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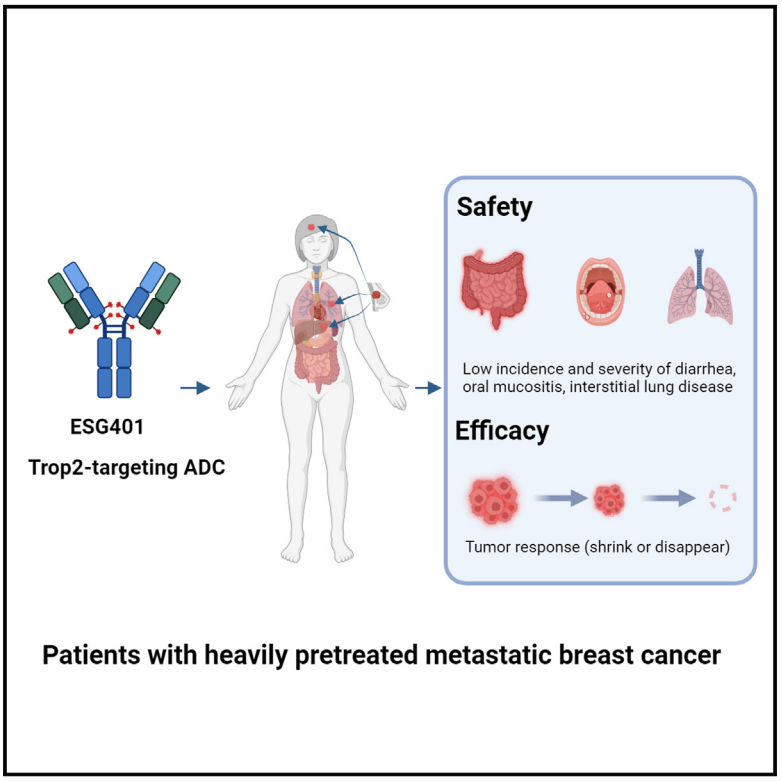
Phase 1a study of ESG401, a Trop2 antibody-drug conjugate, in patients with locally advanced/metastatic solid tumors

Graphical abstract



Highlights

- ESG401 is a Trop2-targeting antibody-drug conjugate with a stable linker
- Multiple dose levels and two regimens are assessed
- ESG401 is well tolerated with a favorable safety profile
- ESG401 demonstrates promising antitumor activity in heavily treated solid tumors

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In brief

Wang et al. report the safety and preliminary antitumor efficacy of an optimized Trop2-targeting antibody-drug conjugate, ESG401, in patients with heavily pretreated locally advanced or metastatic solid tumors, focusing on metastatic breast cancer. They demonstrate that ESG401 exhibits a favorable safety profile and encourages antitumor activity.

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Phase 1a study of ESG401, a Trop2 antibody-drug conjugate, in patients with locally advanced/metastatic solid tumors

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SUMMARY

This phase 1a study assesses ESG401 in patients with heavily pretreated locally advanced or metastatic solid tumors, focusing on metastatic breast cancer. Forty patients are enrolled: three experience dose-limiting toxicities, establishing the maximum tolerated dose at 16 mg/kg on days 1, 8, and 15 of a 28-day cycle. The most common grade $\geq$3 treatment-related adverse events are neutropenia and leukopenia. Among 38 efficacy-evaluable patients, the objective response rate (ORR) is 34.2%, the disease control rate (DCR) is 65.8%, and the clinical benefit rate (CBR) is 50.0% (including stable disease for at least 6 months). The median progression-free survival is 5.1 months, and the median duration of response is 6.3 months. In patients receiving therapeutically relevant doses, the ORR, DCR, and CBR are 40.6%, 75.0%, and 56.3%, respectively. ESG401 demonstrates a favorable safety profile and promising antitumor activity in this heavily treated population. The trial is registered at ClinicalTrials.gov (NCT04892342).

INTRODUCTION

Trophoblast cell-surface antigen 2 (Trop2) is a transmembrane glycoprotein encoded by the tumor-associated calcium signal transducer 2 (TACSTD2) gene, which promotes tumor cell proliferation, induces epithelial-mesenchymal transition, and promotes tumor cell migration, invasion, and anti-apoptosis.[1,2] Accumulating evidence suggests that Trop2 may play a role in tumor development as it is involved in several oncogenic signaling pathways. Furthermore, elevated expression of Trop2 is often associated with invasion, aggression, progression, and metastasis in a variety of tumors.[3–9] Therefore, Trop2 is considered a rational prognostic marker and therapeutic target in human solid tumors,[10–17] especially in the development of antibody-drug conjugates (ADCs).

The discovery of the Trop2 antigen has revolutionized ADC development. Besides sacituzumab govitecan (SG; IMMU-132; Trodelvy), the only Trop2 ADC that has been approved, more than 10 ADCs targeting Trop2 are currently in clinical development. Four products are in the phase 3 stage, including DS-1062 (Daiichi Sankyo/AstraZeneca), SKB264 (KLUS Pharma), ESG401 (Escugen Biotech), and SHR-A1921 (Shanghai Hengrui Pharmaceuticals). Other products are in the early phase 1/2 stage, including FDA018, FZ-AD004, BL-M02D1, BAT8008, DB-1305, 9MW2921, HS-20105, MHB036C, XYD-9668-198, GQ1010, BIO-106, IBI-130, DXC1002, and LCB-84.

