Safety, Efficacy, and Pharmacokinetics of SHR-A1811, a Human Epidermal Growth Factor Receptor 2–Directed Antibody-Drug Conjugate, in Human Epidermal Growth Factor Receptor 2–Expressing or Mutated Advanced Solid Tumors: A Global Phase I Trial

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ABSTRACT

PURPOSE SHR-A1811 is an antibody-drug conjugate composed of an anti–human epidermal growth factor receptor 2 (HER2) antibody trastuzumab, a cleavable linker, and a topoisomerase I inhibitor payload. We assessed the safety, tolerability, antitumor activity, and pharmacokinetics of SHR-A1811 in heavily pretreated HER2-expressing or mutated advanced solid tumors.

METHODS This global, multi-center, first-in-human, phase I trial was conducted at 33 centers. Patients who had HER2-expressing or mutated unresectable, advanced, or metastatic solid tumors and were refractory or intolerant to standard therapies were enrolled. SHR-A1811 was administered intravenously at doses ranging from 1.0 to 8.0 mg/kg once every 3 weeks. The primary end points were dose-limiting toxicity, safety, and the recommended phase II dose.

RESULTS From September 7, 2020, to February 27, 2023, 307 patients who had undergone a median of three (IQR, 2-5) previous treatment regimens in the metastatic setting received SHR-A1811 treatment. As of data cutoff (February 28, 2023), one patient from the 6.4 mg/kg group experienced dose-limiting toxicities (pancytopenia and colitis). The most common grade 3 or higher adverse events (AEs) included decreased neutrophil count (119 [38.8%]) and decreased WBC count (70 [22.8%]). Interstitial lung disease occurred in only eight (2.6%) patients. Serious AEs and deaths occurred in 70 (22.8%) and 13 (4.2%) patients, respectively. SHR-A1811 led to objective responses in 59.9% (184/307) of all patients, 76.3% (90/118) of HER2-positive breast cancer, 60.4% (55/91) of HER2 low-expressing breast cancer, and 45.9% (39/85 with evaluable tumor responses) of the 98 nonbreast tumors.

CONCLUSION SHR-A1811 exhibited acceptable tolerability, promising antitumor activity, and a favorable pharmacokinetic profile in heavily pretreated advanced solid tumors. The recommended phase II dose of 4.8 or 6.4 mg/kg was selected for various tumor types.

ACCOMPANYING CONTENT

Appendix
Data Supplement
Protocol

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2)–targeted therapies have revolutionized the management of HER2-overexpressing or mutated tumors, leading to a significant improvement in survival.[1-4] The progress in anti-HER2 therapy primarily benefits HER2-overexpressing or mutated breast cancer, which includes monoclonal antibodies, tyrosine kinase inhibitors, and antibody-drug conjugates (ADCs) that have received clinical approval for this patient

CONTEXT

Key Objective

To assess the safety, tolerability, antitumor activity, and pharmacokinetics of SHR-A1811 (an antibody-drug conjugate [ADC]) in heavily pretreated human epidermal growth factor receptor 2 (HER2)–expressing or mutated advanced solid tumors.

Knowledge Generated

SHR-A1811 exhibits a manageable safety profile with a very low incidence of interstitial lung disease (2.6%). SHR-A1811 has shown substantial tumor responses in heavily pretreated advanced solid tumors, and the pharmacokinetic profile is favorable. This study provides strong evidence to further establish SHR-A1811 as a novel treatment option for various solid tumors in pivotal studies.

Relevance *(R.G. Maki)*

SHR-A1811, an ADC, is an active agent in HER2-expressing cancers. It may have a different toxicity profile than existing agents, but such determination, as with response endpoints, will require a head-to-head clinical trial.*

*Relevance section written by *JCO* Associate Editor Robert G. Maki, MD, PhD, FACP, FASCO.

population.[5–14] However, extending these anti-HER2 strategies to nonbreast cancers with HER2 overexpression or mutations is relatively challenging,[2] highlighting a persistent unmet medical need beyond breast cancer.

Advancements in ADC technology have recently transformed anti-HER2 therapy,[15–17] both in breast cancer and nonbreast cancers. The approval of trastuzumab deruxtecan, an ADC incorporating a HER2-targeted antibody trastuzumab and a topoisomerase inhibitor, for HER2-positive and HER2-low breast cancer,[10–14] *HER2*-mutated non–small-cell lung cancer (NSCLC),[18] and HER2-positive gastric or gastroesophageal junction (G/GEJ) cancer,[19] represents a significant breakthrough. ADCs, as targeted therapies, combine the specificity of monoclonal antibodies with the cytotoxic potential of chemotherapy, enabling selective drug delivery to targeted cells.[15–17] This approach minimizes off-target toxicity, maximizes therapeutic efficacy, and improves patient outcomes. Despite these advancements, challenges such as the risk of interstitial lung disease (ILD) and the emergence of resistance mechanisms remain,[20–25] emphasizing the need to address limitations in ADC therapy to optimize anti-HER2 therapy both in breast cancers and nonbreast cancers.

SHR-A1811 is a novel ADC composed of anti-HER2 antibody trastuzumab, a cleavable linker, and the topoisomerase I inhibitor payload SHR169265.[26] The payload SHR169265 demonstrates higher membrane permeability and more potent cell-killing efficacy compared with the payload of trastuzumab deruxtecan.[26] To enhance chemical stability, a chiral cyclopropyl group has been introduced between the linker and toxin, preventing uncontrolled toxin release and reducing early release–related side effects. The minimal amount of early-released toxin and the moderate drug-antibody ratio of 6 contribute to a favorable safety profile of SHR-A1811. In this context, we conducted the phase I first-in-human trial to evaluate the safety, tolerability, antitumor activity, and pharmacokinetics of SHR-A1811 in heavily pretreated patients with HER2-expressing or mutated unresectable, advanced, or metastatic solid tumors.

METHODS

Study Design and Participants

This global, phase I, multicenter, first-in-human trial (ClinicalTrials.gov identifier: NCT04446260) was conducted at 33 centers and composed of three stages: dose escalation, pharmacokinetics expansion, and indication expansion.

