



Farletuzumab ecteribulin, a folate receptor alpha (FR α) antibody-drug conjugate, in select advanced cancers: An open-label, multicenter, phase 1/2 dose-finding study

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HIGHLIGHTS

- Treatment with fractionated doses of FZEC reduced the risk of ILD/pneumonitis.
- The onset of ILD/pneumonitis with FZEC treatment may be delayed with steroid use.
- Dose-Optimization-part B will test additional FZEC doses/concomitant steroid use.

ARTICLE INFO

Article history:

Received 12 June 2026

Received in revised form 28 August 2026

Accepted 30 August 2026

Available online xxxx

ABSTRACT

Background. In this phase 1/2 study, we assessed the safety/antitumor activity of farletuzumab ecteribulin (FZEC), a folate receptor alpha (FR α)-targeting antibody-drug conjugate, in patients with pretreated solid tumors.

Methods. Patients aged ≥ 18 years with measurable disease (per RECIST v1.1) were included. Patients with ovarian cancer (OC), endometrial cancer (EC), TNBC, and NSCLC were included in Dose-Escalation (0.9 mg/kg and

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Keywords:

FZEC
ADC
Solid tumors
Folate receptor alpha (FR α)

1.2 mg/kg IV Q3W). Patients with OC/EC were included for Dose-Confirmation (25 mg/m² and 33 mg/m² IV Q3W) and Dose-Optimization-part-A (8 mg/m² D1/D8/D15, 12 mg/m² D1/D8; 25 mg/m² D1 + steroid IV Q3W).

Results. Eighty-nine patients were enrolled (median age: 67.0 years); most (88.7%) patients with OC and 50.0% patients with EC received ≥ 2 previous anticancer regimens. In Dose-Escalation ($n = 25$), interstitial lung disease (ILD)/pneumonitis occurred in 40% of patients. The dosing methodology was amended to body surface area-based dosing in subsequent study parts as an ILD/pneumonitis-mitigation strategy. In Dose-Confirmation ($n = 24$), 33.3% of patients experienced ILD/pneumonitis. In the 25 mg/m² cohort, all ILD/pneumonitis events were grade-1/2. Evaluation of the 33 mg/m² dose was discontinued due to observed ILD/pneumonitis. Dose equivalents of 25 mg/m² were further evaluated in Dose-Optimization-part-A, with steroids/fractionated dosing (to mitigate ILD/pneumonitis). Patients receiving 8 mg/m² D1/D8/D15 experienced no ILD/pneumonitis and achieved more responses versus other regimens, but the subgroup sizes were small. With steroids, incidence of ILD/pneumonitis was similar, but onset appeared delayed.

Conclusions. Fractionated doses of FZEC reduced the risk of ILD/pneumonitis and showed preliminary antitumor activity. Dose-Optimization-part-B will test additional FZEC fractionated doses (alone and in combination with lenvatinib) and concomitant steroid use.

Clinical Trial Registration #: NCT04300556.

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1. Introduction

Ovarian (OC) and endometrial (EC) cancers represent major global health challenges, with >700,000 new cases (EC: 420,368; OC: 324,603) and >300,000 deaths (EC: 97,723; OC: 206,956) reported worldwide in 2022 [1,2]. The incidence and mortality associated with these cancers are predicted to increase by >60% by 2050 [1,2]. Despite treatment improvements, a critical unmet need exists for more effective, personalized options, especially for advanced/recurrent disease.

Folate receptor alpha (FR α) is a cell-surface protein overexpressed in OC (75 to 90%) [3,4] and EC (20 to 50%), making it an attractive target for cancer therapy. The research landscape of FR α -targeting antibody-drug conjugates (ADCs) in OC and EC is evolving [5,6].

FR α -targeting ADCs have established their role in treatment of OC with the approval of mirvetuximab soravtansine by the US Food and Drug Administration and the European Medicines Agency [7,8], which demonstrated significant benefit in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) compared with chemotherapy [9]; however, approvals are limited to a set of higher FR α -expressing cancers. A pipeline of next-generation FR α ADCs is emerging for OC with promising candidates like farletuzumab ecteribulin (FZEC, formerly MORAb-202), sofetabart mipitecan, BAT8006, torvutatug samrotecan, and rinatabart sesutecan [10–15]. These ADCs are in clinical development in earlier lines of therapy or in combination (with bevacizumab or immune checkpoint inhibitors), and in other gynecological cancers including serous endometrial cancer [16–19].