As a first-in-class product, sacituzumab govitecan, developed by Immunomedics, is an ADC consisting of a humanized anti-Trop2 monoclonal antibody (hRS7) conjugated with the active metabolite of irinotecan (SN38) via a cleavable CL2A linker.[18] The payload SN38 is a moderately cytotoxic drug conjugated to a monoclonal antibody, with a high drug-antibody ratio (DAR) of 8. In April 2021, the Food and Drug Administration granted regular approval to Trodelvy for patients with metastatic triple-negative breast cancer (mTNBC) based on data from the confirmatory trial ASCENT.[19] Although SG was the first ADC approved specifically for mTNBC, there is a black box warning for neutropenia and diarrhea on the label,[20] which may be attributed to the use of an unstable linker design. The small-molecule payload SN38 rapidly dissociates in serum, leading to clinical

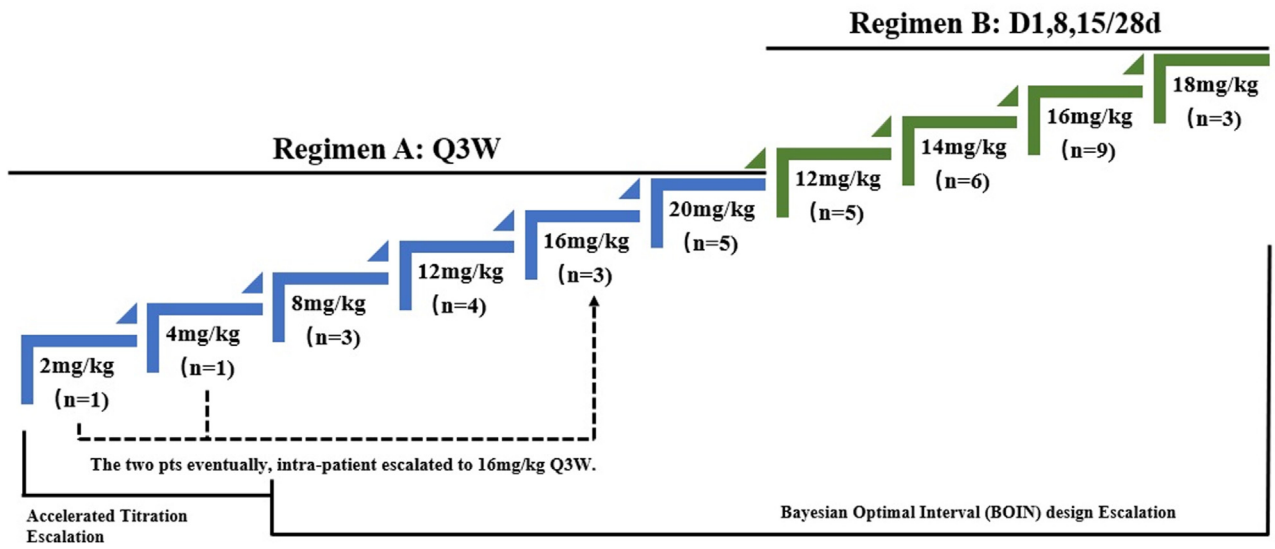

Figure 1. Flowchart

The patients enrolled in a dose-escalation study with planned 10 dose levels were administered intravenously at predetermined doses of 2–20 mg/kg once every 3 weeks (regimen A), or 12–18 mg/kg on day 1, 8, and 15 in a 4-week cycle (regimen B) until disease progression, death, or unacceptable toxicity.

safety concerns. Therefore, there is still room for improvement in terms of both efficacy and safety.

ESG401 is being developed as a further optimized Trop2-targeting ADC with a proprietary stable linker and an SN38 cytotoxic payload to achieve an average DAR of 8. The release of payload upon ESG401 internalization occurs in a Trop2 expression-dependent manner. Through these optimizations, ESG401 is expected to exhibit minimized ''on-target off-tumor'' and ''off-tumor'' toxicities. Unlike the pH-sensitive unstable linker design of IMMU-132, ESG401 enters cellular lysosomes primarily through endocytosis, where the Val-Cit (VC) dipeptide is cleaved by cathepsin, activating the self-destruct reaction of subsequent linker fragments to release free SN38 toxin. The stable linker design enables SN38 to be released for action only after endocytosis by tumor cells, allowing ESG401 to remain stable in serum and normal tissues, thereby effectively reducing toxic side effects. A comparison of the drug design of ESG401 with several other Trop2 ADCs in advanced stages of development is provided in Table S1.

ESG401 has demonstrated excellent non-clinical safety advantages in preclinical studies, as well as outstanding efficacy/pharmacology characteristics and high stability and controllability in pharmaceutical processes. Extensive preclinical studies have demonstrated the antitumor activity of ESG401 *in vitro* in various xenograft animal models, including sensitive TNBC and lung adenocarcinoma models. ESG401 echoed its advantages in prospective stable linker designs in preclinical studies. Compared to SG, ESG401 exhibited a significantly lower maximum plasma concentration (C_{max}) and area under the curve from time zero to the last measurable concentration (AUC_{0-t}) of SN38, with values approximately 79 and 350 times lower, respectively. The half-life of ESG401 in macaques is approximately 43 h, much longer than that of SG (approximately 13.5 h).[21] Preclinical research data of ESG401 are provided in the supplemental information.

This meticulously designed phase 1 study aimed to evaluate the safety, tolerability, pharmacokinetic profile, and preliminary efficacy of ESG401 in Chinese patients with metastatic malignant solid tumors, further confirming the thoughtful considerations in ESG401's design and the findings from preclinical trials. This is expected to achieve a more optimal therapeutic index and effectively address the challenges associated with the current Trop2 ADC products.

RESULTS

Patient characteristics

Between September 9, 2021, and December 4, 2023, 40 patients were enrolled in this phase 1a study (Figure 1). Most patients had metastatic hormonal receptor-positive (HR+) human epidermal growth factor receptor 2 (HER2) negative breast cancer (HR+/HER2−BC) (n = 18) and triple-negative breast cancer (TNBC) (n = 18), followed by HER2+ breast cancer (HER2+BC) (n = 2), with single cases of endometrial cancer (EC) and adenoid cystic carcinoma (ACC). The median age of the patients was 53 years (range, 32–70 years), and all were female, with a median of four prior lines of systemic anticancer treatment in the metastatic setting (range, 1–12). All enrolled patients had distant metastases at baseline, with 10%, 63%, and 60% of the patients having brain, liver, and lung metastases, respectively. The baseline characteristics of the enrolled patients are summarized in Table 1.

