of first documented radiologic PD or death from any cause, whichever occurs first.

OS: Defined as the time from the date of randomization to death from any cause.

ORR: Defined as the proportion of subjects whose best overall response (BOR) is complete response (CR) or partial response (PR), as assessed per RECIST v1.1. For responses of CR or PR, confirmation is required at least 4 weeks (≥ 28 days) after the initial evaluation.

DoR: Defined as the time from the first evaluation of CR or PR to the date of first evaluation of PD or death, whichever occurs first, in subjects who achieve confirmed CR or PR.

DCR: Defined as the proportion of subjects whose BOR is CR, PR, or stable disease (SD), as assessed per RECIST v1.1.

RR: Defined as the proportion of subjects achieving a response according to both RECIST v1.1 and the GCIG CA-125 criteria.

CA-125 RR: Defined as the proportion of subjects achieving a response based on the GCIG CA-125 criteria.

PFS2: Defined as the time from the subject's randomization date to the occurrence of a second disease progression (based on objective radiographic progression or clinical disease progression) or death, whichever occurs first.

8.2.2. Efficacy Evaluation

Assessment of PFS, ORR, DoR and DCR

For endpoints based on tumor response, imaging assessments will be performed by both the IRC (see [Section 10.2.1](#)) and the investigator according to RECIST v1.1 (see [Section 13.5](#)).

During the treatment period, tumor imaging assessments will be conducted every 6 weeks ± 7 days for the first 36 weeks, and every 12 weeks ± 7 days thereafter, until documented PD,

initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor (as specified in [Table 1](#) and [Table 2](#)).

OS assessment

During the safety follow-up period (within 40 days [+7 days] after the last dose of study treatment), data on survival status and subsequent anti-tumor therapies will be collected. After the completion of the safety follow-up, survival follow-up will be conducted every 2 months ± 7 days (additional survival follow-up may be performed as needed). Survival data and information on subsequent anti-tumor therapies will be collected until the subject dies, is lost to follow-up, withdraws informed consent and declines any form of follow-up, or the study is terminated early by the sponsor.

Assessment of RR and CA-125

CA-125 RR will only be assessed in subjects with baseline CA-125 levels $\geq 2 \times$ the ULN (as measured within 7 days prior to the initiation of treatment). A CA-125 response is defined as a $\geq 50\%$ reduction in CA-125 level from the last pre-treatment measurement, confirmed by a second assessment at least 28 days later, with the confirmatory value being $\leq 110\%$ of the previous measurement. The date of CA-125 response is defined as the date when the $\geq 50\%$ reduction is first observed.

CA-125 measurements will be performed concurrently with each imaging assessment (± 3 days). Unscheduled assessments may be conducted at the discretion of the investigator. CA-125 monitoring will continue until documented PD, initiation of other anti-tumor therapy, loss to follow-up, death, or early termination of the study by the sponsor.

Response assessments based on RECIST v1.1 and GCIG CA-125 criteria are presented in [Table 10](#).

Table 10: Response Evaluation Based on RECIST v1.1 and GCIG CA-125 Criteria

Based on RECIST v1.1	Based on GCIG CA-125 Criteria	Overall Evaluation
CR	CA-125 < ULN	Response
PR	Response	Response
PR	Non-response	Response
SD	Response	Response
SD	Non-response	Non-response
PD	Response	PD
PD	Non-response	PD

Abbreviations: CA-125 = cancer antigen 125; CR = complete response; GCIG = Gynecologic Cancer InterGroup; PD = progressive disease; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SD = stable disease; ULN = upper limit of normal.

8.3. Safety Assessments and Procedures

Safety assessments include the collection of AEs and SAEs (see [Section 8.4](#)), as well as clinical laboratory tests, vital signs, 12-lead ECG, and ECOG PS scores.

8.3.1. Laboratory Tests

Samples for laboratory tests will be collected at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#), and analyses will be performed at the local or central laboratory. A summary of laboratory assessments is provided in Section 13.2. Except for tumor marker testing (CA-125), all laboratory assessments are for safety monitoring. Unscheduled clinical laboratory evaluations may be conducted at any time during the study to assess potential safety concerns as needed.

8.3.2. Vital Signs

Vital sign assessments, including body temperature, respiratory rate, pulse, and blood pressure, will be performed at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#).

8.3.3. 12-Lead ECG

The 12-lead ECG will include assessments of heart rate, QT, QTc, and PR interval, conducted at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#).

8.3.4. ECOG-PS Score

ECOG PS will be assessed at the time points specified in [Table 1](#) and [Table 2](#). The scoring criteria are provided in Section 13.6.

8.3.5. Physical Examination

Physical examinations will be conducted at the time points specified in [Table 1](#) and [Table 2](#), and will include general condition, head and face, skin, lymph nodes, eyes (sclerae and pupils), ears, nose, throat, mouth, respiratory system, cardiovascular system, abdomen, reproductive-urinary system (when clinically indicated), musculoskeletal system, nervous system, and mental condition.

8.3.6. Others

Echocardiography, body weight measurement, and bilateral lower extremity deep vein ultrasound will be performed at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#).

8.4. Adverse Events (AEs) and Serious Adverse Events (SAEs)

8.4.1. Definitions of AEs and SAEs

An AE is defined as any untoward medical occurrence associated with the use of the study treatment that occurs after a subject's signed ICF has been obtained and does not necessarily have a causal relationship with the treatment. Therefore, an adverse event can be any unfavorable and unintended sign (including abnormal laboratory findings), symptom(s) or disease temporally associated with the use of study treatment regardless of relatedness with the study treatment.

When a diagnosis is possible, it is preferable to record it, rather than a series of signs or symptoms relating to the diagnosis.

Progression of underlying malignancy should not be reported as an AE or as a serious adverse event (SAE). Adverse events observed at the time of disease progression will be reported as AE or SAEs per guidelines used for such events with a causality assessment by the Investigator.

Examples of AEs include but are not limited to:

1. Exacerbation of a pre-existing (before entering the clinical trial) medical condition/disease (including exacerbation of symptoms, signs, and laboratory abnormalities);
2. Any new AEs: Any new adverse medical conditions (including symptoms, signs, newly diagnosed diseases);
3. Clinically significant abnormal laboratory test results;
4. Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (e.g., for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately)

An adverse event does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected prior to the start of study treatment administration that do not worsen
- Situations where an untoward medical event has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Hospitalizations for study treatment infusions or precautionary measures per institutional policy

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breastfeeding
- Medication error
- Occupational exposure

An SAE refers to any of the following untoward medical occurrences in a subject after receiving the IMP:

- Events leading to death;

- Life-threatening event (at risk of death at the time of the event); Refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Events requiring hospitalization (as defined in Section 12.2.1) or prolongation of hospitalization;
- An event resulting in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Congenital anomaly or birth defect;
- Medically important event:
 - Medical and scientific judgments must be used to judge whether an event is an important medical event. Important medical events may not be immediately life-threatening, result in death, or hospitalization. However, if the event may jeopardize the patient or require intervention to prevent one of the outcomes listed in the definition of SAE above, the important medical event should be reported as an SAE.
 - Examples include allergic bronchospasm requiring emergency treatment in the emergency room or at home, non-hospitalized cachexia or convulsions, and drug dependence or drug abuse.

Further details on AEs and SAEs are provided in Section 12.1 and Section 12.2.

8.4.2. Collection of AEs, SAEs, and Other Events

Safety events in clinical trials, including pre-treatment medical occurrences, AEs, SAEs, adverse events of special interest (AESIs), pregnancy, and overdose, must be collected from the time the subject signs the informed consent form until the end of the safety follow-up period (40 [+7] days after the last dose of IMP) (see Table 11).

Table 11: Collection of Clinical Trial Safety Events

Period	Collection Requirements
Starting from the subjects' signing of informed consent form until the end of the safety follow-up period*	Adverse medical events/AEs/SAEs/AESIs/pregnancy/drug overdose prior to the first dose of IMP If a new anti-tumor therapy is initiated before the end of the safety follow-up period, only AEs/AESIs/SAEs related to the IMP will be collected; Pregnancy and overdose will be collected only after the first dose of the IMP.
After the above period	Only SAEs and AESIs related to the IMP

Abbreviations: AE = Adverse Event; AESI = Adverse Event of Special Interest; IMP = Investigational Medicinal Product; SAE = Serious Adverse Event.

*The end of the safety follow-up period is defined as 40 days (+7 days) after the last dose of IMP.

Note: All deaths that occur before the end of the safety follow-up period must be reported as SAEs, regardless of whether the subject has received other anti-tumor therapies.

8.4.3. Identification of AEs and SAEs

At each visit, the investigator should assess whether the subject experienced AEs and SAEs by questioning, physical examination or laboratory tests of the subject. Events, whether

observed by the investigator or unsolicitedly reported by the subject, must be assessed and recorded by the investigator.

8.4.4. Recording of AEs and SAEs

All AEs should be recorded on the AE page of the eCRF in detail, including: The event terminology, start and end dates, severity, seriousness, causal relationship between the event and the IMP, actions taken with the IMP, and final outcome. If the event meets the SAE criteria, it must be reported according to the SAE reporting procedure.

Further details on assessing severity and causality of AEs and SAEs are provided in Section 12.3 and Section 12.4.

8.4.5. Follow-up of AEs/SAEs

All AEs should be followed up until symptoms disappear, or clinically relevant changes in laboratory tests return to baseline and/or CTCAE Grade ≤ 1 , or a reasonable explanation is obtained (such as loss to follow-up and death).