Eligible patients were age 18 years and older (age 20 years and older in Taiwan and age 19 years and older in Korea), had unresectable, advanced, or metastatic solid tumors, and were refractory or intolerant to standard therapy. In the dose escalation and pharmacokinetics expansion stages, eligible patients had histologically confirmed HER2-expressing or mutated solid tumors. In the indication expansion stage, eligible patients had HER2-positive breast cancer (cohort A), HER2-positive G/GEJ adenocarcinoma (cohort B), HER2 low-expressing breast cancer (cohort C), HER2-expressing or mutated NSCLC (cohort D), or other HER2-expressing or mutated solid tumors (cohort E). The detailed definitions of HER2 expression or mutation are provided in the Data Supplement (online only). Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 or 1 and at least one measurable lesion according to RECIST version 1.1. Patients should have tumor samples at baseline for regular central laboratory confirmation, and HER2 status was centrally reconfirmed.

The study protocol and protocol amendments were approved by the ethics committee of each study center. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Procedures

SHR-A1811 was administered by intravenous infusion once every 3 weeks (one cycle) until disease progression, unacceptable toxicity, death, withdrawal of consent, or an investigator decision, whichever occurred first. Treatment interruption for up to 4 weeks and dose reduction were permitted to manage toxicities.

In the dose escalation stage, an i3+3 design was used, with approximately three patients enrolled for each dose. Dose-limiting toxicity was assessed from the drug administration to day 21 by a safety monitoring committee before escalating to the higher dose. The starting dose of SHR-A1811 was 1.0 mg/kg, which was calculated as approximately one twelfth of the human equivalent dose of the highest non-severely toxic dose in cynomolgus monkeys (40 mg/kg), and was sequentially escalated to 2.0 mg/kg, 3.2 mg/kg,

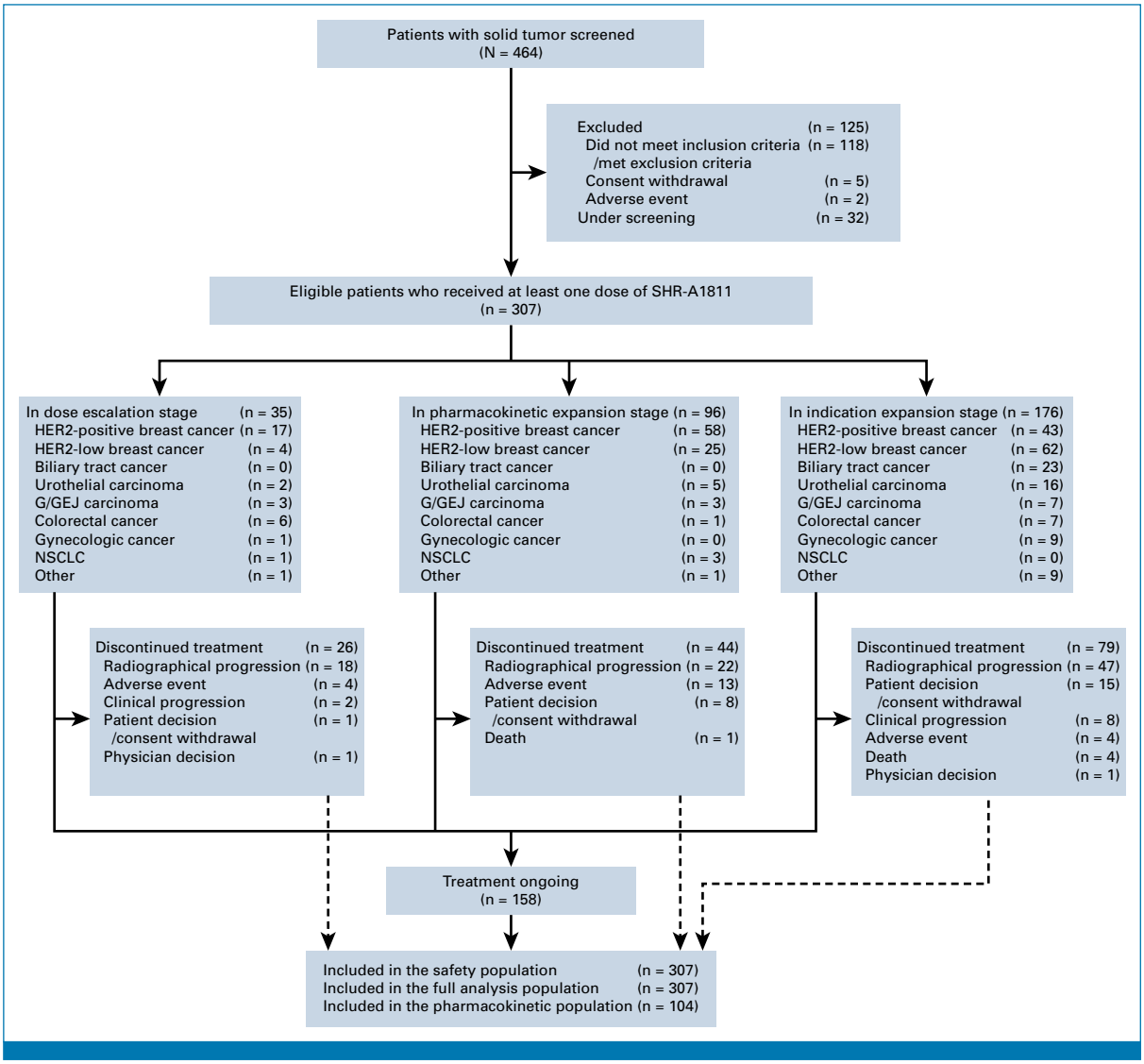

FIG 1. Patient disposition. The doses selected for dose escalation stage were 1.0 mg/kg (n = 6), 2.0 mg/kg (n = 6), 3.2 mg/kg (n = 6), 4.8 mg/kg (n = 6), 6.4 mg/kg (n = 8), and 8.0 mg/kg (n = 3). The doses selected for pharmacokinetics expansion stage were 4.8 mg/kg (n = 28), 5.6 mg/kg (n = 25), 6.4 mg/kg (n = 27), and 8.0 mg/kg (n = 16). The doses selected for indication expansion stage were 4.8 mg/kg (n = 98) and 6.4 mg/kg (n = 78). Other in dose escalation stage indicates esophageal squamous cell carcinoma, in pharmacokinetics expansion stage indicates head and neck cancer, and in indication expansion stage indicates three pancreatic cancers, two major salivary gland cancers, one esophageal squamous cell carcinoma, one appendiceal cancer, one duodenal cancer, and one extramammary Paget's disease. G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; NSCLC, non–small cell lung cancer.