Safety

The reported safety analyses were based on a data cutoff of April 12, 2024. Among the 40 patients who received at least one dose of ESG401 included in the safety analysis, 38 experienced treatment-emergent adverse events (TEAEs), resulting in a total incidence rate of 95.0% (38/40). TEAEs related to the study drug,

Table 1. Baseline characteristics and treatment history of all patients

Patient characteristics	ESG401-101 (*n* = 40)
Age, median (range), years	53 (32–70)
ECOG PS, *n* (%)	
0	8 (20)
1	32 (80)
De novo metastatic disease, *n* (%)	
Yes	6 (15)
No	34 (85)
Visceral metastasis at baseline, *n* (%)	37 (93)
Brain metastasis	4 (10)
Liver metastasis	25 (63)
Lung metastasis	24 (60)
Prior therapies in metastatic setting, median (range), *n*	4 (1–12)
≥2 prior lines of therapy, *n* (%)	36 (90)
≥5 prior lines of therapy, *n* (%)	18 (45)
Previous systemic treatment, *n* (%)	
Taxanes	37 (93)
Anthracyclines	30 (75)
Platinum-based chemotherapy	21 (53)
Immunotherapy	9 (23)
Other ADC	4 (10)
Median time from diagnosis of metastatic disease to enrollment (range)—months	32.6 (4.1–147.0)

with an incidence rate of ≥20%, included leukopenia (85.0%), neutropenia (75.0%), anemia (70.0%), nausea (52.5%), vomiting (42.5%), fatigue (52.5%), alopecia (25.0%), decreased appetite (27.5%), diarrhea (37.5%), elevated aspartate aminotransferase (22.5%), and elevated alanine aminotransferase (20.0%) (Table 2). The most common grade ≥3 adverse events (AEs) related to the study drugs were neutropenia (40.0%), leukopenia (37.5%), and anemia (10.0%) (Table S2). The incidence of treatment-related adverse events (TRAEs) leading to delayed dosing, dose reduction, or permanent discontinuation was 30%, 15%, and 0%, respectively. Three patients experienced dose-limiting toxicities (DLTs) to the protocol criteria. One patient who received 20 mg of Q3 weeks (regimen A) experienced grade 4 neutropenia lasting >5 days and grade 3 febrile neutropenia. Two patients who received 18 mg/kg on days 1, 8, and 15/28 days (regimen B) experienced grade 3 febrile neutropenia or grade 4 neutropenia lasting more than 5 days.

Pharmacokinetics

Standard non-compartmental analysis of pharmacokinetic parameters was performed using Phoenix WinNonlin (version 6.3, Certara USA Inc. Princeton, NJ, USA). The half-life of intact ADC was approximately 35.7 h, with very low exposure to SN38, only 0.004% of the ADC. Across all dosing levels, whether administered as a single dose or as multiple doses, the pharmacokinetic profiles of intact ADC and total antibody exhibited nearly overlapping curves. This observation underscores the robust stability of ESG401 ADC in plasma.

Pharmacometrics

The study utilized pharmacometrics analysis. The preliminary pharmacometrics model adopted a two-compartment model with both linear and nonlinear elimination. In the exposure-response (E-R) analysis for efficacy, ESG401 ADC demonstrated a trend of higher drug exposure correlating with greater objective response rate (ORR) benefit from both C_{max} and C_{avg} perspectives. Based on the predicted clinical effect C_{avg} values of ESG401 derived from ESG401 clinical half-maximal inhibitory concentration (IC_{50}), and referencing the C_{avg} range observed with SG's clinical therapeutic dose (10 mg/kg), the pharmacometrics model recommended two preferred dosing regimens for ESG401: Q2 weeks ≥ 20 mg/kg, day 1 and day 8 in a 3-week cycle, or day 1, day 8, and day 15 in a 4-week cycle ≥ 16 mg/kg. The E-R analysis for safety indicated that the primary dose-limiting safety parameter, grade ≥3 neutropenia, is significantly associated with C_{max} of SN38. Pharmacometrics predictions indicated that, at a dosage of 16 mg/kg on day 1, day 8, and day 15/28, the incidence of grade ≥3 neutropenia would be approximately 40%. However, the actual incidence was 55.6% (5 out of 9 patients). Therefore, more samples need to be accumulated in the future to further calibrate the pharmacometrics model.

Dose assessment

Dosing regimens

The initial dose-escalation study design included 6 dose levels ranging from 2 mg/kg to 20 mg/kg administered every 3 weeks (Q3 weeks), with a total of 17 subjects enrolled. Following the completion of DLT observations in cycle 1 for the last subject, AEs related to ESG401 were predominantly graded 1 or 2, except for grade ≥3 leukopenia and neutrophil count decreases. The initial occurrence of grade ≥3 neutropenia was noted at 16 mg/kg Q3 weeks, with an incidence of 33.3% (1/3); at 20 mg/kg Q3 weeks, it increased to 40.0% (2/5). Notably, one patient treated with 20 mg/kg Q3 weeks experienced grade 4 neutropenia lasting >5 days and grade 3 febrile neutropenia, meeting DLT criteria per protocol. This underscores the need for vigilance when ESG401 dosing reaches 20 mg/kg.