FZEC consists of farletuzumab, a humanized anti-FR α monoclonal antibody, conjugated via a cathepsin-B-cleavable linker (drug-to-antibody ratio: 4:1) to eribulin [20], a potent microtubule dynamics inhibitor approved for metastatic breast cancer and unresectable/metastatic liposarcoma [21–23]. FZEC has shown potent and multiple cytotoxic effects in preclinical studies [24–26] including in FR α -high EC patient-derived xenograft models [27]. FZEC kills FR α -positive cancer cells directly, induces a bystander cytotoxic effect on neighboring tumor cells, and exerts noncytotoxic bystander effects within the tumor microenvironment, further enhancing its antitumor activity [24–26].

In a phase 1 Study-101 (NCT03386942) of FR α -positive solid tumors in Japan, FZEC demonstrated antitumor activity across multiple solid tumors. However, interstitial lung disease (ILD) was identified as an adverse event of special interest (AESI), with 5 of 22 patients (23%)

experiencing ILD related to FZEC in the Dose-Escalation-part. In the Dose-Expansion-part, patients with platinum-resistant OC (PROC) received FZEC at 0.9 mg/kg ($n = 24$) and 1.2 mg/kg ($n = 21$) doses; 1 patient had complete response (0.9 mg/kg group), and responses were seen with both doses. The most common treatment-emergent adverse event (TEAE) was ILD/pneumonitis in the 0.9 mg/kg ($n = 9$; 37.5%) and 1.2 mg/kg ($n = 14$; 66.7%) groups, and most events were grade-1 or –2 [28]. Among patients with ILD/pneumonitis in the 0.9 mg/kg group ($n = 9$), 1 patient died due to a treatment-related lung disorder, and 4 patients (44.4%) showed improvement with corticosteroids and could resume at a lower dose. In the 1.2 mg/kg group ($n = 14$), 2 patients (14.3%) could resume FZEC without corticosteroid treatment after dose interruption, and 9 patients (64.3%) had improvement in ILD/pneumonitis with corticosteroids and were able to resume FZEC [10].

Here, we report results of the Dose-Escalation-part, Dose-Confirmation-part, and Dose-Optimization-part-A of the phase 1/2 study of FZEC (NCT04300556) from sites across the United States, France, Spain, and the United Kingdom to assess safety, tolerability, and antitumor activity, and to inform dose regimen(s) for further evaluation.

2. Methods

2.1. Study design

This multicenter, open-label, phase 1/2 study evaluated the safety, tolerability, and preliminary efficacy of FZEC. This report describes the following parts of the study: Dose-Escalation, Dose-Confirmation, Dose-Optimization-part-A (Fig. 1).

In Dose-Escalation, we assessed the safety and tolerability of FZEC to determine the recommended phase 2 dose (RP2D) across EC, OC, non-small cell lung cancer (NSCLC), and triple-negative breast cancer (TNBC). The RP2D was to be determined based on integrated assessment of safety, efficacy, pharmacokinetic, and any pharmacodynamic data. Patients were accrued using a rolling 6 design [29]. FZEC was administered IV Q3W (on day 1 [D1]), infused over ≥ 60 min in cycle 1 (C1) and >30 min in subsequent cycles if no infusion-related reactions were observed. The 2 dose regimens examined in this part were 0.9 mg/kg and 1.2 mg/kg; these doses were selected based on data from the previous phase 1 study (i.e., body weight-based dosing) [10].