8.4.6. SAE Reporting System

If an SAE occurs, regardless of whether it is the initial or follow-up report, the investigator must immediately fill out “Serious Adverse Event (SAE)/Adverse Event of Special Interest (AESI)/Drug Overdose Report Form”, and sign and date it, and notify the sponsor within 24 hour of the Investigator or their staff becoming aware of the SAE, and promptly report it to the relevant units in accordance with local regulatory requirements. Reporting should be performed by recording as much information as is available at the time.

When further information becomes available, the SAE Form should be updated with the new information and reported immediately via the same contact information. Follow-up reports must be submitted to the Sponsor until the event resolves, the event stabilizes or the event returns to baseline if a baseline value is available. Additional information will be requested by the Sponsor as necessary.

For SAEs that occur after the safety follow-up period, those suspected to be related to the IMP should be collected. For a SAE, the symptoms, severity, correlation with the IMP, time of onset, time of treatment, measures taken, time and method of follow-up, and outcome should be recorded in detail. If the investigator believed that an SAE was unrelated to the IMP but potentially related to the study conditions (e.g., discontinuation of the original treatment, or complications during the study), this relationship was described in detail in the narrative section of the SAE report form.

The email address of the sponsor for receiving reports of SAEs (as well as AESIs, pregnancies, and drug overdose) for this study is:

GlobalClinicalSAE@glenmarkpharma.com

8.4.7. Regulatory Reporting Requirements for SAEs

Except for those SAEs explicitly exempted from immediate reporting per the protocol, the investigator must submit a written report of all SAEs to the sponsor within 24 h of becoming aware of the event. Also, to update to the regulatory authority/EC/Institution as per local regulation/requirement. A detailed written follow-up report must be submitted in a timely manner thereafter.

The sponsor will comply with national-specific regulatory requirements for safety reporting to regulatory authorities, ethics committees, clinical study sites, and investigators. The sponsor will notify local and other regulatory agencies about the safety information related to the study drug, as per the regulatory requirements and the sponsor's policies. The investigator will review the safety reports received from the sponsor detailing the SUSAR or other specific safety information, archive them along with the IB, and notify the ethics committee.

The sponsor will promptly investigate any Serious Adverse Events (SAEs) that occur in the study and take necessary measures to ensure the safety and rights of the subjects.

For reports involving death events, the investigator shall provide the sponsor and the ethics committee with other required information, such as autopsy reports and final medical reports.

8.4.8. Suspected, Unexpected, Serious Adverse Reaction Report

Suspected unexpected serious adverse reaction refers to a serious adverse reaction where the nature and severity of its clinical manifestations exceed the existing data and information such as the investigator's brochure of the investigational drug, the package insert of the marketed drug or the summary of product characteristics.

After the sponsor receives safety-related information from any source, it shall immediately analyze and evaluate it, including seriousness, correlation with the investigational drug, and whether it is an expected event. The sponsor shall quickly report suspected unexpected serious adverse reactions to the drug regulatory authority, the competent health authority and all investigators participating in the clinical trial, and submit them to the clinical trial institution and ethics committee according to the requirements of the study site.

8.4.9. Adverse Events of Special Interest (AESIs)

For the reporting of any AE (AESI) specified in the clinical trial protocol, "Serious Adverse Event (SAE)/Adverse Event of Special Interest (AESI)/Drug Overdose Report Form" must be filled out within 24 h after the investigator learns about it and it should be reported to the sponsor. This procedure applies to all AESIs regardless of whether the SAE criteria are met. The AESI reporting (to sponsor) process is the same as the SAE reporting process. If the definition of SAE is met, it must be reported in accordance with the SAE reporting process.

AESIs in this study include:

- Grade ≥ 3 infusion related reaction;
- Grade ≥ 3 cardiomyopathy or other cardiovascular events; Grade ≥ 3 QTcF prolongation; symptomatic congestive heart failure;
- Grade ≥ 2 non-infectious pneumonia and interstitial lung disease;
- Liver function test abnormalities meeting the criteria in Section 8.4.9.1.

8.4.9.1. Abnormal Liver Function Tests

AST and/or ALT abnormalities accompanied by abnormally increased TBIL that meet the following criteria (1), (2) and (3) (see [Table 12](#)) with no other reasons should always be reported as AESIs.

Table 12: Criteria for Determining Liver Function Test Abnormalities

Condition Met	Determination Criteria
Abnormal ALT or AST	Normal ALT and AST at baseline: ALT or AST $>3 \times$ ULN during the treatment period; Abnormal ALT and AST at baseline: ALT or AST $>2 \times$ baseline level during treatment period, and $>3 \times$ ULN; or $>8 \times$ ULN (whichever is lower).
Abnormal TBIL	Normal TBIL at baseline: TBIL $>2 \times$ ULN during the treatment period; Abnormal TBIL at baseline: TBIL increases by $>1 \times$ ULN during the treatment period or its value is $>3 \times$ ULN (whichever is lower).
No evidence of cholestasis (e.g., serum alkaline phosphatase elevated due to gallbladder or bile duct disease, etc.)	

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, TBIL = total bilirubin, ULN = upper limit of normal.

If a subject had abnormal AST and/or ALT levels and abnormally increased TBIL levels during the treatment period or follow-up period, the subject had to return to the study site for investigation and assessment as soon as possible (preferably within 48 h) after learning about the abnormal results. Examination and assessment should include relevant laboratory tests of liver function, thorough inquiry of medical history and physical examination.

In addition to repeat testing of AST and ALT, liver function tests may include serum albumin, serum creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transpeptidase, prothrombin time/international normalized ratio, and alkaline phosphatase. Recommendations for collection of detailed medical history and relevant information include: History of alcohol use, acetaminophen, soft drugs, various supplements, family diseases, sexual behavior, travel, contact with jaundice patients, surgery, blood transfusion, hepatic diseases, allergies, or possible occupational exposure. Further examinations may also include tests on hepatitis A, B, C, D and E acute infections, as well as imaging examination of the liver (such as the biliary tract).

8.4.10. Management of Common Adverse Reactions

8.4.10.1. Hematological Toxicities

For subjects at high risk of febrile neutropenia (e.g., age >65 years receiving full-dose intensive treatment; prior treatment with febrile neutropenia or prolonged Grade 4 neutropenia; tumor involving the bone marrow; recent surgery and/or open wounds), prophylactic administration of long-acting granulocyte colony-stimulating factor (G-CSF) at the first IMP dose may be considered at the investigator's discretion based on clinical practice guidelines (limited to subjects receiving liposomal doxorubicin in the control group). For subjects who have experienced Grade 3/4 leukopenia, neutropenia, or febrile neutropenia in previous IMP cycles, prophylactic use of long-acting G-CSF is recommended in subsequent IMP cycles. For subjects who have experienced Grade 3/4 platelet count decreased in previous IMP cycles, secondary prophylaxis for platelet count decreased is recommended according to clinical practice guidelines. Recommended agents may include thrombopoietic growth factors and thrombopoietin receptor agonists (TPO-RAs).

The use of G-CSF, erythropoiesis-stimulating agents, thrombopoietin-stimulating agents, transfusions, or blood products for therapeutic purposes is permitted.

8.4.10.2. Nausea or Vomiting

It is recommended that subjects receive prophylactic antiemetic treatment before administration of SHR-A1811, in accordance with clinical practice guidelines. A triple or quadruple regimen is recommended: fosaprepitant + palonosetron + dexamethasone ± olanzapine, or fosrolapitant and palonosetron hydrochloride for injection (RuiTanNing®) + dexamethasone ± olanzapine. Palonosetron may be substituted with tropisetron, and fosaprepitant may be substituted with aprepitant or rolapitant. Use of dolasetron, granisetron, and ondansetron should be approached with caution.

For subjects who experience vomiting, symptomatic treatment should be initiated promptly, including acid suppression, gastrointestinal protection, and antiemetics, followed by close monitoring. If symptoms severely impair oral intake, attention should be paid to maintaining fluid and electrolyte balance.

8.4.10.3. Infusion Reactions or Hypersensitivity Reactions

Throughout the study, the investigator must monitor closely for potential infusion or hypersensitivity reactions, particularly acute immune-mediated adverse reactions (including cytokine release syndrome).

In general, prophylactic medication prior to IMP infusion is not required. Infusion or hypersensitivity reactions are most likely to occur within 24 h of infusion. If such reactions occur, the investigator should assess the relationship to the IMP and, based on clinical judgment, may slow or interrupt the infusion and initiate supportive care, and administer prophylactic premedication prior to subsequent infusions of the IMP. Possible allergic reactions include fever, cold intolerance, chills, headache, rash, itching, joint pain, low or high blood pressure, and bronchospasm.

The management of allergic reactions should be carried out in accordance with the medical practice and guidelines of the study institution. Symptomatic treatment (e.g., oral antihistamines without significant QT interval prolongation, such as cetirizine, loratadine, fexofenadine, desloratadine, levocetirizine, or corticosteroids) should be given for late-onset allergic reactions (e.g., pruritus that occurs only 1 week after the end of infusion). See [Table 13](#) for recommendations for treatment of infusion reactions.