Pharmacokinetic results indicated proportional increases in ESG401 exposure, total antibody, and payload across the 2–20 mg/kg Q3-weeks dose range. However, the half-life (~43 h) is insufficient to support a Q3 weeks dosing interval. Q3-week administration resulted in a "pulse-like" pharmacokinetic curve characterized by excessively high peak concentrations posing safety risks and a brief duration of effective concentration maintenance, insufficient for sustained therapeutic effects. Such a curve is less effective in inhibiting tumor growth compared to a steady and continuous concentration curve achievable by reducing individual doses and increasing dosing frequency. Pharmacometrics analyses aimed at guiding dose selection were conducted, and simulation results suggested that dosing regimen B (day 1, day 8, and day 15 in a 4-week cycle) could maintain ESG401 concentrations above predicted clinical effect C_{avg} values better than regimen A (Q3 weeks), thereby

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Table 2. Summary of treatment-related AEs of any grade (≥20%) in the safety population (all patients who received ≥1 dose of study treatment)

	Regimen A				Regimen B				
The most common TRAEs	8 mg/kg (Q3 weeks) *n* = 3	12 mg/kg (Q3 weeks) *n* = 4	16 mg/kg (Q3 weeks) *n* = 5	20 mg/kg (Q3 weeks) *n* = 5	12 mg/kg (day 1,8,15/28) *n* = 5	14 mg/kg (day 1,8,15/28) *n* = 6	16 mg/kg (day 1,8,15/28) *n* = 9	18 mg/kg (day 1,8,15/28) *n* = 3	Total (*n* = 40)
Leukopenia	1 (33.3)	2 (50.0)	4 (80.0)	5 (100)	4 (80.0)	6 (100)	9 (100)	3 (100)	34 (85.0)
Neutropenia	0	0	3 (60.0)	5 (100)	4 (80.0)	6 (100)	9 (100)	3 (100)	30 (75.0)
Anemia	2 (66.7)	2 (50.0)	1 (20.0)	4 (80.0)	4 (80.0)	6 (100)	6 (66.7)	3 (100)	28 (70.0)
Nausea	1 (33.3)	2 (50.0)	4 (80.0)	1 (20.0)	2 (40.0)	4 (66.7)	4 (44.4)	3 (100)	21 (52.5)
Fatigue	1 (33.3)	2 (50.0)	2 (40.0)	1 (20.0)	4 (80.0)	5 (83.3)	4 (44.4)	2 (66.7)	21 (52.5)
Vomiting	1 (33.3)	0	3 (60.0)	4 (80.0)	2 (40.0)	3 (50.0)	3 (33.3)	1 (33.3)	17 (42.5)
Diarrhea	1 (33.3)	0	1 (20.0)	1 (20.0)	2 (40.0)	4 (66.7)	3 (33.3)	3 (100)	15 (37.5)
Decreased appetite	0	1 (25.0)	3 (60.0)	1 (20.0)	2 (40.0)	2 (33.3)	0	2 (66.7)	11 (27.5)
Alopecia	0	0	4 (80.0)	3 (60.0)	0	0	2 (22.2)	1 (33.3)	10 (25.0)
Elevated aspartate aminotransferase	0	2 (50.0)	0	2 (40.0)	0	2 (33.3)	2 (22.2)	1 (33.3)	9 (22.5)
Elevated alanine aminotransferase	0	1 (25.0)	0	1 (20.0)	0	1 (16.7)	4 (44.4)	1 (33.3)	8 (20.0)

See also Table S2.

enhancing efficacy and maintaining appropriate safety when the dose level does not exceed 20 mg/kg.

Subsequent evaluations were conducted within a dose range of 12–18 mg/kg, administered on day 1, day 8, and day 15 in a 4-week cycle, following protocol amendment.

The maximum tolerated dose

Among all 40 enrolled subjects, three experienced DLT events. These included one patient administered 20 mg/kg Q3 weeks and two others administered 18 mg/kg on day 1, day 8, and day 15/28, as mentioned. Isotonic regression was used to determine the maximum tolerated dose (MTD), which was calculated using the "Select MTD" function in the Bayesian optimal interval (BOIN) online software. The MTD was determined to be 16 mg/kg on days 1, 8, and 15/28 days.

The recommended phase 2 dose

The determination of the recommended phase 2 dose (RP2D) for ESG401 involved a thorough evaluation across several critical perspectives: DLT and safety, efficacy, and pharmacology.

From the perspective of DLT and safety, the regimen of 16 mg/kg on day 1, day 8, and day 15/28 demonstrated a safety profile comparable to that of the 12 mg/kg schedule under the same dosing frequency. Importantly, it also showed a superior safety profile compared to the regimen of 20 mg/kg Q3 weeks. In terms of efficacy, the regimen of 16 mg/kg on day 1, day 8, and day 15/28 exhibited promising results with an ORR of 44.4% (4/9) and a disease control rate (DCR) of 77.8% (7/9). Furthermore, predictions from pharmacometric models indicated that the regimen of 16 mg/kg on day 1, day 8, and day 15/28 strikes a favorable balance between efficacy and safety.

Based on these comprehensive evaluations, the regimen of 16 mg/kg day 1, day 8, and day 15/28 was deemed to offer the optimal benefit-risk ratio and was therefore chosen as the RP2D for ESG401. This decision will be further investigated in subsequent studies.

Trop2 expression level

Trop2 expression is not required for patient eligibility. Membrane Trop2 expression was quantified using a histochemical score (H-score; range 0–300). Of the 40 enrolled patients, 17 provided tissue samples for the Trop2 expression analysis. Of these 17 patients, 64.7% (11/17) were strongly positive for Trop2 (H-score = [200,300]), 23.5% (4/17) were moderately positive (H-score = [100,200]), and 11.8% (2/17) were weakly positive (H-score = [0.100]).

Eleven efficacy-evaluable (EE) patients with TROP2 expression information received therapeutically relevant doses (TRDs). The ORR among patients with strongly positive, moderately positive, and weakly positive Trop2 expression was 33% (2/6), 75% (3/4), and 100% (1/1), respectively. The DCR was 67% for strongly positive and 100% for both moderately and weakly positive expression levels. Due to limited tissue samples for Trop2 expression testing, definitive conclusions regarding the correlation between Trop2 expression level and treatment efficacy cannot be drawn based on current data.