TABLE 1. Demographic and Baseline Characteristics

Characteristics	1.0 mg/kg (n = 6)	2.0 mg/kg (n = 6)	3.2 mg/kg (n = 6)	4.8 mg/kg (n = 132)	5.6 mg/kg (n = 25)	6.4 mg/kg (n = 113)	8.0 mg/kg (n = 19)	Total (N = 307)
Age, years, median (IQR)	59.0 (43.0-65.0)	59.5 (52.0-64.0)	53.5 (49.0-62.0)	56.5 (48.0-66.0)	56.0 (47.0-60.0)	54.0 (47.0-61.0)	55.0 (47.0-62.0)	55.0 (47.0-62.0)
Female, No. (%)	4 (66.7)	5 (83.3)	3 (50.0)	103 (78.0)	24 (96.0)	92 (81.4)	16 (84.2)	247 (80.5)
ECOG performance status, No. (%)								
0	2 (33.3)	2 (33.3)	4 (66.7)	38 (28.8)	14 (56.0)	35 (31.0)	5 (26.3)	100 (32.6)
1	4 (66.7)	4 (66.7)	2 (33.3)	94 (71.2)	11 (44.0)	78 (69.0)	14 (73.7)	207 (67.4)
Race, No. (%)								
Asian	3 (50.0)	3 (50.0)	3 (50.0)	102 (77.3)	23 (92.0)	108 (95.6)	19 (100.0)	261 (85.0)
White	3 (50.0)	3 (50.0)	3 (50.0)	20 (15.2)	2 (8.0)	5 (4.4)	0	36 (11.7)
Black or African American	0	0	0	5 (3.8)	0	0	0	5 (1.6)
Others	0	0	0	4 (3.0)	0	0	0	4 (1.3)
Unknown	0	0	0	1 (0.8)	0	0	0	1 (0.3)
Cancer type, No. (%)								
HER2-positive breast cancer	4 (66.7)	3 (50.0)	2 (33.3)	44 (33.3)	10 (40.0)	41 (36.3)	14 (73.7)	118 (38.4)
HER2 low-expressing breast cancer	0	1 (16.7)	0	37 (28.0)	14 (56.0)	37 (32.7)	2 (10.5)	91 (29.6)
Biliary tract cancer	0	0	0	8 (6.1)	0	15 (13.3)	0	23 (7.5)
Urothelial carcinoma	1 (16.7)	0	0	15 (11.4)	0	6 (5.3)	1 (5.3)	23 (7.5)
Colorectal cancer	0	1 (16.7)	1 (16.7)	6 (4.5)	0	6 (5.3)	0	14 (4.6)
Gastric or gastroesophageal junction carcinoma	1 (16.7)	1 (16.7)	0	4 (3.0)	0	5 (4.4)	2 (10.5)	13 (4.2)
Gynecologic cancer	0	0	1 (16.7)	8 (6.1)	0	1 (0.9)	0	10 (3.3)
Non–small cell lung cancer	0	0	1 (16.7)	1 (0.8)	1 (4.0)	1 (0.9)	0	4 (1.3)
Others	0	0	1 (16.7)	9 (6.8)	0	1 (0.9)	0	11 (3.6)
Hormone receptor status,[a] No. (%)								
Positive	4 (66.7)	2 (33.3)	1 (16.7)	49 (37.1)	21 (84.0)	53 (46.9)	10 (52.6)	140 (45.6)
Negative	0	2 (33.3)	1 (16.7)	31 (23.5)	2 (8.0)	22 (19.5)	6 (31.6)	64 (20.8)
Unknown	2 (33.3)	2 (33.3)	4 (66.7)	52 (39.4)	2 (8.0)	38 (33.6)	3 (15.8)	103 (33.6)
No. of metastatic sites, No. (%)								
0	0	0	1 (16.7)	4 (3.0)	0	0	1 (5.3)	6 (2.0)
1-2	3 (50.0)	5 (83.3)	4 (66.7)	77 (58.3)	12 (48.0)	67 (59.3)	8 (42.1)	176 (57.3)
≥3	3 (50.0)	1 (16.7)	1 (16.7)	51 (38.6)	13 (52.0)	46 (40.7)	10 (52.6)	125 (40.7)
Sites of metastases, No. (%)								
Visceral disease	5 (83.3)	3 (50.0)	5 (83.3)	106 (80.3)	22 (88.0)	97 (85.8)	16 (84.2)	254 (82.7)
Brain	1 (16.7)	0	0	5 (3.8)	1 (4.0)	6 (5.3)	2 (10.5)	15 (4.9)
Liver	2 (33.3)	2 (33.3)	2 (33.3)	64 (48.5)	10 (40.0)	64 (56.6)	6 (31.6)	150 (48.9)
Lung	4 (66.7)	1 (16.7)	4 (66.7)	54 (40.9)	17 (68.0)	57 (50.4)	9 (47.4)	146 (47.6)

(continued on following page)

TABLE 1. Demographic and Baseline Characteristics (continued)

Characteristics	1.0 mg/kg (n = 6)	2.0 mg/kg (n = 6)	3.2 mg/kg (n = 6)	4.8 mg/kg (n = 132)	5.6 mg/kg (n = 25)	6.4 mg/kg (n = 113)	8.0 mg/kg (n = 19)	Total (N = 307)
Sum of diameters in target lesion, mm, median (IQR)	77.7 (64.1-87.0)	67.1 (21.0-88.4)	57.8 (16.6-83.0)	52.7 (32.0-85.0)	57.0 (32.0-60.8)	48.5 (29.0-78.0)	52.0 (23.0-77.0)	52.0 (30.6-79.9)
Previous lines of regimens in metastatic setting, median (IQR)	4 (2-5)	2 (2-3)	4 (2-4)	3 (1-4)	3 (2-5)	3 (2-5)	4 (2-6)	3 (2-5)
<3, No. (%)	2 (33.3)	4 (66.7)	2 (33.3)	65 (49.2)	11 (44.0)	44 (38.9)	6 (31.6)	134 (43.6)
≥3, No. (%)	4 (66.7)	2 (33.3)	4 (66.7)	67 (50.8)	14 (56.0)	69 (61.1)	13 (68.4)	173 (56.4)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

[a]The hormone receptor status of five patients with breast cancer is unknown. Hormone receptor status testing is not common for nonbreast cancer patients, and all nonbreast cancers are categorized as unknown.