Table 13: Recommendations for Treatment of Infusion Reactions

CTCAE Grade	Clinical Management	Action Taken with IMP
Grade 1 Transient and mild reaction; does not require infusion interruption or treatment	Observe and closely monitor the bedside until recovery; Prophylactic medication is recommended before infusion subsequently: at least 30 min prior to infusion, administer diphenhydramine 50 mg or equivalent and/or acetaminophen 325–1,000 mg.	Continue. When the infusion reaction is observed, the infusion rate can be reduced by 50%, and then the patient is closely monitored. If no other reactions occur, the initial infusion rate can be restored.
Grade 2 Requires interruption of treatment or infusion	Normal saline via intravenous drip, diphenhydramine 50 mg IV or equivalent and/or acetaminophen 325-1,000 mg;	Interrupt treatment. Resume the study treatment at 50% of

CTCAE Grade	Clinical Management	Action Taken with IMP
and prompt symptomatic treatment (e.g., antihistamines, NSAIDs, analgesics, IV administration); requires ≤24 h of prophylactic medication	Observe at the bedside, closely monitor until recovery; Corticosteroids or bronchodilators may be considered as clinically needed; Document volume of IMP infused in the subject's source records; Prophylactic medication is recommended before infusion subsequently: at least 30 min prior to infusion, administer diphenhydramine 50 mg or equivalent and/or acetaminophen 325–1,000 mg. Cortisol hormone (equivalent to hydrocortisone 25 mg) when necessary.	the initial rate after symptoms disappear. If there are no complications within 30 min, the infusion rate can be increased to the original 100%. Monitor closely. If symptoms recur, the current IMP will no longer be infused.
Grade 3 Delayed response to symptoms (e.g., no immediate symptomatic treatment and/or brief interruption of infusion); recurrence after initial improvement; clinical sequelae requiring hospitalization	Immediately discontinue IMP infusion; Start intravenous drip of saline; Bronchodilators, 0.2–1 mg of 1:1000 epinephrine solution via subcutaneous injection or 0.1–0.25 mg of 1:10,000 epinephrine solution via slow intravenous injection, and/or diphenhydramine 50 mg plus methylprednisolone 100 mg or equivalent via intravenous injection (if necessary), are recommended;	Permanently discontinue the IMP.
Grade 4 Life-threatening: requires emergency intervention	Follow the guidelines for treatment of allergic reactions of the study institution; Observe at the bedside, closely monitor until recovery.	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IMP = investigational medicinal product; IV = intravenous.

8.4.10.4. Pulmonary Toxicity

It is recommended that pulmonary toxicity (including non-infectious pneumonitis and interstitial lung disease [ILD]) be closely monitored according to the following procedures:

- If ILD/non-infectious pneumonitis is suspected, additional assessments may be performed as needed, including high-resolution chest CT, chest X-ray, pulmonary function tests, arterial blood gas analysis, and/or serologic tests. A multidisciplinary team (MDT) including oncologists, pulmonologists, radiologists, pathologists, and pharmacists should review medical records and imaging/pathology to reach a diagnosis and coordinate management.
- A diagnosis of drug-related ILD should meet the following criteria: (1) imaging findings suggest new pulmonary lesions; (2) a temporal relationship exists between pulmonary lesions and drug administration; (3) other causes of pulmonary lesions have been excluded.
- If a subject develops ILD/noninfectious pneumonitis, management should follow the recommendations in [Table 14](#).

Table 14: Recommendations for the Management of Interstitial Lung Disease/Noninfectious Pneumonitis

CTCAE Grade	Clinical Management
Grade 1	Interrupt the IMP until full recovery; if drug-related ILD/non-infectious pneumonitis resolves within ≤ 28 days, resume treatment at the original dose; if resolution takes > 28 days, reduce the dose by one level. If onset occurs on or after Day 22 of the treatment cycle and does not resolve within 49 days of the last dose, permanently discontinue the IMP. Close monitoring is required; Consider repeat imaging within 1–2 weeks (or as clinically indicated); consider initiating corticosteroid therapy (e.g., ≥ 0.5 mg/[kg·d] prednisone or equivalent) until improvement, followed by tapering over at least 4 weeks; If ILD/noninfectious pneumonitis worsens despite corticosteroid treatment, manage as Grade 2.
Grade 2	Permanently discontinue the IMP; Immediately initiate corticosteroid therapy (e.g., ≥ 1 mg/[kg·d] prednisone or equivalent) for at least 14 days until complete clinical and radiographic resolution, then taper over at least 4 weeks. Monitor symptoms closely and repeat imaging as clinically indicated; If no clinical or radiographic improvement is observed within 5 days, consider increasing corticosteroid dosage (e.g., 2 mg/[kg·d] prednisone or equivalent) and switching to intravenous administration (e.g., methylprednisolone); Reassess potential alternative diagnoses and escalate management as clinically indicated.
Grade ≥ 3	Permanently discontinue the IMP and hospitalize the subject; Immediately initiate high-dose intravenous methylprednisolone (e.g., 500–1000 mg/day for 3 consecutive days), followed by ≥ 1 mg/[kg·d] oral prednisone (or equivalent) for at least 14 days or until complete clinical and radiographic resolution, with tapering over ≥ 4 weeks. Repeat imaging as clinically indicated; If no improvement is observed within 3–5 days, reassess for alternative etiologies, conduct further evaluations, and consider additional immunosuppressants and/or treatment per local clinical practice.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IMP = investigational medicinal product; IV = intravenous.

Note: Asymptomatic subjects should still be classified as CTCAE Grade 1, even if corticosteroids are administered.

8.4.10.5. Cardiotoxicity

LVEF will be assessed by echocardiography at the time points specified in [Table 1](#) and [Table 2](#). If the investigator suspects that the subject may have experienced a cardiac-related AE, additional assessments and increased monitoring frequency may be conducted as deemed necessary, and the relationship to the IMP should be evaluated. Subjects diagnosed with symptomatic congestive heart failure must permanently discontinue IMP. Recommendations for the management of asymptomatic LVEF decline are provided in [Table 15](#).

Table 15: Recommendations for the Management of Cardiotoxicity

Cardiotoxicity	Action Taken with IMP
LVEF $> 45\%$ and absolute decline of 10%–20% from baseline	Continue.

Cardiotoxicity		Action Taken with IMP
LVEF 40%–45%	Absolute decline from baseline <10%	Continue. LVEF should be re-evaluated within 3 weeks.
	Absolute decline from baseline 10%–20%	Interrupt treatment. Re-evaluate LVEF within 3 weeks. If the decline from baseline remains ≥10%, permanently discontinue IMP. If the decline is <10%, resume treatment at the original dose.
LVEF <40% or absolute decline >20% from baseline		Interrupt treatment. Re-evaluate LVEF within 3 weeks. If LVEF <40% or decline from baseline remains >20%, permanently discontinue IMP.
Symptomatic congestive cardiac failure.		Permanently discontinue IMP.

Abbreviations: IMP = investigational medicinal product; LVEF = left ventricular ejection fraction.

8.5. Pregnancy

Subjects who become pregnant during the clinical trial must discontinue treatment with the IMP. The investigator should fill out the “Pregnancy Report Form” within 24 h after becoming aware of the pregnancy event to report it to the sponsor, and report the event to the relevant authority according to local requirements. The report should contain as much information as possible and should be sent to:

Email: GlobalClinicalSAE@glenmarkpharma.com

The investigator is required to follow up on the pregnancy event until the final outcome (including any early termination of pregnancy or delivery), which, in the case of delivery, would be 1 month thereafter, and report the pregnancy outcome to the sponsor or to other relevant authorities according to local requirements. If the pregnancy outcome meets the SAE criteria (such as ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, congenital anomaly, etc.), the investigator should report it according to the SAE procedures.

8.6. Pharmacokinetics (PK)

Subjects in the treatment group receiving SHR-A1811 will undergo PK blood sampling at the time points and according to the requirements specified in Table 3. Validated methods will be used to measure concentrations of antibody-conjugated toxin and free toxin SHR169265. The information on the collection, processing, storage and transportation of blood samples is provided in the study manual. An aliquot of the serum samples may be used for assay setup and/or future exploratory analysis or to address any specific scientific questions related to SHR-A1811.

8.7. Immunogenicity

Subjects in the treatment group receiving SHR-A1811 will undergo immunogenicity blood sampling at the time points and according to the requirements specified in Table 3. Validated methods will be used to analyze ADA and NAb against SHR-A1811. The information on the collection, processing, storage and transportation of blood samples is provided in the study manual. An aliquot of the serum samples may be used for assay setup and/or future exploratory analysis or to address any specific scientific questions related to SHR-A1811.

8.8. Biomarkers

Subjects in both the treatment and control groups during the randomized treatment phase will provide tumor tissue samples at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#) for the assessment of HER2 expression levels in tumor tissue (IHC and H-score). See the laboratory manual for the collection and disposal of tumor samples.

8.9. Patient-Reported Outcome (PRO)

Subjects are required to complete the EQ-5D-5L and FOSI questionnaires at the time points and according to the requirements specified in [Table 1](#) and [Table 2](#). Paper-based questionnaires will be used in this study (see Sections [13.7](#) and Section [13.8](#)). If a subject has difficulty reading, the investigator may read the questions aloud and record the subject's answers. The investigator must review all questionnaires for completeness before the subject leaves the site.

8.10. Genetics

This study does not involve genetic assessments.

8.11. Healthcare Resource Utilization and Health Economics

This study does not involve healthcare resource utilization or health economics evaluations.

9. STATISTICAL CONSIDERATIONS

The data collection and analysis methods for this trial are detailed in the Statistical Analysis Plan (SAP). Separate SAPs will be developed for the main and extension cohorts. The pooled data from the main cohort and the extension cohort will be analyzed using the same statistical method used in the main cohort analysis. It is planned to perform subgroup analyses in the extension cohort. The details of analyses will be defined in the SAP.

General Analysis

Unless otherwise specified, descriptive statistics will be used to summarize the data according to the following general principles:

Categorical variables will be summarized using frequency counts and percentages. Continuous variables will be summarized using number of subjects, mean, standard deviation, median, maximum, and minimum. For PK concentration data, depending on the data type, summaries may include number of subjects, mean, geometric mean, standard deviation, coefficient of variation, geometric coefficient of variation, median, maximum, and minimum.