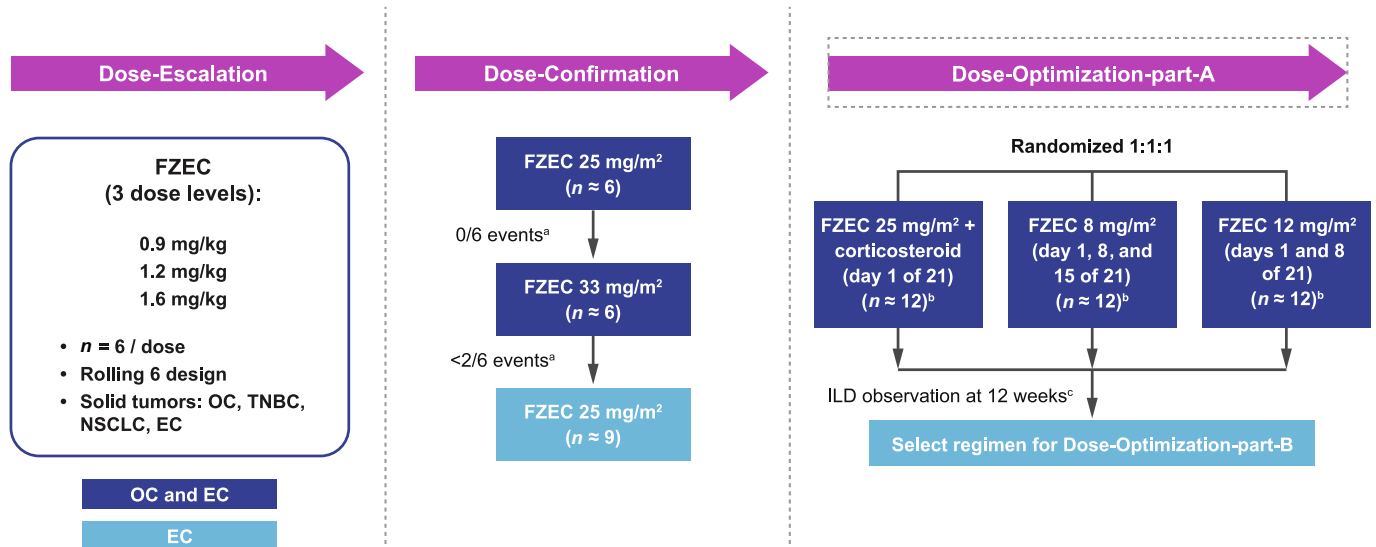


Fig. 1. Study design.

The 1.6 mg/kg dose level was not tested in the Dose-Escalation-part of the study. The dosing cohorts for Dose-Confirmation were 33 mg/m² (exposure comparable to 0.9 mg/kg) and 25 mg/m² (exposure comparable to 0.68 mg/kg).

^a Events: grade ≥ 3 ILD.

^b Patients were randomized to 3 arms targeting approximately 12 patients in each arm, with allowance for either slightly more or less for operational flexibility; 40 patients were enrolled. ^c Enrollment in any cohort stopped if ≥ 3 out of 6 enrolled patients developed ILD/pneumonitis (any grade); a cohort could not be selected for further evaluation in part B if $\geq 4/12$ patients developed ILD/pneumonitis (any grade). Dose resumption after ILD/pneumonitis = 17 mg/m² every 21 days.

The 3 dose cohorts in Dose-Optimization-part-A were equivalent to 25 mg/m² (administered on day 1 + steroid) ($n = 13$), 8 mg/m² (administered on days 1/8/15) ($n = 14$) and 12 mg/m² (administered on days 1/8) ($n = 13$).

EC, endometrial cancer; FZEC, farletuzumab ecteribulin; ILD, interstitial lung disease; m, patients with both baseline and at least 1 postbaseline target lesion assessment; NSCLC, non-small cell lung cancer; OC, ovarian cancer; TNBC, triple-negative breast cancer.

Pharmacokinetic and exposure-response analyses suggested patients with higher body weight had higher FZEC exposure and increased ILD risk, so dosing was changed to body surface area (BSA)-based dosing to reduce excessive exposure [30]. Following cases of ILD/pneumonitis in the Dose-Escalation-part, mitigation measures, including lower doses of FZEC, BSA-based dosing, additional pulmonary eligibility criteria, dose fractionation, and concomitant prophylactic corticosteroid administration, were updated as data accumulated during the study. Management of ILD/pneumonitis is detailed in **Supplementary Table 1**.

In Dose-Confirmation, we evaluated 25 mg/m² and 33 mg/m² Q3W (IV infusion on D1), corresponding to approximately 0.68 mg/kg and 0.9 mg/kg, respectively, in patients with OC or EC.