TABLE 2. Adverse Events by Dose Group

Adverse Events	1.0 mg/kg (n = 6), No. (%)	2.0 mg/kg (n = 6), No. (%)	3.2 mg/kg (n = 6), No. (%)	4.8 mg/kg (n = 132), No. (%)	5.6 mg/kg (n = 25),[a] No. (%)	6.4 mg/kg (n = 113), No. (%)	8.0 mg/kg (n = 19), No. (%)	Total (N = 307), No. (%)
Any	6 (100.0)	6 (100.0)	6 (100.0)	128 (97.0)	23 (92.0)	112 (99.1)	19 (100.0)	300 (97.7)
Neutrophil count decreased	2 (33.3)	1 (16.7)	2 (33.3)	80 (60.6)	14 (56.0)	86 (76.1)	19 (100.0)	204 (66.4)
Anemia	1 (16.7)	2 (33.3)	2 (33.3)	83 (62.9)	11 (44.0)	80 (70.8)	19 (100.0)	198 (64.5)
Nausea	3 (50.0)	5 (83.3)	4 (66.7)	76 (57.6)	13 (52.0)	74 (65.5)	13 (68.4)	188 (61.2)
WBC count decreased	1 (16.7)	1 (16.7)	2 (33.3)	66 (50.0)	13 (52.0)	72 (63.7)	15 (78.9)	170 (55.4)
Decreased appetite	3 (50.0)	3 (50.0)	2 (33.3)	44 (33.3)	4 (16.0)	54 (47.8)	11 (57.9)	121 (39.4)
Vomiting	1 (16.7)	1 (16.7)	4 (66.7)	51 (38.6)	8 (32.0)	45 (39.8)	11 (57.9)	121 (39.4)
Alopecia	0	2 (33.3)	2 (33.3)	52 (39.4)	5 (20.0)	49 (43.4)	10 (52.6)	120 (39.1)
Platelet count decreased	1 (16.7)	0	0	29 (22.0)	6 (24.0)	56 (49.6)	15 (78.9)	107 (34.9)
AST increased	2 (33.3)	0	0	38 (28.8)	5 (20.0)	40 (35.4)	5 (26.3)	90 (29.3)
ALT increased	3 (50.0)	0	0	44 (33.3)	6 (24.0)	30 (26.5)	3 (15.8)	86 (28.0)
Fatigue	3 (50.0)	5 (83.3)	5 (83.3)	26 (19.7)	2 (8.0)	31 (27.4)	5 (26.3)	77 (25.1)
COVID-19	0	0	0	29 (22.0)	7 (28.0)	27 (23.9)	8 (42.1)	71 (23.1)
Hypoalbuminemia	1 (16.7)	2 (33.3)	1 (16.7)	23 (17.4)	7 (28.0)	31 (27.4)	5 (26.3)	70 (22.8)
Proteinuria	1 (16.7)	1 (16.7)	1 (16.7)	29 (22.0)	6 (24.0)	23 (20.4)	4 (21.1)	65 (21.2)

NOTE. AEs occurring in 20% or more of patients are listed. Events are shown in descending order of frequency in the total patient. AEs were classified according to Medical Dictionary for Regulatory Activities, version 24.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Abbreviation: AEs, adverse events.

[a]The median follow-up period of 5.6 mg/kg group was 2.0 months (IQR, 1.4-2.6).

mg/kg, 6.4 mg/kg, and 8.0 mg/kg. On the basis of the safety, tolerability, and pharmacokinetics data obtained from the dose escalation stage, 2-4 dose groups with approximately 15 patients for each dose were selected for pharmacokinetics expansion in Asian sites. In the indication expansion stage, the sample size for each cohort was designed by Simon's two-stage design (the minimax design).

Assessments

Safety assessments were conducted at each study visit, and adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0. Tumor response assessments were conducted at baseline, every 6 weeks for the first 24 weeks, and every 12 weeks thereafter, regardless of treatment interruptions. Tumor responses were measured using high-resolution computed tomography (CT) or magnetic resonance imaging (MRI), and assessed by investigators according to RECIST guidelines, version 1.1. Complete response (CR) or partial response (PR) needed confirmation by repeat assessment at least 4 weeks later at the next tumor assessment. Protocols for pharmacokinetic analysis are provided in the Data Supplement.

Outcomes

The primary end point was dose-limiting toxicity, safety, and recommended phase II dose. The secondary end points were pharmacokinetics parameters (Data Supplement), immunogenicity, and efficacy end points.

Efficacy end points included objective response rate (ORR; the proportion of patients with a best overall response of CR or PR), duration of response (DoR; the time from the first CR or PR to death or progression, whichever occurs first), progression-free survival (PFS; the time from treatment initiation to the first disease progression or death from any cause), and disease control rate (DCR; the proportion of patients with a best overall response of CR, PR, or stable disease).

Statistical Analysis

The sample size assumptions are provided in the Data Supplement. Efficacy and safety were assessed in the full analysis set and safety set, respectively, both of which included all patients who received at least one dose of SHR-A1811. Plasma drug concentration, pharmacokinetic parameters, and immunogenicity analyses were conducted in patients who received at least one dose of SHR-A1811 and met specific criteria for qualified data (Data Supplement).

Baseline demographics, safety results, pharmacokinetics, and immunogenicity data were summarized using descriptive statistics. The Kaplan-Meier method was used to estimate time-to-event end points, including PFS and DoR, and their corresponding 95% CIs were calculated using the Brookmeyer-Crowley method. The ORR and DCR were presented with accompanying 95% CIs calculated on the basis of the Clopper-Pearson exact method. The pharmacokinetic parameters of SHR-A1811, the total anti-HER2 antibody, and the released toxin SHR169265 were estimated using a noncompartmental model by Phoenix WinNonlin software (Certara, Princeton, NJ), version 8.3. All statistical analyses were performed using SAS (SAS Institute, Cary, NC), version 9.4 or higher.

RESULTS

Patients

Between September 7, 2020, and February 27, 2023, a total of 307 patients were enrolled in this study and received at least one dose of SHR-A1811 (209 breast cancers, 23 urothelial carcinomas, 23 biliary tract cancers, 14 colorectal cancers, 13 G/GEJ adenocarcinomas, 10 gynecologic cancers [including four endometrial cancers, three ovarian cancers, two cervical cancers, and one high-grade serous carcinoma of the right fallopian tube], four NSCLCs, and 11 other cancer types [including three pancreatic cancers, two esophageal squamous cell carcinomas, two major salivary gland cancers, one head and neck cancer, one appendiceal cancer, one duodenal cancer, and one extramammary Paget's disease]; Fig 1).