9.1. Analysis Populations

Intent-to-Treat (ITT) Analysis Set: All randomized subjects, analyzed according to the treatment group to which they have been randomized.

Safety Analysis Set (SS): All enrolled subjects who have received at least one dose of the IMP.

Pharmacokinetic Concentration Set (PKCS): All enrolled subjects who have received at least one dose of the SHR-A1811 and have at least one evaluable PK concentration data point.

Immunogenicity Analysis Set (IMS): All enrolled subjects who have received at least one dose of the SHR-A1811 and have both baseline and at least one post-baseline immunogenicity assessment results.

Patient-Reported Outcome (PRO) Analysis Set: The PRO analysis set is a subset of the ITT analysis set and includes subjects who have completed both a baseline PRO assessment and at least one post-baseline assessment. Subjects will be analyzed according to the treatment group assigned at randomization.

9.2. Analyses for Primary Objective

9.2.1. Statistical Models, Assumptions, and Analysis Methods

Hypothesis testing:

The primary endpoint of the study is PFS as assessed by the IRC based on RECIST v1.1. The hypothesis test in the main cohort is as follows:

$$H_{01}: HR_{PFS} \geq 1 \text{ vs. } H_{11}: HR_{PFS} < 1$$

The hypothesis test for the primary endpoint OS is as follows:

$$H_{02}: HR_{OS} \geq 1 \text{ vs. } H_{12}: HR_{OS} < 1$$

No formal hypothesis testing will be conducted for the extension cohort.

Multiplicity analysis:

The hypothesis tests for the primary endpoint (IRC-assessed PFS) and the primary endpoint (OS) will be conducted sequentially in the main cohort in a fixed order to control the overall type I error rate at 0.025 (one-sided). An interim analysis for efficacy in the main cohort will be conducted for OS. The Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries will be used to determine the efficacy boundaries at both interim and final analyses, ensuring that the overall one-sided type I error rate does not exceed 0.025. If the above analysis strategy is changed, it will be revised in the protocol or other explanatory documents before any formal analysis is performed.

Analyses for the extension cohort will report only nominal p-values, with no multiplicity adjustment.

Analysis method:

Primary estimand - PFS (as assessed by the IRC per RECIST v1.1) will be analyzed as follows:

Based on the ITT analysis set, to compare differences between treatment groups, a stratified Cox proportional hazards model will be used to estimate the HR (experimental group vs. control group) and the corresponding 95% CI, separately in the main cohort and in the extension cohort, accounting for the randomization stratification factors. These estimates will then be combined to estimate the overall HR and 95% CI. The randomization stratification factors are all collected by the randomization system: 1) HER2 expression status by immunohistochemistry (IHC) (HER2 IHC 1+ vs. HER2 IHC 2+/3+); 2) prior treatment with VEGF/VEGFR inhibitors such as bevacizumab (Yes vs. No).

The Kaplan-Meier method will be used to estimate PFS survival rates by treatment group and to generate time-PFS survival curves. PFS survival rates at specific time points (e.g., 6 months/12 months) will also be estimated, along with their 95% CIs. The CIs will be calculated by first applying a log-log transformation to the survival probability, then using a normal approximation to compute the 95% CI on the transformed scale, and finally back-transforming the CI to obtain the 95% CI for the survival probability. In addition, the 25th, 50th (median), and 75th percentiles of PFS for each treatment group will be estimated using the Kaplan-Meier method, and their 95% CIs will be calculated using the Brookmeyer-Crowley method.

Descriptive statistics will be provided by treatment group, including the number and proportion of subjects with PFS events (including PD and death without PD), as well as the number and proportion of censored subjects. Reasons for censoring will be categorized and summarized.

Primary Estimand – OS will be analyzed, based on the ITT analysis set, similar to the primary estimand – PFS.

9.2.2. Handling of Intercurrent Events for the Primary Estimand

Intercurrent event: Premature discontinuation of treatment

Handled using a treatment policy strategy; that is, imaging assessment data obtained after early treatment discontinuation will be included in the PFS analysis;

Handled using a treatment policy strategy; that is, follow-up data (survival or death) obtained after early treatment discontinuation will be included in the OS analysis;

Intercurrent event: Initiation of new anti-tumor therapy

Handled using a hypothetical strategy; the event time will be censored at the date of the last valid tumor assessment prior to or on the day of the initiation of new anti-tumor therapy;

Handled using a treatment policy strategy; that is, follow-up data (survival or death) collected on or after the first day of receiving a new anticancer therapy will be included in the OS analysis.

9.2.3. Handling of Missing Data

No imputation will be made for missing data related to PK, immunogenicity, efficacy, or safety endpoints.

Handling of incomplete dates will be detailed in the SAP.

9.2.4. Sensitivity Analyses

Primary estimand - PFS as assessed by the IRC per RECIST v1.1:

Sensitivity analysis 1: An unstratified Cox proportional hazards model will be used to estimate the HR and its 95% CI.

Sensitivity analysis 2: A stratified Cox proportional hazards model will be used, incorporating the stratification factors as recorded in the electronic data capture (EDC) system, to calculate the HR and its 95% CI.

Primary estimand - OS:

Sensitivity analyses 1 and 2 will be performed using the same methods as for sensitivity analyses 1 and 2 of estimand 1.

Sensitivity analysis 3: Considering that some subjects in the control group may receive ADCs with a topoisomerase inhibitor payload after disease recurrence, an appropriate method (e.g., two-stage method) will be applied for correction and analysis depending on data availability, as further detailed in the Statistical Analysis Plan (SAP).

9.2.5. Supplementary Analyses

Primary estimand - PFS (as assessed by the IRC per RECIST v1.1): Not applicable.

Primary estimand - OS: Since OS may be influenced by subsequent anti-tumor therapies, different strategies for handling intercurrent events will be applied for these subsequent anti-tumor therapies. For example, for treatment with ADCs containing a topoisomerase inhibitor payload, a hypothetical strategy will be adopted. In this case, data will be censored at the start date of treatment with such ADCs prior to the occurrence of the event

9.3. Supportive Analyses for Secondary Objectives

9.3.1. Secondary efficacy analysis:

Secondary endpoints will be analyzed separately based on the ITT analysis set.

For investigator-assessed PFS based on RECIST v1.1, the same analysis approach as the primary analysis for the primary endpoint (IRC-assessed PFS based on RECIST v1.1) will be applied. For DoR assessed by the IRC/investigator according to RECIST v1.1, the Kaplan-Meier method will be used to estimate survival rates for each endpoint by treatment group and to generate time-PFS survival curves. Survival rates for each endpoint at specific time

points (e.g., 6 months/12 months) will also be estimated, along with their 95% CIs. In addition, the 25th, 50th (median), and 75th percentiles of each endpoint for each treatment group will be estimated using the Kaplan-Meier method, and their 95% CIs will be calculated using the Brookmeyer-Crowley method.

For ORR and DCR assessed by the IRC according to RECIST v1.1, and for ORR, DCR, RR, and CA-125 RR assessed by the investigator based on RECIST v1.1, point estimates and two-sided 95% CIs will be calculated by treatment group based on the ITT analysis set using the Clopper-Pearson method. The between-group differences (experimental group minus control group) and corresponding two-sided 95% CIs will be calculated using the normal approximation method.

9.3.2. PK Analysis

Based on the PKCS, the serum concentrations of the toxin-conjugated antibody SHR-A1811 and the free toxin will be analyzed.

Descriptive statistics will be used to summarize the serum drug concentrations in subjects by analyte, treatment cycle, and scheduled sampling time points.

9.3.3. Immunogenicity Analysis

If applicable, based on the IMS, the proportion of subjects with positive immunogenicity results, time to first positive immunogenicity (onset), duration of positive immunogenicity (persistence), and neutralizing activity (for confirmed positive ADA) will be reported. To explore potential correlations between immunogenicity and serum trough drug concentrations, safety, and efficacy, the incidence and types of AEs may be further analyzed in relation to overall trough drug concentration and immunogenicity status.

9.4. Analyses to Support Exploratory Objectives

9.4.1. Biomarker Analysis

Based on the ITT analysis set, the relationship between HER2 expression levels in tumor tissue (IHC and H-score) and efficacy endpoints (e.g., PFS, OS, ORR) will be explored.

9.4.2. PRO Analysis

Based on the PRO analysis set, descriptive statistics will be used to summarize PRO scores and changes from baseline over visits by treatment group, including data from the EQ-5D-5L and FOSI instruments.

9.4.3. PFS2 Analysis

Time to a second disease progression/death (PFS2) will be summarized and analyzed based on the ITT analysis set.

9.5. Safety Analysis

Based on the SS, descriptive statistics will be used to summarize AEs, laboratory tests, ECG, ECOG PS scores, and other safety parameters, including but not limited to:

- Incidence and severity of AEs;
- Correlation of AEs with the IMP;

- AEs leading to treatment discontinuation, dose reduction, or treatment interruption;
- SAEs;
- AEs resulting in death;
- Normal and abnormal changes from baseline in laboratory tests, ECG, and ECOG PS scores.

9.6. Other Analyses

Subgroup analysis

To assess the consistency of treatment efficacy, subgroup analyses of IRC-assessed PFS (based on RECIST v1.1) and OS will be conducted across demographic characteristics and baseline disease conditions (including but not limited to the following situations), and a forest plot will be drawn. Type 1 error control will not be performed for subgroup analysis:

- Age (<65 years vs. ≥65 years)
- ECOG PS score (0 vs. 1)
- HER2 IHC expression (HER2 IHC 1+ vs. HER2 IHC 2+/3+)
- Prior use of VEGF/VEGFR inhibitors (e.g., bevacizumab: Yes vs. No)
- Country/region

Subgroup analyses to be conducted will be defined in detail in the SAP.