In Dose-Optimization-part-A, we evaluated alternative regimens intended to reduce ILD/pneumonitis while preserving exposure at approximately the 25 mg/m² Q3W level, which had shown preliminary activity with acceptable tolerability. Regimens included 8 mg/m² D1/D8/D15, 12 mg/m² D1/D8, and 25 mg/m² D1 plus a 3-day oral corticosteroid course beginning on D8 of each 21-day cycle in patients with OC or EC. Corticosteroids were employed in Dose-Optimization-part-A, as they are recommended treatment for drug-induced ILD/pneumonitis (including ADC-related) [31,32] and have previously worked effectively in managing ILD/pneumonitis in patients treated with FZEC [10]. Data from Dose-Optimization-part-A further informed evaluations in part-B (ongoing).

2.2. Patients

2.2.1. Inclusion/exclusion criteria

Patients aged ≥ 18 years with select solid tumors and measurable disease were included. Patients with certain tumor histologies or platinum-refractory OC were excluded. The complete list of inclusion/exclusion criteria is included in the **Appendix**.

2.3. Endpoints and study assessments

The primary endpoints were to determine the RP2D of FZEC, evaluate safety, and assess preliminary ORR based on investigator assessment.

Secondary endpoints included evaluating the duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR), PFS, and OS across all study parts. Furthermore, secondary endpoints involved determining the pharmacokinetic profile of FZEC and exploring the relationship between FR α -expression levels in tumor tissue and clinical outcomes.

Tumor response was assessed using CT/MRI scans according to RECIST v1.1. Scans were performed at screening, then Q6W for the first 24 weeks, and subsequently Q12W, following C1D1. To monitor for ILD/pneumonitis, chest CT scans were conducted before dosing and Q6W thereafter.

Safety was evaluated by monitoring and recording all adverse events (AEs), serious AEs, and AESIs (definitions and additional details regarding safety and pharmacokinetic sampling are in the **Appendix**).

Data on the known mutation status of patients were collected (if available). Tumor tissue was required for FR α -expression analysis by central immunohistochemistry (IHC) (**Appendix**); no minimum FR α -expression percentage was required.

2.4. Statistical methods

Best overall response (BOR), ORR, DCR, and CBR were summarized with the corresponding Clopper and Pearson exact 2-sided 95% CIs. Both complete response (CR) and partial response (PR) were confirmed at a subsequent tumor assessment conducted ≥ 4 weeks later.

Medians of DOR, PFS, and OS were estimated using the Kaplan-Meier method. CIs for medians were calculated using a generalized Brookmeyer and Crowley [33] method.

Table 1
Patient and disease characteristics.