Pilot efficacy

In the phase 1a study, 40 enrolled patients received at least one dose of ESG401. Two patients were excluded from the efficacy analysis owing to missing post-treatment assessments, leaving 38 evaluable patients. The ORR of evaluable patients was 34.2% (13 of 38 patients) (95% confidence interval [CI]: 19.6, 51.4). The clinical benefit rate (CBR) (including stable disease for at least 6 months) was 50.0% (19 of 38 patients) (95% CI: 33.4, 66.6). The DCR was 65.8% (25 of 38 patients) (95% CI: 48.6, 80.4). The median progression-free survival (PFS) was 5.1 months (95% confidence interval [CI], 1.9 to 8.2) (Figure 2A). The median duration of response (DOR) was 6.3 months (95% CI, 2.8 to 8.5) (Figure 2B).

The efficacy endpoints for all patients administered at different dose levels are summarized in Table 3. In this dose-escalation study, the initial dose level at which a partial response (PR) was observed, that is, 16 mg/kg Q3 weeks, and subsequent escalating dose levels or higher exposure levels were considered TRDs. In Figure 3, a waterfall plot shows the change in target lesions at the best response for patients treated with TRD with at least one post-treatment imaging assessment. In these patients, the ORR was 40.6% (13/32) (95% CI: 23.7, 59.4). The CBR was 56.3% (18/32) (95% CI: 37.7, 73.6). The DCR was 75.0% (24/32) (95% CI: 56.6, 88.5).

Seventeen EE patients with HR+/HER2− breast cancer were treated with TRD. Eight patients achieved a PR, and four others had stable disease as the best response. The ORR was 47.0% (8/17) (95% CI: 23.0, 72.2). The DCR was 70.6% (12/17) (95% CI: 44.0, 89.7). In the 17 EE patients with TNBC, the ORR was 29.4% (5/17) (95% CI: 10.3, 56.0). The DCR was 52.9% (9/17) (95% CI: 27.8, 77.0).

DISCUSSION

Previous studies have highlighted the potential of Trop2 as a therapeutic target.[22–29] ESG401 is an innovative Trop2 ADC that conjugates the moderately toxic payload, SN38, with a humanized anti-Trop2 monoclonal antibody via a proprietary stable cleavable linker, achieving a highly homogeneous DAR of approximately 8. This is the phase 1 trial of ESG401, aimed at evaluating the safety, tolerability, pharmacokinetic profile, and preliminary efficacy of ESG401 in Chinese patients with metastatic solid tumors, further confirming that improvements in ADC molecular composition enhance safety and efficacy.

The ESG401 demonstrated good safety and tolerability. In dose escalation, dosing regimen A, even at doses as high as 20 mg/kg, did not reach the MTD. In dosing regimen B, which aimed to reduce single doses and increase drug exposure by reducing the dosing interval, 16 mg/kg on day 1, day 8, and day 15/28 showed good safety and tolerability. Additionally, the safety profile of ESG401 was favorable, with neutropenia, the most common AE, being unperceivable and easily manageable. Compared to SG, ESG401 had low rates of grade $\geq$3 neutropenia (ESG401 vs. SG: 40% vs. 51%), thrombocytopenia (0% vs. 2%), diarrhea (0% vs. 11%), nausea (0% vs. 3%), and vomiting (0% vs. 2%). For AEs that can be perceived by patients and significantly impact their quality of life, such as diarrhea and oral mucositis, the incidence of ESG401 was 0%, whereas SG had an incidence of 11% for grade 3 or higher diarrhea.[22] No cases of