9.7. Interim Analysis

An interim efficacy analysis for OS is planned for the main cohort. The interim efficacy analysis in the main cohort for OS is planned when approximately 184 OS events have been observed, representing approximately 72% of the total planned OS events, which is expected to occur around 29 calendar months after enrollment of the first subject. If the PFS analysis time point and the OS interim analysis time point are close, the two analyses may be combined; otherwise, only a descriptive analysis of OS will be performed at the PFS analysis, and the OS interim analysis will be conducted when approximately 184 OS events have been collected. If the OS interim analysis does not demonstrate superiority, a final OS analysis will be conducted when approximately 257 OS events have been collected, which is expected to occur around 26 calendar months after the last subject is enrolled. The interim efficacy analysis of OS will use the Lan-DeMets alpha-spending function with O'Brien-Fleming boundaries to determine efficacy thresholds. The planned boundary values for the interim and final analyses of OS are presented in [Table 16](#).

Table 16: Boundary Values for Planned Interim and Final Analyses of OS

		Timepoint 1	Timepoint 2
Calendar Time		~29 months	~46 months
OS	Number of events	184 (72%)	257 (100%)
	P-value boundary	≤0.0081	≤0.0226
	Z-value boundary	≤-2.4056	≤-2.0035
	HR boundary	≤0.7014	≤0.7788

The number of events analyzed during the interim analysis does not meet the planned number of events as the number of events observed may be lower than the expected number of events during the study. The boundary for efficacy will be adjusted using the previously set alpha spending function based on the actual number of events observed. Therefore, the Z value at the interim analysis will be compared to the updated efficacy margin. If the trial can continue to the final analysis, the end-of-period test level will use the value adjusted for the actual number of events at the time of the interim analysis.

For the extension cohort, the analysis will be initiated at the time of PFS analysis in the main cohort. The OS analysis will be initiated at the time of the interim OS analysis in the main cohort, if superiority is demonstrated, or at the time of the final OS analysis. The calculation rules for all efficacy, safety, patient-reported outcome (PRO), and pharmacokinetic (PK) variables will be consistent with the methods described in Section 8.

9.8. Sample Size Determination

This is a randomized, open-label, controlled, multicenter Phase 3 clinical trial. The primary endpoint is PFS and OS assessed by the IRC based on RECIST v1.1. Superiority testing will be conducted between the experimental and control groups. A total of approximately 350 subjects is planned for enrollment in the main cohort. The assumptions and details for sample size determination are as follows:

Subjects will be randomized 1:1, with an anticipated enrollment period of 20 months and uniform enrollment rate.

As described in Section 2.1.4, for the primary endpoint PFS, it is assumed that the median PFS in the control group is 4 months, and the HR comparing the experimental group to the control group is 0.612. The annual dropout rate is assumed to be 10% for the experimental group and 20% for the control group. With a type I error controlled at 0.025 (one-sided), based on approximately 175 PFS events collected in the main cohort (corresponding to a sample size of 302), there is about a 90% power to detect the superiority of the experimental group over the control group.

For the primary endpoint OS, whether the experimental group is superior over the control group will be tested if the test for PFS in the main cohort reaches statistical significance. Based on the above assumptions for enrollment duration and sample size, as described in Section 2.1.4, it is assumed that the median OS in the control group is 13 months, and the HR comparing the experimental group to the control group is 0.67. The annual dropout rate for OS is assumed to be 5%. An interim efficacy analysis for OS will be performed in the main cohort after approximately 184 OS events have been collected, accounting for approximately 72% of the total expected OS events. With a type I error rate controlled at 0.025 (one-sided), approximately 257 OS events are expected to be collected around 26 months after the last subject is enrolled in the main cohort, providing approximately 89% power to demonstrate superiority of the experimental group over the control group.

In the extension cohort, the sample size is not based on statistical hypotheses, and approximately 70 subjects are planned to be enrolled in India, Australia and/or other countries.

9.9. Protocol Deviations

A protocol deviation refers to any change and non-compliance with the clinical trial protocol design and relevant process documents involved in the protocol. Different protocol deviations have different effects on the rights and interests of subjects and on the integrity, accuracy and reliability of trial data. Protocol deviation can come from subjects, investigators, or study staff. Depending on the root cause of the deviation, corrective and preventive measures need to be formulated and implemented promptly. Refer to the “Project Protocol Deviation Management Plan” for details.

10. GENERAL CONSIDERATIONS: REGULATORY, ETHICAL, AND STUDY OVERSIGHT

10.1. Regulatory and Ethical Considerations

This study must be conducted in compliance with the protocol, ethical principles of the Declaration of Helsinki, current GCP and relevant laws and regulations. Before the start of the study, the protocol and its amendments, informed consent form and other relevant documents (such as recruitment materials, etc.) should be provided to the ethics committee before the start of the study. This study must be approved by the relevant regulatory authorities and the ethics committee of the hospital before it can be implemented.

Neither the sponsor nor the investigator shall unilaterally amend the protocol of this study without the consent of both parties. Any amendment to the protocol must be reviewed and approved by the ethics committee before it can be implemented. If necessary, other relevant documents should be revised at the same time and submitted and/or reviewed and approved in accordance with the requirements of the ethics committee.

If the investigator has to initiate a process that deviates from the protocol to eliminate emergency hazards to a subject, the ethics committee and the sponsor must be notified in writing immediately after the deviation is implemented, along with an explanation and documentation of any protocol deviations made. In addition, the investigator is responsible for submitting the interim reports of the study on a regular basis in accordance with the relevant requirements of the ethics committee and shall notify the ethics committee of the completion of the study.

10.2. Committees

10.2.1. Independent Review Committee (IRC)

An IRC will be established for this study to perform independent assessments of all tumor imaging data. The IRC will determine tumor response and PD based on RECIST v1.1. (When the investigator first determines that a subject has PD, the corresponding imaging data must be promptly uploaded to the independent imaging system for confirmation.) The IRC assessment results will be used to determine whether a subject should discontinue IMP treatment and for the analysis of study results. Detailed rules and guidelines for tumor imaging assessment by the IRC will be described in a separate independent read charter, image acquisition guidelines, and central operations manual.

10.2.2. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will also be established to periodically review safety data. The IDMC will provide recommendations to the sponsor on the measures it considers necessary to protect the subjects and the overall safety evaluation.

The IDMC is a consultant to the sponsor's study team (independent from the sponsor, study team, and investigators). The sponsor study team is responsible for the overall conduct of the study, including managing the communication and communication of study data, and making decisions on the continuation of the study, amendment of the study, or termination of the study as recommended by the IDMC.

After the start of the study, the IDMC will meet regularly to evaluate safety data to ensure that the safety of subjects is carefully monitored. The sponsor may also consult with the IDMC in a retrospective manner based on the identified safety signals and conduct retrospective safety review meetings as needed. After each meeting, the IDMC will provide recommendations on whether to continue, modify, or terminate the study, based on the safety data reviewed. Prior to the meeting, the IDMC will obtain access to and review of the study data, including characteristics of the study population, dosing information, and safety data.

The meeting schedule, composition, responsibilities, operations, and governance of the IDMC will be described in a separate IDMC charter.

10.3. Informed Consent Process

Informed consent process: Informed consent begins before a subject agrees to participate in the clinical trial and continues throughout the entire clinical trial process. The investigator or designated study personnel must provide the latest version of the informed consent form approved by the ethics committee, discuss the risks and potential benefits of subjects' participation in the trial with subjects or their guardians in detail, introduce the details of the trial, and answer any questions raised by subjects or their guardians. Subjects may only start participating in the trial after providing written informed consent. Subjects may voluntarily withdraw from the trial at any time during the clinical trial. A copy of the informed consent form will be kept by the subject. Even if subjects refuse to participate in this trial, their rights and interests will be fully protected, and the quality of their medical care will not be affected in any way.

Requirements for Informed Consent for Re-Screening: Re-screening is permitted for subjects who fail screening. Each subject can only be re-screened once. Re-screening requires a newly signed informed consent form and re-registration to obtain a new subject identification number (as specified in [Table 1](#) and [Table 2](#)).

10.4. Data Protection

10.4.1. Confidentiality of Subject Information

Subject privacy and confidentiality of personal information will be strictly maintained by the investigator, study personnel, and the sponsor. Confidentiality also covers biological samples and genetic tests in addition to subjects' clinical information. No subject information pertaining to the study may be disclosed to any unauthorized third party without prior written approval from the sponsor.

All study procedures will be conducted in compliance with applicable confidentiality regulations.

Clinical research associates, other authorized representatives of the sponsor, Ethics Committees, and regulatory authorities may request to inspect all documents and records maintained by the investigator, including but not limited to medical records and treatment administration records of subjects. The site must allow access to these records to ensure subject safety and compliance with applicable laws and regulations.

Subject contact information and identifying data will be retained solely at the site and securely stored for internal use during the study. At the end of the study, all records will continue to be stored in a secure place in accordance with the time limit specified by the local ethics committee and regulations.

10.4.2. Data Protection

All parties will comply with all applicable laws, including those related to the implementation of institutional and technical measures to ensure the protection of subject data.

Subjects' personal data will be stored at the study site in encrypted electronic and/or paper form, password protected or in a locked storage room to ensure that only authorized study staff have access. The study site will take appropriate technical and organizational measures to ensure that personal data can be restored in the event of a disaster. In the event of a potential personal data breach, the site will be responsible for determining if a personal data breach has occurred and, if so, for providing a breach notification as required by law.