Category	Dose-Escalation		Dose-Confirmation		Dose-Optimization-Part-A			Total (N = 89)
	All Patients							
	0.9 mg/kg (n = 13)	1.2 mg/kg (n = 12)	25 mg/m ² (n = 17)	33 mg/m ² (n = 7)	25 mg/m ² D1 + steroid (n = 13)	8 mg/m ² D1/D8/D15 (n = 14)	12 mg/m ² D1/D8 (n = 13)	
Median age, years (range)	66.0 (41–73)	69.5 (53–77)	71.0 (40–85)	72.0 (55–79)	67.0 (45–71)	59.5 (35–81)	66.0 (39–75)	67.0 (35–85)
ECOG PS, n (%)								
0	7 (53.8)	4 (33.3)	12 (70.6)	4 (57.1)	6 (46.2)	7 (50.0)	8 (61.5)	48 (53.9)
1	6 (46.2)	8 (66.7)	5 (29.4)	3 (42.9)	7 (53.8)	7 (50.0)	5 (38.5)	41 (46.1)
Tumor type								
TNBC	1 (7.7)	0	0	0	0	0	0	1 (1.1)
NSCLC	1 (7.7)	0	0	0	0	0	0	1 (1.1)
OC ^a	10 (76.9)	10 (83.3)	6 (35.3)	1 (14.3)	10 (76.9)	10 (71.4)	6 (46.2)	53 (59.6)
High-grade serous carcinoma	4 (30.8)	3 (25.0)	5 (29.4)	1 (100.0)	9 (69.2)	10 (71.4)	6 (46.2)	38 (71.7)
Clear-cell carcinoma	0	0	0	0	1 (10.0)	0	0	1 (1.9)
Mucinous carcinoma	0	0	1 (16.7)	0	0	0	0	1 (1.9)
Metastatic papillary serous carcinoma	0	1 (10.0)	0	0	0	0	0	1 (1.9)
EC ^a	1 (7.7)	2 (16.7)	11 (64.7)	6 (85.7)	3 (23.1)	4 (28.6)	7 (53.8)	34 (38.2)
Endometrioid	1 (100)	0	4 (36.4)	2 (33.3)	2 (66.7)	3 (75.0)	3 (42.9)	15 (44.1)
Serous	0	0	4 (36.4)	1 (16.7)	1 (33.3)	1 (25.0)	1 (14.3)	8 (23.5)
Papillary serous	0	1 (50.0)	0	0	0	0	1 (14.3)	2 (5.9)
Clear cell	0	1 (50.0)	1 (9.1)	0	0	0	1 (14.3)	3 (8.8)
Carcinosarcoma	0	0	1 (9.1)	1 (16.7)	0	0	0	2 (5.9)
Patients with OC								
Category	0.9 mg/kg (n = 10)	1.2 mg/kg (n = 10)	25 mg/m ² (n = 6)	33 mg/m ² (n = 1)	25 mg/m ² D1 + steroid (n = 10)	8 mg/m ² D1/D8/D15 (n = 10)	12 mg/m ² D1/D8 (n = 6)	Total (n = 53)
Median age, years (range)	66.5 (41–71)	69.5 (53–74)	51.0 (40–85)	79.0 (79–79)	67.5 (45–71)	58.5 (35–73)	67.0 (39–75)	65.0 (35–85)
ECOG PS, n (%)								
0	6 (60.0)	4 (40.0)	5 (83.3)	1 (100)	4 (40.0)	6 (60.0)	3 (50.0)	29 (54.7)
1	4 (40.0)	6 (60.0)	1 (16.7)	0 (0.0)	6 (60.0)	4 (40.0)	3 (50.0)	24 (45.3)
FRα-expression level, TPS ^a								
n	9	10	6	1	10	10	6	52
≥75, n (%)	3 (30.0)	6 (60.0)	2 (33.3)	0	7 (70.0)	7 (70.0)	5 (83.3)	30 (56.6)
25–74, n (%)	5 (50.0)	4 (40.0)	3 (50.0)	0	2 (20.0)	1 (10.0)	1 (16.7)	16 (30.2)
5–24, n (%)	1 (10.0)	0	0	0	0	1 (10.0)	0	2 (3.8)
<5, n (%)	0	0	1 (16.7)	1 (100)	1 (10.0)	1 (10.0)	0	4 (7.5)
Previous systemic anticancer therapy, n (%)								
1	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	1 (10.0)	3 (50.0)	6 (11.3)
2	2 (20.0)	2 (20.0)	4 (66.7)	1 (100)	6 (60.0)	7 (70.0)	1 (16.7)	23 (43.4)
3	3 (30.0)	3 (30.0)	2 (33.3)	0 (0.0)	3 (30.0)	2 (20.0)	2 (33.3)	15 (28.3)
≥4	4 (40.0)	5 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (17.0)
Patients with EC								
Category	0.9 mg/kg (n = 1)	1.2 mg/kg (n = 2)	25 mg/m ² (n = 11)	33 mg/m ² (n = 6)	25 mg/m ² D1 + steroid (n = 3)	8 mg/m ² D1/D8/D15 (n = 4)	12 mg/m ² D1/D8 (n = 7)	Total (n = 34)
Median age, years (range)	66.0 (66–66)	68.5 (60–77)	72.0 (61–77)	71.5 (55–79)	61.0 (45–70)	73.0 (64–81)	65.0 (46–70)	70.0 (45–81)
ECOG PS, (%)								
0	0 (0.0)	0 (0.0)	7 (63.6)	3 (50.0)	2 (66.7)	1 (25.0)	5 (71.4)	18 (52.9)
1	1 (100)	2 (100)	4 (36.4)	3 (50.0)	1 (33.3)	3 (75.0)	2 (28.6)	16 (47.1)