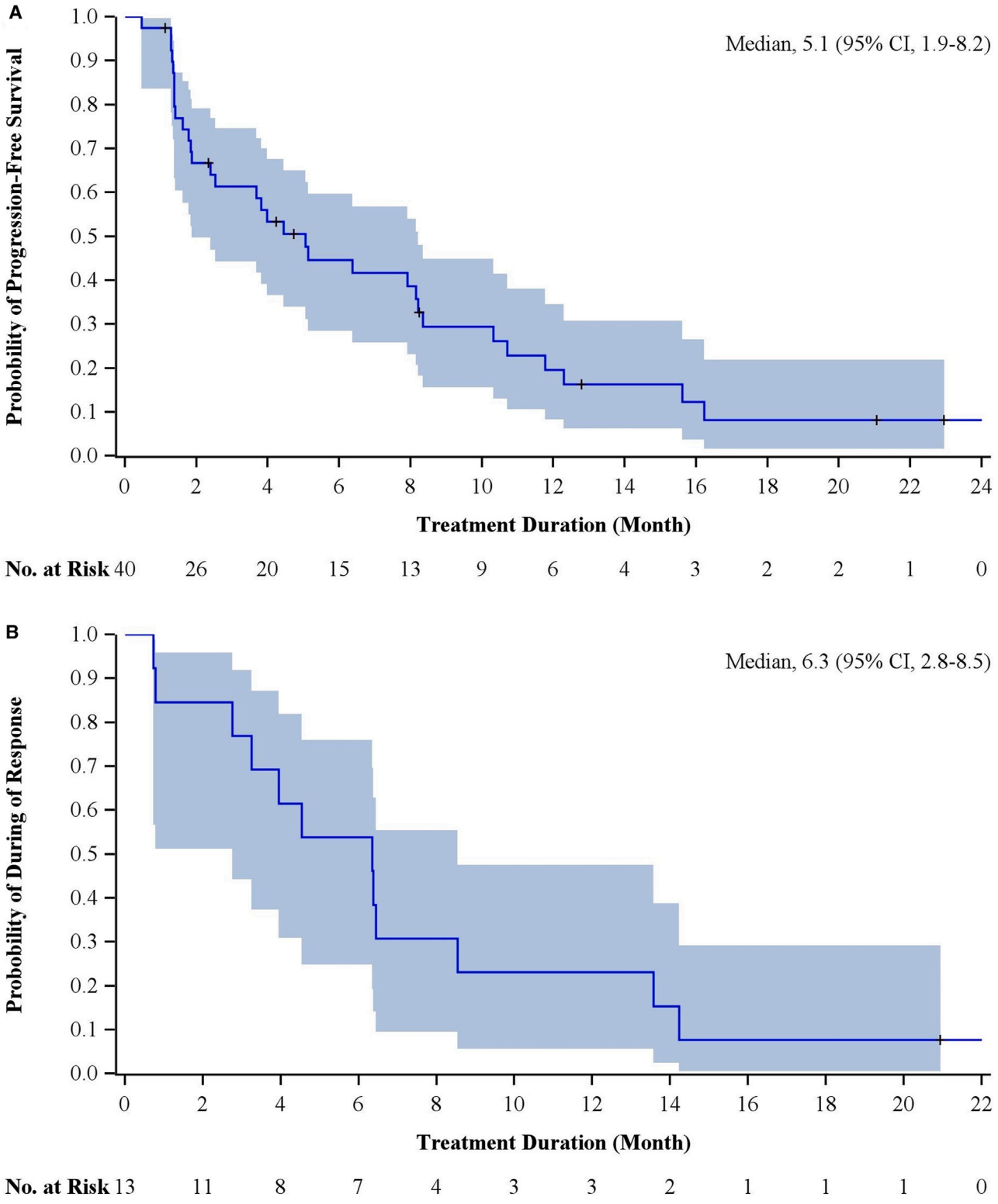

Figure 2. Analysis of progression-free survival and duration of response

Kaplan-Meier (KM) curves depicting progression-free survival (A) and duration of response (B) in patients. The dashed lines represent the 95% confidence intervals for each KM curve. Abbreviations: CI, confidence interval.

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Table 3. Efficacy by dose level

	Regimen A				Regimen B			
	8 mg/kg (n = 3)	12 mg/kg (n = 3)	16 mg/kg (n = 5[a])	20 mg/kg (n = 5)	12 mg/kg (n = 5)	14 mg/kg (n = 6)	16 mg/kg (n = 9)	18 mg/kg (n = 2)
ORR, n (%)	0	0	2 (40.0)	2 (40.0)	3 (60.0)	1 (16.7)	4 (44.4)	1 (50.0)
PR[b]	0	0	2	2	3	1	4	1
CBR, n (%)	1 (33.3)	0	3 (60.0)	3 (60.0)	3 (60.0)	2 (33.3)	5 (55.5)	2 (100.0)
DCR, n (%)	1 (33.3)	0	3 (60.0)	3 (60.0)	4 (80.0)	5 (83.3)	7 (77.7)	2 (100.0)
SD	1	0	1	1	1	4	3	1
SD $\geq$ 6 months	1	0	1	1	0	1	1	1
PD	2	3	2	2	1	1	2	0

[a]Include patients who were assigned to 2 mg/kg (n = 1) and 4 mg/kg Q3 weeks (n = 1) while eventually, intra-patient escalated to 16 mg/kg Q3 weeks. Sixteen mg/kg Q3 weeks is the initial dose level at which a partial response (PR) was observed. Therefore, 16 mg/kg Q3 weeks and subsequent escalating dose levels or higher exposure levels were considered therapeutically relevant doses (TRDs) in the study.
[b]Per Response Evaluation Criteria in Solid Tumors 1.1, but including single-point PRs, not confirmed responses.

interstitial lung disease were observed in this study. We speculate that the improvement in ESG401's safety, including the increase in tolerable dosage and the optimization of the safety profile, is precisely related to its stable linker modification. Owing to the unstable linker used in SG, payload SN38 is rapidly released into the serum, leading to safety concerns. Severe delayed diarrhea and granulocytopenia resulting from high exposure to free SN38 have not been effectively addressed. The trial results suggest that, compared to SG, ESG401 exhibits significantly improved systemic stability and a prolonged half-life (ESG401 at 16 mg/kg on day 1, day 8, and day 15/28: 35.7 h vs. SG: 23.4 h) (20), and the systemic exposure of SN38 is significantly reduced, being only 1/11th of SG. This mechanistically explains the observed reduction in both the incidence and severity of off-target toxicities caused by SN38, namely severe neutropenia and diarrhea, in clinical settings with ESG401 compared to SG.

ESG401 demonstrated promising antitumor activity in patients with various heavily treated, locally advanced or metastatic solid tumors. Among the 38 patients with EE, the ORR was 34.2% and the DCR was 65.8%. Notably, responses or disease stabilization occurred in three out of four patients who had previously undergone therapy with other ADCs targeting different antigens than Trop2, including DS-8201, T-DM1, or DX126-262. One patient who was treated with DS-8201 and subsequently experienced