To protect the rights and freedoms of the subjects with respect to data processing, subjects will be assigned a separate specific identification number. Any subject records or datasets transferred to the sponsor will contain this identification number; the subject's first name will not be transferred. All other identifiable data transferred to the sponsor will be replaced by this separate specific identification number. The study site will maintain a confidential list of subjects participating in the trial that can link each subject's identification number to their actual identity and medical records. During the data transfer process, the sponsor will protect the confidentiality of the subjects' personal data in accordance with the trial protocol and applicable privacy laws.

10.5. Premature Termination or Suspension of the Study

This study can be reasonably terminated or suspended. This may be due to the decision of the drug regulatory authority, changes in the comments of the ethics committee, issues with the efficacy or safety of SHR-A1811, or the judgment of the sponsor. In addition, the sponsor reserves the right to stop the development of SHR-A1811 at any time.

If the sponsor terminates or suspends the trial prematurely, it shall immediately inform the investigator, the clinical trial institution and the drug regulatory authority, and explain the reasons. Upon receipt of the notification, the investigator shall promptly notify the subjects and give the subjects appropriate treatment and follow-up. In addition, the investigator shall immediately report to the clinical trial institution and ethics committee, and provide a detailed written explanation.

Reason(s) for premature termination or suspension of the trial may include the following:

- Unexpected, significant, or unacceptable risks to subjects are identified;
- The available efficacy results support early termination of the study;
- The investigator fails to comply with the protocol, the requirements of the ethics committee or drug regulatory authority, the sponsor's procedures, or the current GCP;
- Other situations, such as enrollment difficulties, no longer complying with medical practice, and adjustment of the sponsor's research and development strategy, are identified.

The trial may continue once the drug safety, protocol compliance, and data quality issues, etc. that caused the suspension of the trial are resolved, and the approval of the sponsor, ethics committee, or the drug regulatory authority is obtained.

11. GENERAL CONSIDERATIONS: RISK MANAGEMENT AND QUALITY ASSURANCE

11.1. Data Quality Assurance

In order to ensure the quality of the trial, the sponsor and the investigator will jointly discuss and formulate the clinical trial plan before the official start of the trial, and ensure that the study staff participating in the implementation of the trial have received appropriate training on GCP.

Each study site shall manage the IMPs in accordance with the SOP, including receipt, storage, dispensing, recovery and destruction.

According to the GCP guidelines, necessary procedures should be taken during the design and implementation stages of the trial to ensure that the collected data are accurate, consistent, complete and credible. All observed results and abnormal findings in the clinical trial shall be verified and recorded promptly to ensure the reliability of the data. The instruments, equipment, reagents and standards, among others, used for all examinations in the clinical trial shall be subject to strict quality standards, and their use under normal conditions shall be ensured.

The sponsor or designee will conduct monitoring to confirm that the data completed in the eCRF by the study site staff are complete, accurate, and traceable to ensure that the safety and rights of the subjects are protected and that the trial is conducted in accordance with the protocol, the GCP and all relevant laws and regulations. The investigator must ensure the accuracy of the source documents (source data) for the information entered into the eCRF.

The drug regulatory authority, the Ethics Committee, the sponsor's monitors and/or auditors may conduct systematic inspections on relevant activities and documents of the clinical trial to evaluate whether the study is conducted in accordance with the requirements of the study protocol, SOPs and relevant regulations, and whether the study data are recorded in a timely, truthful, accurate and complete manner. The audit shall be conducted by personnel not directly involved in the clinical trial.

Detailed monitoring strategies (e.g., risk-based operations and quality management measures, such as risk management and mitigation strategies, and controls based on risk analysis), methods, responsibilities, and requirements, including handling and monitoring techniques (site-level, remote, or on-site monitoring) for non-compliance issues, will be provided in the monitoring plan.

The sponsor or its designated personnel is responsible for the data management of this study, including data quality checks.

The sponsor is responsible for actions delegated to other individuals (e.g., CRO).

11.2. Source Data

The source documents provide evidence for subjects' participation in the clinical study and confirm the integrity of the data collected. The original documents are archived at the investigator's institution.

The data in the eCRF must be consistent with the source documents, or the discrepancy must be reasonably explained. Depending on the needs of the trial, the investigator may require

previous medical records or transcribed records. In addition, current medical records must be provided.

The composition of source data and its origin are defined in the sponsor's data monitoring plan.

A record of instructions for the use of the electronic informatization system is defined in the sponsor's data management plan.

The investigator must ensure that the data filled in the eCRF can be traced back to the original records and that the original documents are archived.

12. APPENDIX: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS – DEFINITIONS, SEVERITY AND CAUSAL RELATIONSHIP

12.1. Clarification and Addition to the Definition of AE

12.1.1. Drug Overdose

A drug overdose is defined as a subject receiving a dose of SHR-A1811 ≥ 10 mg/kg Q3W under the supervision of the investigator.

Drug overdose does not need to be recorded as an AE on the AE page of the eCRF.

For all cases of drug overdose, regardless of whether they result in an AE, the investigator must complete the “Serious Adverse Event (SAE)/Adverse Event of Special Interest (AESI)/Drug Overdose Report Form,” sign and date it, and notify the sponsor within 24 h of becoming aware of the event. If an AE occurs as a result of the overdose, the AE must be recorded in the eCRF and included in the “SAE/AESI/Drug Overdose Report Form” along with the overdose incident, and reported to the sponsor.

If the event of a drug overdose meets the SAE criteria, it must be reported according to the SAE reporting procedure.

12.2. Clarification and Addition to Definition of SAE

12.2.1. Hospitalization

Hospitalization is defined as any first admission (even if less than 24 hours) or prolongation of hospitalization. Hospitalization does not include the following:

- Rehabilitation facility;
- Nursing home;
- Routine admission to the emergency department (less than 24 h);
- Same-day surgery (such as outpatient/same-day/ambulatory surgery).

Hospitalization or prolonged hospitalization unrelated to AE is not considered an SAE. For example, the following are not considered SAEs:

- hospitalization for treatment of a pre-existing disease that is not related to any new AE and does not involve aggravation of the pre-existing disease (e.g., hospitalization for diagnosis and investigation of laboratory test abnormalities that have been present before the study);
- administrative admission (e.g., for yearly physical examination);
- protocol-specified admission during the clinical trial (e.g., for a procedure required by the protocol);
- elective hospitalization unrelated to AE (e.g., elective cosmetic surgery);
- pre-scheduled treatments or surgical procedures (these should be recorded in the baseline data for the entire protocol and/or for the individual subject); and

- admission for the administration of blood products only.

Diagnostic or therapeutic invasive (such as surgery) and non-invasive procedures should not be reported as AEs but should be reported when the disease condition leading to this procedure meets the definition of AE. Acute appendicitis that develops during the AE reporting period and meets the AE requirements should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

12.2.2. Progressive Disease (PD) and Death

PD is defined as the progression or deterioration of the subject's condition caused by the study indications, including radiographic progression of pre-existing disease and progression of clinical symptoms and signs. The appearance of new metastases from the primary tumor or the progression of existing metastases is considered to be PD.

In the study population of this clinical trial, PD (including imaging findings, laboratory tests, and clinical signs and symptoms) is an anticipated event and should not be recorded as an AE, even if it meets criteria for seriousness such as being life-threatening, requiring hospitalization or prolongation of hospitalization, or resulting in permanent or significant disability/incapacity (i.e., substantial disruption of a person's ability to conduct normal life functions). It does not need to be reported as an SAE. However, if the investigator considers that the event may not be attributable to PD, is more severe than expected, or believes it may be related to the IMP or study procedures, the event should be reported as an AE or SAE.

In the clinical trial, if a subject dies before the completion of the safety follow-up period, it must be reported as an SAE, regardless of whether the investigator evaluated that it may be related to PD, or whether the subject has received other anti-tumor therapies. The word "death" should not be used as an SAE term, but as the result of event. The investigator must record the event leading to death as an SAE. If the cause of death cannot be determined at the time of reporting, the SAE term will be recorded as "unexplained death" and the investigator should obtain further information to clarify the cause of death.

12.2.3. Other Anti-tumor Therapies

If a subject begins other anti-tumor therapy before the end of the safety follow-up period, for non-fatal SAEs, unless it is suspected to be related to the IMP, the reporting period will be until the start of the new anti-tumor therapy. If death occurs during the safety follow-up period, it must be reported as an SAE regardless of whether the subject receives other treatments.

12.3. Severity

Refer to NCI CTCAE v6.0 Grading Criteria for Adverse Drug Events. If an AE is not listed in NCI-CTCAE v6.0, the severity should be graded based on the criteria provided in [Table 17](#).

Table 17: Criteria for Judging the Severity of Adverse Events

Grade	Clinical Description of Severity
1	Mild; asymptomatic or with mild clinical symptoms; clinical or laboratory abnormalities only; intervention not indicated.

Grade	Clinical Description of Severity
2	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL or mild/moderate impact on age appropriate normal daily activity.
3	Severe or medically significant but not immediately lifet-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs or severe impact on age-appropriate normal daily activity. Self-care ADLs refer to: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
4	Life-threatening; urgent intervention indicated.
5	Death related to AE.

Abbreviations: AE = adverse event.

12.4. Causal Relationship

The determination of the causal relationship between an AE and the IMP refers to the determination of whether there is a reasonable possibility for the IMP to cause or contribute to the AE through comprehensive assessment. Determination factors include whether the occurrence of an AE has a reasonable temporal relationship with the administration of the IMP, whether an AE is consistent with the known mechanism of action, characteristics or known adverse reactions of the IMP, whether an AE can be explained by the impact of the subjects' PD (including concomitant diseases), the effect of concomitant medications, other treatment measures or interfering factors, and dechallenge and rechallenge reactions. Facts (evidence) or arguments demonstrating the causal relationship should usually be provided.