FR α -expression level, TPS ^a								
<i>n</i>	1	2	10	6	3	4	7	33
≥75, <i>n</i> (%)	0	0	2 (18.2)	0	2 (66.7)	2 (50.0)	0	6 (17.6)
25–74, <i>n</i> (%)	0	1 (50.0)	4 (36.4)	5 (83.3)	0	2 (50.0)	4 (57.1)	16 (47.1)
5–24, <i>n</i> (%)	0	0	1 (9.1)	0	1 (33.3)	0	3 (42.9)	5 (14.7)
<5, <i>n</i> (%)	1 (100)	1 (50.0)	3 (27.3)	1 (16.7)	0	0	0	6 (17.6)
Previous systemic anticancer therapy, <i>n</i> (%) ^b								
1	0 (0.0)	1 (50.0)	4 (36.4)	4 (66.7)	2 (66.7)	2 (50.0)	4 (57.1)	17 (50.0)
2	1 (100)	1 (50.0)	7 (63.6)	2 (33.3)	1 (33.3)	2 (50.0)	3 (42.9)	17 (50.0)

EC, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; FR α , folate receptor alpha; FZEC, farletuzumab ecteribulin; FR α TPS, FR α tumor proportion score (1+, 2+, 3+); OC, ovarian cancer.

^a The percentages for subtypes of tumors are based on the total number of patients with OC or EC.

^b All prior lines were counted here, including those that were not counted as a prior line of treatment for eligibility (as per protocol eligibility criteria) so that the study team could assess prior treatment in view of any impact on the safety and efficacy profile of FZEC.

For patients from the Dose-Escalation-part and a subset of patients from the Dose-Confirmation-part, FZEC pharmacokinetic parameters were determined using noncompartmental analyses. Serum concentration data of FZEC for Dose-Optimization-part-A were summarized.

3. Results

3.1. Patients

Between August 6, 2020, and December 31, 2024 (data cutoff date for this analysis), 89 patients were enrolled in the study, including 25 patients in the Dose-Escalation-part (OC, *n* = 20; EC, *n* = 3; TNBC, *n* = 1; and NSCLC, *n* = 1); 24 patients in the Dose-Confirmation-part (OC, *n* = 7; EC, *n* = 17); and 40 patients in Dose-Optimization-part-A (OC, *n* = 26; EC, *n* = 14). Each patient received at least 1 dose of FZEC.

Baseline disease history and characteristics for each study part are presented in Table 1. Overall, the median age of patients was 67.0 years (range 35–85 years); all patients had an ECOG PS of 0 (*n* = 48, 53.9%) or 1 (*n* = 41, 46.1%). Forty-seven (88.7%) patients with OC and 17 (50.0%) of patients with EC received ≥2 previous anticancer regimens. Further details are included in the Appendix (under Results and in Supplementary Tables 2, 3).

3.2. Safety

3.2.1. Dose-Escalation

All patients in the Dose-Escalation-part (*n* = 25) experienced TEAEs (Supplementary Table 4). Ten patients (40.0%) experienced ILD/pneumonitis episodes (Table 2). In the 0.9 mg/kg cohort (*n* = 13), a total of 7 ILD/pneumonitis episodes occurred in 5 patients (38.5%). Most patients (*n* = 2 each) had episodes of worst severity grade-2 or grade-3 (Table 2). In the 1.2 mg/kg cohort (*n* = 12), a total of 6 ILD/pneumonitis episodes occurred in 5 patients (41.7%). Two patients had episodes of worst severity grade-1 and one patient each had episodes of grades-2, -3, and -4. No grade-5 ILD/pneumonitis was noted in either cohort; however, the patient with grade-4 ILD/pneumonitis died due to respiratory failure (not reported as ILD/pneumonitis by site) outside the 28-day AE-reporting period. ILD/pneumonitis events were managed with dose modifications; further details are in Table 2.