During the dose escalation stage, 35 patients were enrolled and received at least one dose of SHR-A1811, with six patients each in the 1.0 mg/kg, 2.0 mg/kg, 3.2 mg/kg, and 4.8 mg/kg groups, eight patients in the 6.4 mg/kg group, and three patients in the 8.0 mg/kg group. One patient from the 6.4 mg/kg group experienced dose-limiting toxicities (pancytopenia and colitis). On the basis of the data obtained

TABLE 3. Summary of Interstitial Lung Disease

Interstitial Lung Disease	1.0–3.2 mg/kg (n = 18), No. (%)	4.8 mg/kg (n = 132), No. (%)	5.6 mg/kg (n = 125), No. (%)	6.4 mg/kg (n = 113), No. (%)	8.0 mg/kg (n = 19), No. (%)	Total (N = 307), No. (%)
Any grade	0	3 (2.3)	0	1 (0.9)	4 (21.1)	8 (2.6)
Grade 1	0	0	0	0	2 (10.5)	2 (0.7)
Grade 2	0	2 (1.5)	0	1 (0.9)	1 (5.3)	4 (1.3)
Grade 3	0	1 (0.8)	0	0	0	1 (0.3)
Grade 4	0	0	0	0	0	0
Grade 5	0	0	0	0	1 (5.3)	1 (0.3)

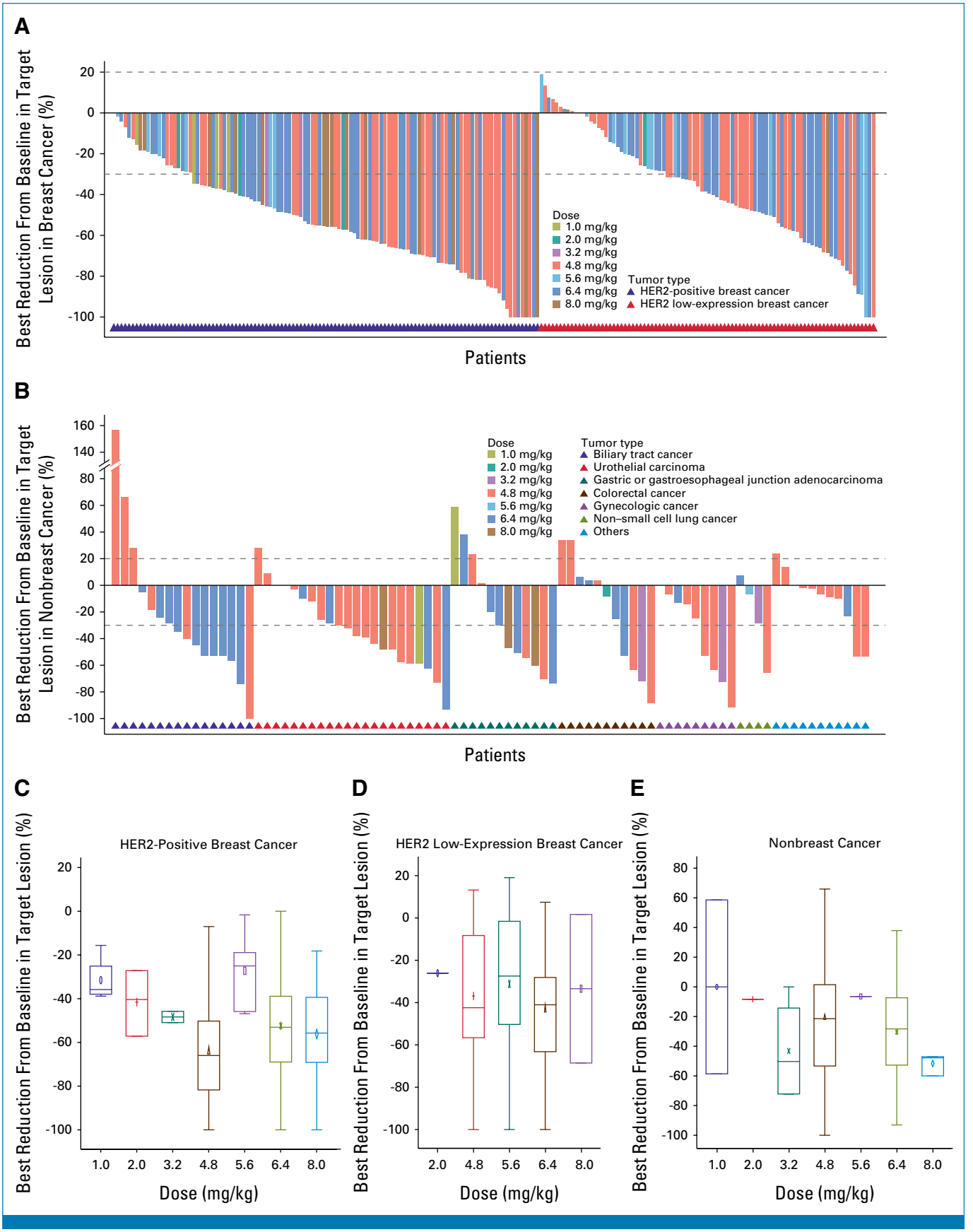

FIG 2. Best percentage change from baseline in tumor size in HER2-overexpressing or *HER2*-mutated solid tumors. Best percentage change from baseline in the sum of diameters in target lesions in (A) breast cancers and (B) nonbreast cancers. Best percentage change from baseline in the sum of diameters in target lesions by dose cohort in (C) HER2-positive breast cancers, (D) HER2 low-expressing (continued on following page)

FIG 2. (Continued). breast cancers, and (E) nonbreast cancers. In B, the 10 gynecologic cancers included four endometrial cancers, three ovarian cancers, two cervical cancers, and one high-grade serous carcinoma of the right fallopian tube; others included three pancreatic cancers, two esophageal squamous cell carcinomas, two major salivary gland cancers, one head and neck cancer, one appendiceal cancer, one duodenal cancer, and one extramammary Paget's disease. HER2, human epidermal growth factor receptor 2.

from the dose escalation stage, SHR-A1811 doses of 4.8 mg/kg (28 patients), 5.6 mg/kg (25 patients), 6.4 mg/kg (27 patients), and 8.0 mg/kg (16 patients) were selected for pharmacokinetic expansion. In the indication expansion stage, 98 and 78 patients received SHR-A1811 at doses of 4.8 mg/kg and 6.4 mg/kg, respectively.