The investigator is requested to assess the causal relationship between an AE and the IMP as "related" or "not related" and provide a rationale.

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility.
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility.

For each AE, the Investigator should answer the following question with Yes (Related) or No (Not related):

- Was there a reasonable possibility (evidence) that the drug caused the AE?

A reasonable possibility means that there are facts (evidence) or arguments to suggest a causal relationship. (NOTE: For subjects that have not started receiving study medication, the answer must be No.)

13. APPENDIX: DEFINITIONS AND DETAILS OF SUPPORTING OPERATIONS

13.1. Contraception and pregnancy tests

13.1.1. Definition related to fertility

Females are not required to use contraception if they are considered infertile in the following circumstances:

1. Postmenopausal status is defined as natural menopause for at least 12 months without any other medical reasons. Follicle-stimulating hormone (FSH) levels in the postmenopausal range in women without hormonal contraception or hormonal replacement therapy can be used to confirm postmenopausal status. However, if menopause is less than 12 months, FSH alone at postmenopausal levels is not sufficient to confirm postmenopausal status.
or
2. Hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy;
or
3. Infertility caused by congenital or acquired conditions (e.g., uterine hypoplasia, Turner's syndrome, ovarian failure, etc. as confirmed by a gynecologist).

13.1.2. Contraception

Female subjects of childbearing potential must agree to use contraception, refrain from egg donation from the signing of the informed consent form to 7 months after the last dose of the IMP, and comply with one of the following requirements:

- Abstinence (avoidance of heterosexual intercourse)[†].
or
- Use of a highly effective method of contraception during heterosexual intercourse.

A highly effective method of contraception is defined as: one with a failure rate of less than 1% per year when used consistently and correctly, including the following:

- Contraceptive pills (containing estrogen/progestin or progestogen) proven to be effective, administered orally, by injection, intravaginally, implantably, or transdermally;
- Properly placed intrauterine device or effective intrauterine hormone-releasing system;
- Medically confirmed vasectomy of a female subject's male partner, provided that the partner is the sole sexual partner of the female subject;
- Bilateral tubal ligation or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

[†] The reliability of sexual abstinence needs to be assessed based on the duration of the clinical trial and the subject's personal preference and lifestyle. Sexual abstinence (refraining from heterosexual intercourse) alone may be used to prevent pregnancy in subjects who normally choose not to have sex at all. Periodic abstinence (e.g., based

on ovulation, symptomatic body temperature, etc.), use of spermicides only, lactational menopause, and withdrawal are not acceptable methods of contraception.

Additionally, the subject must be informed to immediately notify the investigator if she discontinues the chosen method of contraception, suspects pregnancy, or confirms pregnancy.

13.1.3. Pregnancy Test

Female subjects of childbearing potential will undergo pregnancy testing at the time points and according to the requirements specified in the schedule of activities. If a pregnancy test is positive and pregnancy is subsequently confirmed, the subject must discontinue treatment with the IMP.

13.2. Laboratory Tests

The laboratory test items in this study are summarized in [Table 18](#).

Table 18: Laboratory Test Items

Item	Content
Routine blood test	White blood cell count, absolute neutrophil count, absolute lymphocyte count, red blood cell count, hemoglobin, platelet count
Biochemistry	Serum albumin, serum total protein, serum alkaline phosphatase, serum ALT, serum AST, serum TBIL, serum γ -glutamyl transferase, serum direct bilirubin, indirect bilirubin (if applicable), serum triglycerides, serum total cholesterol, BUN/serum urea (serum urea preferred), serum creatinine, uric acid, serum potassium, serum sodium, serum chloride, serum total calcium, serum magnesium, serum inorganic phosphate, serum lactate dehydrogenase, and fasting plasma glucose Serum lipase or serum amylase
Urinalysis	Urine white blood cells, urine protein, urine red blood cells, and urine occult blood
Routine stool test	Fecal occult blood
Coagulation	Prothrombin time, international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen, and D-dimer
Thyroid function	Free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH)
Cardiac enzymes	Serum creatine kinase (CK), creatine kinase-MB (CK-MB), troponin I or troponin T, and N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP)
Viral test	Hepatitis B serology panel (if HBsAg is positive, quantitative HBV-DNA testing is required), HCV antibody (if positive, HCV-RNA testing is required), and HIV antibody
Pregnancy test	Serum HCG
Tumor marker	CA-125

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CA-125 = cancer antigen 125; DNA = deoxyribonucleic acid; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCG =

human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid; TBIL = total bilirubin.

For abnormal liver function tests that meet the criteria (refer to Section 8.4.9.1 for the detailed criteria), in addition to repeat AST and ALT tests, serum albumin, serum creatine kinase, serum TBIL, serum direct and indirect bilirubin, serum gamma-glutamyltransferase, prothrombin time/international normalized ratio, and serum ALP may also be included.

13.3. Country-Specific Variations

Not applicable.

13.4. Amendment History of Previous Protocol Versions

GSP 402-301 (Version 1.0)	Extension of SHR-A1811-315 (Version 3.0)
Version 2.0	Amendment 1
Version 3.0	Amendment 2

13.5. Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

1. Measurability of Tumor at Baseline

1.1. Definition

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

Measurable lesions

Tumor 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 slice thickness should be no more than 5 mm)
- 10 mm by conventional instruments in clinical examination (lesions which cannot be accurately measured by calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: 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 up.

Non-measurable lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 mm 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 identified by physical exam that is not measurable by reproducible imaging techniques, and cystic lesions.

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 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 lesions.

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:

- Tumor 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

Measurement of lesions

All measurements should be recorded in metric notation during clinical evaluation. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

Method of evaluation

The same method of assessment and the same technique should be used to characterize 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 in diameter during the measurement (e.g., skin nodules). For patients with skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. 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, especially when tumor progression is an important clinical 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 display clear borders and are surrounded by aerated lung.

CT, MRI: CT is currently the best available and reproducible method for efficacy evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is ≤ 5 mm. If 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 after the measurement due to its operational dependence, and it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are discovered by ultrasound in the course of the study, CT or MRI should be used for confirmation. If there is concern about the radiation exposure of CT, MRI can be used instead.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific criteria 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 CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors may 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 tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumor Response Evaluation

2.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (including target nodes and non-target nodes) 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, the sum must also demonstrate an absolute increase of at least 5 mm (the appearance of one or more new lesions is also considered progressive disease).

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.

2.2. 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, it cannot be said that all the lesions have disappeared even if the complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. eCRF or other data collection methods may therefore be designed to have target lymph node lesions recorded in a specific location: For CR, all lymph nodes must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the target lymph nodes is to be included in the sum of diameters 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 become so fuzzy on CT scan that the radiologist may have difficulty assigning an exact measure and may report them as being “too small to measure”. When this occurs, it is very important to record the last value on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, it should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen, and an accurate measurement value cannot be given, a default value of 5 mm can 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 of 5 mm is derived from the CT slice thickness (but this value should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will reduce the risk of false evaluation based upon measurement error. However, it must be reiterated that the actual value must be recorded if the radiologist can give the exact value of the lesion size, even if the lesion diameter is less than 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 longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

2.3. Evaluation of non-target lesions

This section defines the criteria used to determine the tumor response for 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 normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-complete response/non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive disease: Unequivocal progression of existing non-target lesions. Notes: The appearance of one or more new lesions is also considered a progression.

2.4. Special notes on evaluation of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows: When the patient has measurable non-target lesions, and his/her target lesions are evaluated as SD or PR, to identify unequivocal progression of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions sufficiently to merit discontinuation of treatment. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify unequivocal progression. The designation of overall tumor progression solely on the basis of change in non-target lesions in the face of SD or PR of target lesions will therefore be extremely rare.

When the patient has only non-measurable non-target lesions: This circumstance arises in some Phase 3 trials when it is not an inclusion criterion to have measurable lesion. The same general concepts apply here as noted above, but, in this instance, there is no measurable data of the lesion. Because worsening in non-target lesions 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-target lesions is comparable in magnitude to the increase that would be required to declare progressive disease for target lesions: i.e., an increasing tumor 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 “localized” to “widespread”, or may be described in protocols as “sufficient to require a change in treatment”. Examples include an increase in a pleural effusion from trace to large, lymphatic involvement spreading from the primary site to distant sites, or may be described in protocols as “a change in treatment is necessary”. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable lesion, it can be noted that the additional criteria must be reliable.

2.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are very 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 tumor (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 a truly new disease. If repeat scans confirm there is definitely a new lesion, then progressive disease 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:

Negative FDG-PET at baseline, with a positive FDG-PET scan at follow-up is a sign of PD based on a new lesion.

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 progressive disease.

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 progressive disease will be the date of the initial abnormal FDG-PET scan).

If the positive result of the follow-up FDG-PET scan corresponds to a pre-existing lesion on CT, and the lesion has not progressed on imaging test, the disease has not progressed.

2.6. Missing assessments and inevaluable designation

When no imaging or measurement of the lesion is done at all at a particular time point, the patient is not evaluable at that time point. If only part of the lesions can be evaluated in an evaluation, this is usually regarded as not evaluable at that time point, unless there is evidence that the missing lesion will not affect the efficacy response evaluation at the specified time point.

2.7. Special notes on response assessment

When nodular lesion is included in the evaluation of the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have lesion size 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 subjects whose efficacy is complete response will not be recorded as 0 on the eCRF.

In trials where confirmation of response is required, repeated "not evaluable" time points may complicate the best response evaluation. The analysis plan for the study must address how these missing data/evaluations can be explained clearly when determining efficacy. For example, in most studies, it is reasonable to consider a patient with responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence to prove it should be reported as symptomatic progression. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response, but a reason for stopping treatment. The objective response status of such subjects is to be assessed through the target and non-target lesions shown in Schedules 1 to 3.