Eighteen (72.0%) patients experienced ≥1 treatment-related adverse event (TRAE); 6 (24.0%) experienced grade ≥3 TRAEs (Supplementary Table 5). There were no fatal TRAEs. The most frequent TRAE (Table 3) was fatigue (*n* = 7, 28%). TRAEs led to discontinuation of FZEC in 3 (12.0%) patients (all in the 1.2 mg/kg cohort): grade-3 pneumonitis (*n* = 1), grade-3 nausea, vomiting, and fatigue (*n* = 1); grade-4 ILD/pneumonitis (*n* = 1) (Supplementary Table 5).

One (8.3%) patient experienced a dose-limiting toxicity (grade-3 fatigue) related to FZEC 1.2 mg/kg, and FZEC treatment was withdrawn.

3.2.2. Dose-Confirmation

In the Dose-Confirmation-part (*n* = 24), most patients (*n* = 23; 95.8%) experienced TEAEs (Supplementary Table 4). Eight patients (33.3%) experienced ILD/pneumonitis episodes. In the 25 mg/m² cohort (*n* = 17), a total of 4 ILD/pneumonitis episodes occurred in 4 patients (23.5%). Most patients (*n* = 3) had episodes of worst severity grade-1 (Table 2). In the 33 mg/m² cohort (*n* = 7), a total of 4 ILD/pneumonitis episodes occurred in 4 patients (57.1%). Most patients (*n* = 3) had episodes of worst severity grade-1; one patient died due to grade-5 ILD/pneumonitis related to treatment (after the 28-day period since last dose/resolution for TRAE categorization). Enrollment in the 33 mg/m² cohort was stopped at 7 patients, due to the observed incidence of severe ILD. ILD/pneumonitis events were managed with dose modifications; further details are in Table 2.

Twenty-one (87.5%) patients experienced at least 1 TRAE and 4 (16.7%) experienced grade ≥3 TRAEs (Supplementary Table 5). The most frequent TRAE (Table 3) was fatigue (25%). A TRAE of grade-3 ILD/pneumonitis led to FZEC discontinuation in 1 patient (4.2%, in the 33 mg/m² cohort) (Supplementary Table 5).

3.2.3. Dose-Optimization-part-A

In Dose-Optimization-part-A (*n* = 40), most patients (*n* = 39; 97.5%) experienced TEAEs (Supplementary Table 4). Four patients had ILD/pneumonitis (10.0%) and all events were grade-1 (Table 2). ILD/pneumonitis occurred in 3 patients (3 episodes) in the 25 mg/m² D1 + steroid cohort, and the median time to onset was 24.0 weeks. ILD/pneumonitis occurred in 1 patient (1 episode) in the 12 mg/m² D1/D8 cohort and the time to onset of ILD/pneumonitis was 7.1 weeks. No ILD/pneumonitis events were observed in the 8 mg/m² D1/D8/D15 cohort. ILD/pneumonitis events were managed with dose modifications; further details are in Table 2.

Thirty-two (80.0%) patients experienced at least 1 TRAE; no patient experienced a grade ≥3 TRAE (Supplementary Table 5). The most frequent TRAE was asthenia (20.0%) (Table 3). TRAEs led to FZEC discontinuation in 2 (5%) patients (1 patient with grade-1 pneumonitis, and 1 patient with grade-1 ILD, both in the 25 mg/m² D1 + steroid cohort) (Supplementary Table 5).

In the presented parts, the RP2D was not determined, and further dose optimization is being pursued in the ongoing part B of the study.

3.3. Antitumor activity

3.3.1. Ovarian cancer cohorts

In Dose-Escalation, among patients with OC, ORR was 20.0% (95% CI: 2.5–55.6; 2 PRs) in the 0.9 mg/kg cohort (*n* = 10) and 10.0% (95% CI: 0.3–44.5; 1 PR) in the 1.2 mg/kg cohort (*n* = 10) (Table 4).

In Dose-Confirmation, ORR was 33.3% (95% CI: 4.3–77.7; 2 PRs) in patients who received 25 mg/m² (*n* = 6) and 0% (95% CI: 0.0–97.5) in the patient who received 33 mg/m² (*n* = 1) (Table 4).

Table 2
ILD/pneumonitis: Incidence, grade, duration, and recovery.