The demographics and baseline characteristics of the patients are summarized in Table 1 and the Data Supplement (Tables S1-S3). The patients had undergone a median of three (IQR, 2-5) previous regimens of treatment in the metastatic setting. As of the data cutoff on February 28, 2023, the median duration of follow-up was 7.5 months (IQR, 3.7-11.5). A total of 149 (48.5%) patients discontinued treatment, mainly because of radiographical progression.

Safety

AEs were reported in 300 (97.7%) of the 307 patients, with decreased neutrophil count (204 [66.4%]), anemia (198 [64.5%]), and nausea (188 [61.2%]) being the most common ones (Table 2). AEs of grade ≥3 were reported in 187 (60.9%) patients (Data Supplement, Table S4). The most frequently reported AEs of grade ≥3 included decreased neutrophil count (119 [38.8%]), decreased WBC count (70 [22.8%]), and anemia (59 [19.2%]). Treatment-related AEs of grade ≥3 were reported in 166 (54.1%) patients. When considering regional classifications, the incidence of treatment-related AEs of grade ≥3 in Asians and non-Asians was 56.7% (148/261) and 39.1% (18/46), respectively (Data Supplement, Table S5).

Serious AEs were reported in 70 (22.8%) patients, with 40 (13.0%) considered treatment-related (Data Supplement, Table S6). Dose reductions and treatment interruptions of SHR-A1811 because of AEs were reported in 67 (21.8%) and 125 (40.7%) patients, respectively. Eighteen (5.9%) patients permanently discontinued SHR-A1811 treatment as a result of AEs, and 13 (4.2%) patients discontinued treatment because of treatment-related AEs (Data Supplement, Table S7). Thirteen (4.2%) patients died due to AEs (Data Supplement, Table S8), and four (1.3%) deaths were considered treatment-related (one patient with pneumonia at 4.8 mg/kg, one patient with colitis and pancytopenia at 6.4 mg/kg, one patient with unknown reason at 6.4 mg/kg, and one patient with ILD and bacterial pneumonia at 8.0 mg/kg).

ILD was reported in eight (2.6%) patients. All these events were considered treatment-related. Two of the 307 patients had grade ≥3 ILD (one grade 3 at 4.8 mg/kg; one grade 5 at 8.0 mg/kg; Table 3). The median time to the onset of ILD was 120 days (IQR, 96-174). As of data cutoff, three patients (all grade 2) had recovered from ILD, and the duration from

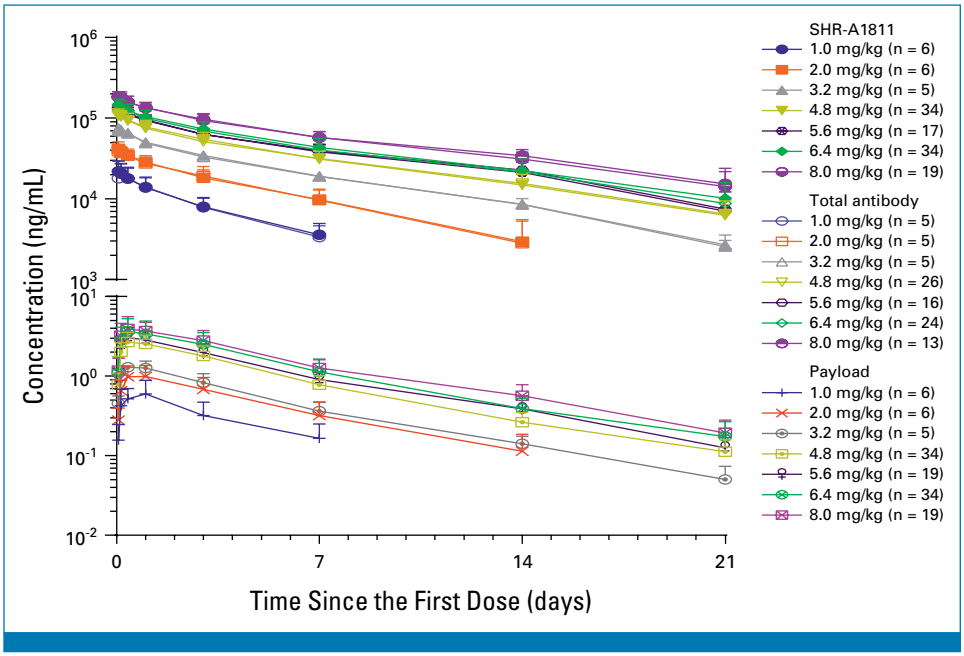

FIG 3. Mean serum concentration versus time curve of SHR-A1811, total antibody, and the released payload after single dose of SHR-A1811.

onset to regression in these patients was 18 days, 140 days, and 154 days, respectively.

Antitumor Activity

SHR-A1811 led to substantial tumor responses in a variety of heavily pretreated advanced solid tumors (Data Supplement, Table S9), and the ORR in the 307 patients with solid tumors was 59.9% (184/307; 95% CI, 54.2 to 65.5).

In the 209 patients with breast cancer, the median duration of follow-up was 8.9 months (IQR, 5.6-12.0). The ORR was 76.3% (90/118; 95% CI, 67.6 to 83.6) in patients with HER2-positive breast cancer and 60.4% (55/91; 95% CI, 49.6 to 70.5) in patients with HER2 low-expressing breast cancer (Data Supplement, Table S10; Figs 2A and 2C-2D). The tumor responses were durable (Data Supplement, Figs S1 and S2).

In the 98 patients with nonbreast solid tumors, the median duration of follow-up was 4.1 months (IQR, 2.3-6.5). Of the 85 patients whose tumor responses were evaluable, objective responses were achieved in 39 (45.9%; 95% CI, 35.0 to 57.0) patients. This included 13 (59.1%) of 22 patients with urothelial carcinoma, nine (56.3%) of 16 patients with biliary tract cancer, six (50.0%) of 12 patients with G/GEJ carcinoma, four (36.4%) of 11 patients with colorectal cancer, four (44.4%) of nine patients with gynecologic cancer, one (25.0%) of four patients with NSCLC, and two (18.2%) of 11 patients with other nonbreast solid tumors (Figs 2B and 2E). Subgroup analysis showed that tumor shrinkage was observed across different immunohistochemistry (IHC) statuses (Data Supplement, Fig S3); and objective responses were observed in 20 (54.1%) of the 37 patients with IHC3+, 10 (41.7%) of the 24 patients with IHC2+, seven (50.0%) of the 14 patients with IHC1+, and two (20.0%) of the 10 patients with *HER2* gene mutation and/or amplification (Data Supplement, Table S11). The DCR was 88.2% (95% CI, 79.4 to 94.2) in the 85 nonbreast cancer patients whose tumor response were evaluable. The median time to response was 1.4 months (95% CI, 1.2 to 2.7) and the tumor responses were durable with nonbreast solid tumors (Data Supplement, Fig S4). As of data cutoff, only 38 (38.8%) of the 98 patients experienced disease progression or death events. Median PFS data were immature and the 6-month PFS rate was 52.1% (95% CI, 34.3 to 60.3).