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

In some circumstances, it is difficult to distinguish local lesions from normal tissues. When the evaluation of complete response depends upon this definition, we recommend performing a biopsy before evaluating the efficacy of complete response for local lesions. When the radiographic abnormalities of some subjects' local lesions are considered to represent fibrosis or scarring, FDG-PET may be used as an evaluation standard similar to biopsy to confirm the efficacy of complete response. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by specialist medical literature for this situation. However, it must be realized that due to the limitations of FDG-PET and the biopsy themselves (including the resolution and sensitivity of the two), it will lead to false positive result in complete response evaluation.

Table 19: Time Point Response - Subjects with Target Lesions (Including or Excluding Non-Target Lesions)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	None	CR
CR	Non-CR/non-PD	Absent	PR
CR	Not evaluable	None	PR
PR	Non-PD or not all evaluated	None	PR
SD	Non-PD or not all evaluated	None	SD
Not all evaluated	Non-PD	None	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Notes: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

Table 20: Time Point Response - Patients with Non-Target Lesions Only

Non-target Lesions	New Lesions	Overall Response
CR	None	CR
Non-CR or non-PD	None	Non-CR or non-PD
Not all evaluated	None	Not evaluable
Equivocal PD	Yes or No	PD
Any	Yes	PD

Note: “Non-CR/non-PD” is preferred over SD for non-target lesions. As SD is increasingly used as an endpoint for evaluation of efficacy, non-CR/non-PD efficacy is formulated to target situations where there is no measurable lesion.

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 evaluation. If disease progression is confirmed at the next evaluation, the date of progression should be the earlier date when progression is suspected.

Table 21: Best Overall Response Required for Confirmation of CR and PR

Overall Response at the First Time Point	Overall Response at 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

Note: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is not evaluable. Superscript “a”: If the criteria for CR are truly met at the first time point, and any disease appears at a subsequent time point, then even if the subject’s efficacy meets the PR criteria relative to the baseline, the efficacy evaluation at later time points will still be considered PD (since the disease reappears after CR). Best response depends on whether SD occurs within the shortest treatment interval. However, the first evaluation is sometimes a CR, and subsequent timepoint scans suggest that small lesions still appear, so the actual efficacy in the subject at the first time point should be PR rather than CR. Under these circumstances, the first CR should be changed to PR and the best response is PR.

2.8. Confirmatory measurement/duration of response

Efficacy confirmation

In non-randomized clinical studies where tumor response is the primary study endpoint, the efficacy of PR and CR must be confirmed to ensure that the efficacy is not the result of evaluation error. In studies with stable disease or progressive disease as the primary study endpoint, efficacy confirmation is no longer necessary because it is of no value for the interpretation of the study results. In the case of SD, measurements must have met the SD criteria at least once within the shortest time interval after the start of the study (generally not less than 6 – 8 weeks).

Duration of overall response

The duration of overall response is measured from the time of the first measurement meeting either CR or PR criteria (whichever is first measured) to the time of the first actual documented disease recurrence or disease progression (with the minimum recorded measurement during the study serving as a reference for PD). The duration of overall complete response is measured from the time of the first measurement meeting CR criteria to the time of the first actual documented disease recurrence or progression.

Duration of stable disease

The duration is measured from the start of treatment to the time of disease progression (starting from the time of randomization in randomized studies), using the smallest sum in the study as a reference (if the baseline sum is the smallest, it shall serve as 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 maintaining stable disease for a minimum period of time is taken as the study endpoint in a particular study, the protocol should specify the minimal time interval required between two measurements for the determination of SD.

Note: The duration of response and stable disease as well as the PFS 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 of follow-up should take into account many factors, such as the type and stage of the disease, the treatment cycle, standard norms, etc. However, the limitations of the accuracy of these measured endpoints should be taken into account when comparing between studies.

2.9 PFS/TTP

Many trials of advanced tumors use PFS or TTP as the primary endpoint. If the protocol requires that all patients have measurable lesions, the progression evaluation is relatively simple. More and more trials allow both patients with measurable lesions and non-measurable lesions to enter the trial. In this case, the clinical findings of disease progression in patients with non-measurable lesions must be described in detail. As there are often deviations in the progression date, the observation time points of each trial group should be the same.

13.6. Eastern Cooperative Oncology Group Performance Status (ECOG PS) Scoring Criteria

Score	Description
0	Asymptomatic, fully active, able to carry on all pre-disease performance without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Symptomatic, ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours <50% in bed during the day.
3	Symptomatic, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours, but having not yet become bedridden.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead

13.7. EuroQol Five-Dimension Five-Level Scale (EQ-5D-5L)

Under each heading, please place a “√” on the box that best describes your health today.

Mobility

- I have no difficulties walking around ☐
- I have a little difficulty walking around ☐
- I have moderate difficulties walking around ☐
- I have severe difficulties walking around ☐
- I can't walk around ☐

Self-care

- I have no difficulties washing or dressing myself ☐
- I have a little difficulty washing or dressing myself ☐
- I have moderate difficulties washing or dressing myself ☐
- I have severe difficulties washing or dressing myself ☐
- I am unable to bathe or dress myself ☐

Daily activities (such as work, school, housework, family or leisure activities)

- I have no difficulties doing my daily activities ☐
- I have a little difficulty doing my daily activities ☐
- I have moderate difficulties doing my daily activities ☐
- I have severe difficulties doing my daily activities ☐
- I am unable to perform my daily activities ☐

Pain or discomfort

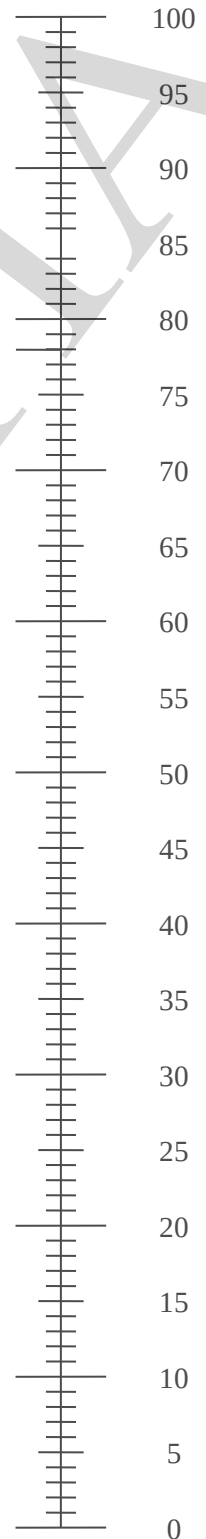
- I have no pain or discomfort ☐
- I have a little pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have very severe pain or discomfort ☐

Anxiety or frustration

- I am not anxious or frustrated ☐
- I am a little anxious or frustrated ☐
- I have moderate anxiety or frustration ☐
- I have severe anxiety or frustration ☐
- I am very anxious or depressed ☐

- We want to know how good or bad your health is **today**.
- This scale has a number from 0 to 100.
- 100 represents the best health you can imagine.
0 represents the worst health you can imagine.
- Please place an “X” on the scale to indicate how your health is **today**.
- Now, in the space below, write the number you marked on the scale.

Your health TODAY=



The worst health
you can imagine

13.8. Functional Assessment of Cancer Therapy - Ovarian Symptom Index Questionnaire (FOSI)

Below is a list of statements that other people with your illness have said are important. **By circling one number per item, please indicate how true each statement has been for you during the past 7 days.**

		Not at all	A little bit	Some what	Quite a bit	Very Much
GP1	I have a lack of energy	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
GP4	I feel pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
O1	I have swelling in my stomach area	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4

14. ABBREVIATIONS

Abbreviation	Expansion/Full Term
ADA	Anti-Drug Antibody
ADC	Antibody-Drug Conjugate
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AxMP	Auxiliary Medicinal Product
BOR	Best Overall Response
BRCA	Breast Cancer Susceptibility Gene
CA-125	Cancer Antigen 125
CI	Confidence Interval
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete Remission
CT	Computed Tomography
CYP	Cytochrome P450
DCR	Disease Control Rate
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
FISH	Fluorescence in Situ Hybridization
FOSI	Functional Assessment of CancerTherapy-Ovarian Symptom Index
GCIG	Gynecologic Cancer InterGroup
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2

Abbreviation	Expansion/Full Term
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
H-score	Histochemistry Score
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IRC	Independent Review Committee
IRT	Interactive Response Technology
ITT	Intention-to-Treat
IV	Intravenous(ly)
LVEF	Left Ventricular Ejection Fractions
MedDRA v27.0	Medical Dictionary for Regulatory Activities Version 27.0
MRI	Magnetic Resonance Imaging
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI-CTCAE v6.0	National Cancer Institute-Common Terminology Criteria for Adverse Events Version 6.0
NIMP	Non-Investigational Medicinal Product
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly ADP-Ribose Polymerase
PD	Progressive Disease
PFS	Progression Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PR	Partial Response
PRO	Patient Reported Outcome
Q3W	Once Every 3 Weeks
Q4W	Once Every 4 Weeks
QTc	Corrected QT Interval
QTcF	QT Interval Corrected by the Fridericia Formula
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic Acid

Abbreviation	Expansion/Full Term
RP2D	Recommended Phase 2 Dose
RR	Response Rate
PKCS	Pharmacokinetic Concentration Analysis Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SS	Safety Analysis Set
TBIL	Total Bilirubin
TKI	Tyrosine Kinase Inhibitor
TPO-RA	Thrombopoietin Receptor Agonist
TROP2	Trophoblast Cell Surface Antigen 2
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

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