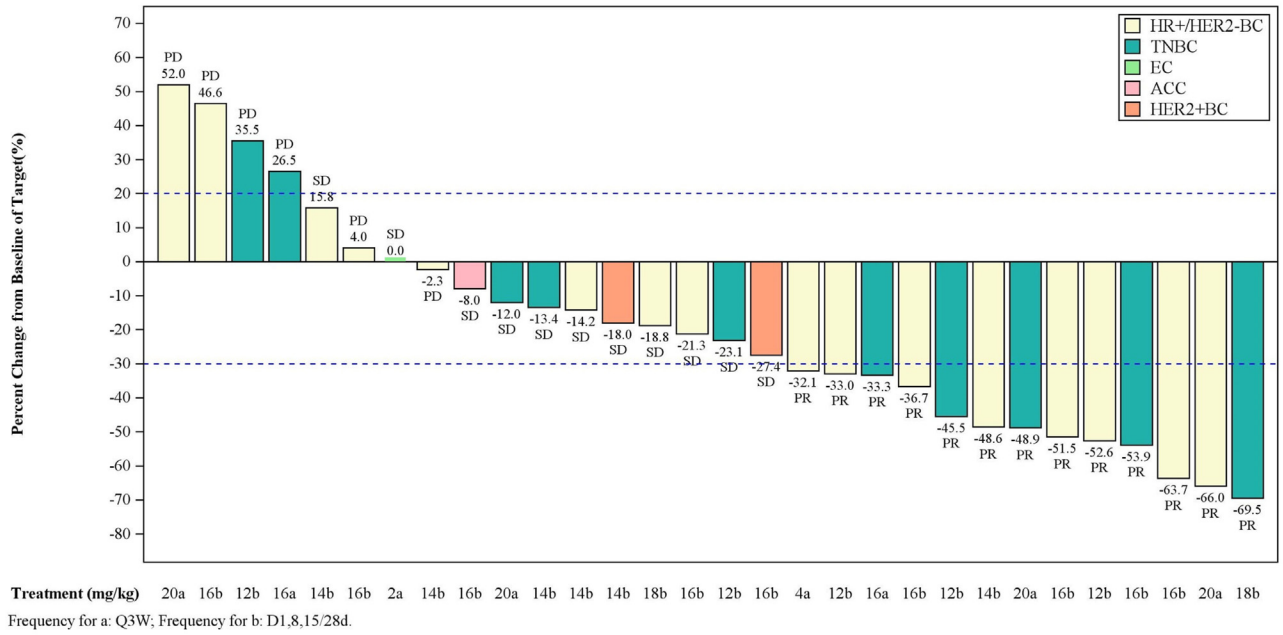

Figure 3. Change in tumor size

Waterfall plot: best percentage change from baseline in the sum of the diameters of the target lesions (longest for non-nodal and short axis for nodal lesions) of patients treated with TRD. Two patients are not shown in this graph because not all evaluations of the target lesions were performed. Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease.

disease progression responded to ESG401. The patient achieved PR in the overall target lesion and complete response (CR) in the brain lesion.

In our study, ESG401 demonstrated promising efficacy in patients with the subtypes of breast cancer. Although heavily treated, the ORR for HR+/HER2− breast cancer patients was 47.0% (8/17) and 29.4% (5/17) for TNBC, respectively. Two patients with HER2+ breast cancer, who progressed following adequate anti-HER2 treatment, were enrolled in this study. One patient who was still receiving treatment experienced an 18.0% reduction in target lesions, with a prolonged response duration of 20.9 months. The other patient had tumor shrinkage of 27.4%. This indicates that Trop2-targeting ADC ESG401 may be effective across different subtypes of breast cancer classified according to the traditional hormone receptor and HER2 status.

Similarly, we speculate that ESG401's promising efficacy might also be related to its structural improvements. On one hand, the enhanced safety due to the stability of the ADC allows for higher dosing, which can lead to greater drug exposure. Generally, higher drug exposure produces better efficacy. On the other hand, as demonstrated in the study, ESG401 resulted in TRAEs leading to delayed dosing, dose reduction, or permanent discontinuation in 30%, 15%, and 0% of cases, respectively. Compared to SG, the incidence was numerically lower (20), ensuring that patients obtain adequate drug exposure and timely and sufficient dosing, thereby benefiting from treatment efficacy. Moreover, the safety of ESG401 provides a unique advantage for future combination therapies.

In our trial, we deliberately compared the safety and efficacy of the two dosing regimens. Based on our trial results, we found that ESG401 in dosing regimen B can achieve the goal of increasing the average drug exposure level by reducing single doses and decreasing the dosing interval, thereby enhancing safety and efficacy. This finding provides a basis for the selection of dosing regimens for future ESG401 trials as well as a valuable example for other ADC drugs to explore dosing regimens.

Trop2 expression was assessed in archived tumor tissues from 17 patients by immunohistochemistry. Consistent with the SG report, most patients had an H-score of $\geq$100 or higher. Although we attempted to collect archival tumor specimens from the enrolled patients, due to the limited number of cases, no correlation between Trop2 expression and efficacy was observed. Further research on biomarkers is required to identify patients who may benefit from ADC drugs that target this class.

Limitations of the study

This study had some limitations. The single-arm nature of the study, without comparator arms and its small sample size, limits its findings and does not allow definitive statistical inference. This will be further investigated in subsequent experiments. Furthermore, there were too few patients with archived tumor tissues collected for the detection of the expression level of Trop2 to find a correlation with efficacy. There are several ongoing or planned studies on ESG401, including a phase 1b study,[30] phase 3 ESG401-301 in patients with late-line HR+/HER2−BC,[31] and phase 3 ESG401-302 in patients with first-line TNBC at a dose of 16 mg/kg on day 1, day 8, and day 15/28. Further prospective trials are required to address this limitation.

In conclusion, ESG401 demonstrated a favorable safety profile, tolerability, and promising preliminary antitumor activity in Chinese patients with advanced solid tumors. These results warrant further investigation in a larger population-based phase 2/3 study and the evaluation of its efficacy in combination with immunotherapy or other targeted therapies.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Fei Ma (drmafei@126.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper and any additional information required to reanalyze the data will be shared by the lead contact upon reasonable request. Specifically, de-identified individual patient-level data such as baseline clinical variables, treatment outcomes including treatment response and survival, and incidence and grade of adverse events for each trial participant will be available upon request. Any additional information regarding individual participants that may result in a breach of patient confidentiality will not be provided. Data sharing statement is provided in Data S1A.
- This publication does not generate new code.
- Any additional information required to reanalyze the data reported in this working paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conceptualization, J.W., Z.T., Y.T., Y.S., Y.W., Q.Z., X.X., X.C., F.Q., and F.M.; methodology, J.W., Z.T., Y.T., Y.S., Y.W., Q.Z., X.X., X.C., F.Q., and F.M.; investigation, J.W., Z.T., Y.T., Y.S., Y.W., F.Q., and F.M.; data curation, J.W., Z.T., and Y.S.; writing – original draft, J.W., Z.T., Y.T., F.Q., and F.M.; writing – review and editing, Y.S., Q.Z., X.X., and X.C.; visualization, X.C.; supervision, F.Q. and F.M.