Pharmacokinetics

A total of 123 patients were included in the pharmacokinetic parameter population. After a single dose, the plasma exposures (C_{max} and AUC_{0-21d}) of SHR-A1811, total antibody, and the payload increased proportionally over a dose range of 3.2-8.0 mg/kg (Fig 3). The pharmacokinetic parameters of SHR-A1811 and total antibody were similar at all dose levels, with low plasma exposure of released payload observed. The mean serum concentration versus time curve of SHR-A1811, total antibody, and the payload after multiple doses of SHR-A1811 are presented in the Data Supplement (Fig S5). Detailed pharmacokinetic parameters of SHR-A1811, total antibody, and payload are presented in the Data Supplement (Tables S12-S14).

The immunogenicity analysis showed that among the 276 (89.9%) patients whose samples were evaluable for immunogenicity, none of them developed treatment-emergent antidrug antibody.

DISCUSSION

This first-in-human study showed that SHR-A1811 had a manageable safety profile, with a very low incidence of ILD (only 2.6%) in heavily pretreated unresectable, advanced, or metastatic solid tumors. Most ILD cases were mild or moderate, which can be controlled by corticosteroids. SHR-A1811 led to substantial tumor responses in various types of heavily pretreated advanced solid tumors, and the responses were durable. The pharmacokinetics profile was also favorable.

The safety profile of SHR-A1811 in this solid tumor study was generally similar to that of trastuzumab deruxtecan.[10-14,18,19,27-31] Only one patient who received a dose of 6.4 mg/kg experienced dose-limiting toxicity. Although no dose-limiting toxicity was observed in the 8.0 mg/kg group, the incidence of grade 3 or higher treatment-related AEs and treatment-related serious AEs was higher than that of lower doses, indicating that patients may have limited tolerance to the 8.0 mg/kg dose. Therefore, the use of the 8.0 mg/kg dose is not recommended in subsequent phase II pivotal studies and phase III studies. The incidence of treatment-related AEs leading to treatment discontinuation for SHR-A1811 (4.2%) was numerically lower than that for trastuzumab deruxtecan in various types of advanced or metastatic solid tumors (14.4%-25%).[10-14,18,19] Additionally, the most concerning safety issue for trastuzumab deruxtecan is ILD.[20,21,23] In our study, SHR-A1811 demonstrated a numerically lower incidence of ILD (2.6%) than trastuzumab deruxtecan (9.6%-26.4%).[10-14,18,19] The stronger growth inhibition IC_{50} of the toxin SHR169265 in SHR-A1811 against various cell lines compared with the toxin of trastuzumab deruxtecan, coupled with the drug-antibody ratio of 6 in SHR-A1811, which led to similar antitumor activity at a 25% reduction in toxin dose relative to trastuzumab deruxtecan (Data Supplement, Table S15),[26] aligns with the low incidences of drug-related AEs leading to treatment discontinuation and ILD in our first-in-human study. Furthermore, the low incidence of toxicity indicates that the therapeutic window for SHR-A1811 has the potential to be extended, which could improve the antitumor outcomes of SHR-A1811.

The ORR of SHR-A1811 in HER2-positive breast cancer and HER2 low-expressing breast cancer cohorts was 76.2% and 60.4%, respectively, and that of trastuzumab deruxtecan in these two patient populations was 60.9%-79.0% and 52.3%, respectively.[10-14] The high ORR in the 91 patients with HER2 low-expressing breast cancer further confirmed the

high bystander effect observed in the preclinical study of SHR-A1811. The DESTINY-Lung01 study reported an ORR of 55% for trastuzumab deruxtecan in patients with NSCLC who had received a median of previous two lines of treatment.[18] In our study, only four patients with NSCLC were enrolled, and one patient achieved confirmed objective response as of data cutoff. Another phase I/II study of SHR-A1811 conducted in 50 patients with activating *HER2*-mutant advanced NSCLC who had received a median of previous three lines of treatment showed an ORR of 40%.[32] The enrollment of patients in this single-arm pivotal study in NSCLC is still ongoing, and updated results will be reported later. Objective responses were achieved in six (50.0%) of 12 patients with G/GEJ carcinoma in our study, and the ORR for trastuzumab deruxtecan in DESTINY-Gastric01 study was 51%.[19] The ORRs in biliary tract cancer and gynecologic cancer in our study were 56.3% (9/16) and 44.4% (4/9), respectively. Studies assessing SHR-A1811 in a larger cohort of patients with HER2-positive advanced or metastatic G/GEJ carcinoma (ClinicalTrials.gov identifier: NCT05671822) and HER2-expressing gynecologic cancer (ClinicalTrials.gov identifier: NCT05896020) are currently underway and actively recruiting participants. Cross-trial comparisons should be interpreted with caution as they involve diverse patient populations; however, these data showed that advanced solid tumors with different levels of HER2 expression benefit from treatment with SHR-A1811.

The study has several limitations, including enrollment of predominantly patients with breast cancer, resulting in a limited sample size of nonbreast solid tumor patients. Ongoing larger cohort clinical studies are addressing this limitation. The relatively short follow-up period, especially in the nonbreast cancer cohort, restricts the maturity of survival data, and central laboratory testing for HER2 status is still pending completion. The study used a less frequent measurement schedule for CT or MRI scans compared with certain studies involving trastuzumab deruxtecan. Therefore, further confirmation of the observed lower incidence of ILD is warranted in ongoing phase III SHR-A1811 studies (ClinicalTrials.gov identifiers: NCT05424835, NCT05814354, NCT06057610, and NCT06126640) and independent adjudication of ILD should be considered. The patient population predominantly consists of Asians, with a minority of Caucasian White and Black patients, and no Hispanics or other races, limiting generalization to other racial groups. However, our preliminary findings suggest similar pharmacokinetics and antitumor activity across Asian and non-Asian populations. Subsequent global studies with expanded non-Asian cohorts are warranted to further investigate SHR-A1811 in diverse patient populations.