DECLARATION OF INTERESTS

The following individuals had affiliations with Shanghai Escugen Biotechnology Co., Ltd.: Q.Z., X.X., and X.C. All three individuals were employees of Shanghai Escugen Biotechnology Co., Ltd. All authors declare no personal fees (lectures, presentations, speakers' bureaus, manuscript writing, or educational events) from Shanghai Escugen Biotechnology Co., Ltd. during the conduct of the study.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Biological samples		
Blood samples for pharmacokinetics analysis	This paper	N/A
Formalin-fixed paraffin-embedded archival tumor specimens	This paper	N/A
Chemicals, peptides, and recombinant proteins		
ESG401	Shanghai Escugen Biotechnology Co., Ltd.	N/A
Deposited data		
Patient data	This paper	N/A
Software and algorithms		
WinNonlin Phoenix v8.3	Certara™ Company, USA	https://www.certara.com/
NONMEM 7.4	ICON Development Solutions, USA	https://www.iconplc.com/
SAS software version 9.4	SAS Institute, Cary, NC, USA	https://www.sas.com

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and local institutional review board at the participating site. The study was approved by the ethics committees of all sites. The ethics committee approval number of the leading site, the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, is 21/264–2935. Ethic approvals are provided in Data S1B.

Human subjects

Patients with histologically confirmed solid tumor were enrolled in this study. Demographic information is provided in Table 1. All patients provided written consent prior to enrollment.

Patient eligibility

Eligible patients were male, non-pregnant, non-lactating females aged 18–75 years who had been diagnosed with locally advanced or metastatic solid tumors. The patients were required to have at least one measurable metastatic lesion. Other key criteria included adequate hematological, liver, and renal function, and no known history of anaphylactic reactions to irinotecan or gastrointestinal diseases (such as chronic gastritis, chronic enteritis, or gastric ulcers). Patients without symptomatic central nervous system (CNS) metastases or those not requiring ongoing treatment for CNS metastases, including steroids and antiepileptic agents, were enrolled. The main participant inclusion and exclusion criteria are presented in Table S3. More detailed inclusion and exclusion criteria can be found in the supplemented study protocol in Data S1C.

Subject allocation

The trial reported here is a single-arm study with no control group.

METHOD DETAILS

Study design

The study is an open-label, multiple-dose, dose escalation, and cohort expansion phase I/II trial, consisting of dose-escalation (Phase Ia), and cohort expansion (Phase Ib). In phase I, a dose-escalation study followed a Bayesian Optimal Interval (BOIN) design after an accelerated titration escalation scheme. The estimation of the starting dose and dosing frequency is primarily based on a comprehensive assessment of preclinical research data (see Tables S4 and S5), including pharmacokinetics (PK), cynomolgus monkey toxicology, and reference to the clinical therapeutic doses of SG. The patients enrolled in a dose-escalation study with planned 10 dose levels were administered intravenously at predetermined doses of 2–20 mg/kg once every 3 weeks (Regimen A), or 12–18 mg/kg Day 1,8 and 15 in a 4-week cycle (Regimen B) until disease progression, death, or unacceptable toxicity. Dose escalation continued until the identification of the MTD or the predicted efficacy dose if an MTD is not identified, owing to the paucity of DLTs. Toxicity, including dose-limiting toxicity (DLT) observed in cycle 1, was used to determine the escalation to the next dose level, as described below.

Endpoints

The primary endpoint was the safety and tolerability of ESG401 in Chinese patients with advanced malignant solid tumors. The secondary endpoints included pharmacokinetic parameters and investigator-assessed antitumor effects, including objective response rate (ORR), defined as the proportion of patients with complete response [CR] and partial response [PR] as the best overall response) and disease control rate (DCR, defined as the proportion of patients with CR, PR, or stable disease [SD]) according to the solid tumor efficacy evaluation criteria, that is, Response Evaluation Criteria in Solid Tumors (RECIST version 1.1),[32] duration of response (DOR), and progression-free survival (PFS).

Pharmacokinetic and pharmacodynamic evaluations

Blood samples were collected from all the patients for PK analysis of intact ADC, total antibodies, and free SN-38. Non-compartmental analysis was conducted using WinNonlin Phoenix (version 8.3; Pharsight, Certara Company, USA). PK parameters, including C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, CL, and $T_{1/2}$, were determined.

A pharmacokinetic/pharmacodynamic (PK/PD) model was developed to support optimal dose selection. Following a graphical exposure-response (E-R) analysis for selected PD (efficacy/safety endpoints), a linear or nonlinear model was developed to characterize PD in relation to the exposure variable.

Safety assessments

Safety assessments were performed at all visits to the study center and throughout the study. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0.[33]

Dose-limiting toxicity (DLT) was determined during the DLT observation period (first 21 or 28 days). DLT was defined as grade 4 neutropenia lasting $\geq$5 days, grade $\geq$3 febrile neutropenia, grade 3 neutropenic infection, grade 3 thrombocytopenia with bleeding or requiring platelet transfusion, grade 4 (life-threatening) anemia, any grade $\geq$4 non-hematologic toxicity, grade 3 toxicities of any duration except for laboratory abnormalities with no clinical significance, diarrhea, nausea, vomiting, or rash, which improved to grade 2 or less severity within 3 days of the institution of supportive care, or grade $\geq$2 non-hematological toxic effects judged as dose-limiting by the investigator.

QUANTIFICATION AND STATISTICAL ANALYSIS

All statistical analyses were performed using descriptive statistics. All safety, tolerance, PK, and antitumor data from each dose group were tabulated and summarized according to the statistical analysis plan (see Data S1D). The response rate and exact 95% confidence intervals were calculated using the Clopper–Pearson method. PFS was summarized using the Kaplan-Meier method. All data processing, summaries, and analyses were performed using Statistical Analysis System (SAS) version 9.4.

Other supplementary information

Additional supplemental information includes the comparison of drug design (Table S1), eligibility criteria (Table S3), the structure of ESG401 (Figure S1), and the confirmation file from the Chinese regulatory authority's agreement on the phase 3 study of ESG401 (see Data S1E).

ADDITIONAL RESOURCES

This study is registered with ClinicalTrials.gov, NCT04892342.