In conclusion, this phase I first-in-human trial demonstrates that SHR-A1811 showed promising antitumor activity and had a manageable safety profile for heavily pretreated advanced solid tumors with HER2 overexpression or mutation. This phase I study had paved the way for further development of SHR-A1811 as a new treatment option for patients with HER2-expressing or mutated advanced solid tumors.

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DATA SHARING STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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REFERENCES

1. Goutsouliak K, Veeraraghavan J, Sethunath V, et al: Towards personalized treatment for early stage HER2-positive breast cancer. Nat Rev Clin Oncol 17:233-250, 2020
2. Oh DY, Bang YJ: HER2-targeted therapies—A role beyond breast cancer. Nat Rev Clin Oncol 17:33-48, 2020
3. Suwaidan AA, Lau DK, Chau I: HER2 targeted therapy in colorectal cancer: New horizons. Cancer Treat Rev 105:102363, 2022
4. Meric-Bernstam F, Johnson AM, Dumbrava EEI, et al: Advances in HER2-targeted therapy: Novel agents and opportunities beyond breast and gastric cancer. Clin Cancer Res 25:2033-2041, 2019
5. Baselga J, Cortes J, Kim SB, et al: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366:109-119, 2012
6. Swain SM, Baselga J, Kim SB, et al: Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 372:724-734, 2015
7. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-1791, 2012
8. Dieras V, Miles D, Verma S, et al: Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): A descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 18:732-742, 2017
9. von Minckwitz G, Huang CS, Mano MS, et al: Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 380:617-628, 2019
10. Modi S, Saura C, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med 382:610-621, 2020
11. Andre F, Hee Park Y, Kim SB, et al: Trastuzumab deruxtecan versus treatment of physician's choice in patients with HER2-positive metastatic breast cancer (DESTINY-Breast02): A randomised, open-label, multicentre, phase 3 trial. Lancet 401:1773-1785, 2023
12. Cortes J, Kim SB, Chung WP, et al: Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. N Engl J Med 386:1143-1154, 2022
13. Hurvitz SA, Hegg R, Chung WP, et al: Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: Updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet 401:105-117, 2023
14. Modi S, Jacot W, Yamashita T, et al: Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 387:9-20, 2022
15. Thomas A, Teicher BA, Hassan R: Antibody-drug conjugates for cancer therapy. Lancet Oncol 17:e254-e262, 2016
16. Fu Z, Li S, Han S, et al: Antibody drug conjugate: The "biological missile" for targeted cancer therapy. Signal Transduct Target Ther 7:93, 2022
17. Chau CH, Steeg PS, Figg WD: Antibody-drug conjugates for cancer. Lancet 394:793-804, 2019
18. Li BT, Smit EF, Goto Y, et al: Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer. N Engl J Med 386:241-251, 2022
19. Shitara K, Bang YJ, Iwasa S, et al: Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 382:2419-2430, 2020
20. Abuhelwa Z, Alloghbi A, Alqahtani A, et al: Trastuzumab deruxtecan-induced interstitial lung disease/pneumonitis in ERBB2-positive advanced solid malignancies: A systematic review. Drugs 82:979-987, 2022
21. Powell CA, Modi S, Iwata H, et al: Pooled analysis of drug-related interstitial lung disease and/or pneumonitis in nine trastuzumab deruxtecan monotherapy studies. ESMO Open 7:100554, 2022
22. Conte P, Ascierto PA, Patelli G, et al: Drug-induced interstitial lung disease during cancer therapies: Expert opinion on diagnosis and treatment. ESMO Open 7:100404, 2022
23. Tarantino P, Modi S, Tolaney SM, et al: Interstitial lung disease induced by anti-ERBB2 antibody-drug conjugates: A review. JAMA Oncol 7:1873-1881, 2021
24. Khoury R, Saleh K, Khalife N, et al: Mechanisms of resistance to antibody-drug conjugates. Int J Mol Sci 24:9674, 2023
25. Guidi L, Pellizzari G, Tarantino P, et al: Resistance to antibody-drug conjugates targeting HER2 in breast cancer: Molecular landscape and future challenges. Cancers (Basel) 15:1130, 2023
26. Zhang T, You L, Xu J, et al: Abstract LB031: SHR-A1811, a novel anti-HER2 ADC with superior bystander effect, optimal DAR and favorable safety profiles. Cancer Res 83, 2023 (suppl 8; abstr LB031)
27. Tsurutani J, Iwata H, Krop I, et al: Targeting HER2 with trastuzumab deruxtecan: A dose-expansion, phase I study in multiple advanced solid tumors. Cancer Discov 10:688-701, 2020

28. Tamura K, Tsurutani J, Takahashi S, et al: Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: A dose-expansion, phase 1 study. Lancet Oncol 20:816-826, 2019
29. Modi S, Park H, Murthy RK, et al: Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: Results from a phase Ib study. J Clin Oncol 38:1887-1896, 2020
30. Shitara K, Iwata H, Takahashi S, et al: Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: A dose-expansion, phase 1 study. Lancet Oncol 20:827-836, 2019
31. Doi T, Shitara K, Naito Y, et al: Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: A phase 1 dose-escalation study. Lancet Oncol 18:1512-1522, 2017
32. Lu S, Jian H, Hong W, et al: Abstract CT204: Safety, tolerability, pharmacokinetics, and efficacy of SHR-A1811, an antibody-drug conjugate, in patients with advanced HER2-mutant non-small cell lung cancer (NSCLC): A multicenter, open-label, phase 1/2 study. Cancer Res 83, 2023 (suppl 8; abstr CT204)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety, Efficacy, and Pharmacokinetics of SHR-A1811, a Human Epidermal Growth Factor Receptor 2–Directed Antibody-Drug Conjugate, in Human Epidermal Growth Factor Receptor 2–Expressing or Mutated Advanced Solid Tumors: A Global Phase I Trial

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. PARTICIPATING SITES INVESTIGATORS

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Jian Zhang	Fudan University Shanghai Cancer Center, Shanghai, China	8
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Yung-Chang Lin	Chang Gung Memorial Hospital, Taoyuan, Taiwan	2
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