Category	Dose-Escalation		Dose-Confirmation		Dose-Optimization-Part-A			Total (N = 89)
	0.9 mg/kg (n = 13)	1.2 mg/kg (n = 12)	25 mg/m ² (n = 17)	33 mg/m ² (n = 7)	25 mg/m ² D1 + Steroid (n = 13)	8 mg/m ² D1/D8/D15 (n = 14)	12 mg/m ² D1/D8 (n = 13)	
Number of patients having ILD/pneumonitis, n (%)	5 (38.5)	5 (41.7)	4 (23.5)	4 (57.1)	3 (23.1)	0 (0.0)	1 (7.7)	22 (24.7)
Total number of episodes per cohort	7	6	4	4	3	0	1	25
Toxicity grade ≥3 at onset of first ILD/pneumonitis, n (%)	1 (7.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)
Worst toxicity grade, n (%)								
Grade 1	1 (7.7)	2 (16.7)	3 (17.6)	3 (42.9)	3 (23.1)	0 (0.0)	1 (7.7)	13 (14.6)
Grade 2	2 (15.4)	1 (8.3)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.5)
Grade 3	2 (15.4)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)
Grade 4	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Grade 5	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)
Median time to onset of first ILD/pneumonitis (weeks)	5.9 (3–24)	11.7 (4–50)	11.4 (6–36)	6.9 (5–12)	24.0 (5–25)	–	7.1 (7–7)	8.6 (3–50)
Median ILD/pneumonitis duration (days)	NE (46.0, NE)	NE (43.0, NE)	63.0 (43.0, NE)	429.0 (65.0, NE)	NE (85.0, NE)	–	91.0 (NE, NE)	429.0 (70.0, NE)
Recovered/resolved ^b	2 (28.6)	1 (16.7)	3 (75.0)	2 (50.0)	1 (33.3)	0 (0.0)	1 (100)	10 (40.0)
Number of patients taking steroids due to ILD/pneumonitis ^a , n (%)								
Yes	4 (80.0)	4 (80.0)	4 (100)	3 (75.0)	3 (100)	0 (0.0)	1 (100)	19 (86.4)
No	1 (20.0)	1 (20.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.6)
Duration of steroid use (days)								
n ^b	4	4	4	3	3	0	1	19
Median (95% CI)	NE (6.0, NE)	NE (3.0, NE)	43.0 (35.0, NE)	NE (42.0, NE)	NE (32.0, NE)		50.0 (NE, NE)	50.0 (35.0, NE)
FZEC withdrawn ^b	1 (14.3)	2 (33.3)	0 (0.0)	1 (25.0)	2 (66.7)	0 (0.0)	0 (0.0)	6 (24.0)
FZEC dose reduced ^b	1 (14.3)	1 (16.7)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (100)	4 (16.0)
FZEC interrupted ^b	2 (28.6)	0 (0.0)	4 (100)	2 (50.0)	1 (33.3)	0 (0.0)	0 (0.0)	9 (36.0)

CI, confidence interval; D, day; FZEC, farletuzumab ecteribulin; ILD, interstitial lung disease; group term including acute respiratory distress syndrome, ILD, pneumonitis, and pulmonary fibrosis; NE, not estimable.

^a Total number of patients having ILD/pneumonitis was used as denominator.

^b Total number of episodes of ILD was used as denominator.

In Dose-Optimization-part-A, ORR was 0% (95% CI: 0.0–30.8) in the 25 mg/m² D1 + steroid cohort (n = 10), 10.0% (95% CI: 0.3–44.5; 1 PR) in the 8 mg/m² D1/D8/D15 cohort (n = 10), and 0% (95% CI: 0.0–45.9) in the 12 mg/m² D1/D8 cohort (n = 6) (Table 4).

3.3.2. Endometrial cancer cohorts

In Dose-Escalation, among patients with EC, ORR was 0% (95% CI: 0.0–97.5) in the FZEC 0.9 mg/kg cohort (n = 1) and 50.0% (95% CI: 1.3–98.7; notably, 1 CR) in the 1.2 mg/kg cohort (n = 2) (Table 4).

In Dose-Confirmation, ORR was 9.1% (95% CI: 0.2–41.3; 1 PR) in patients who received 25 mg/m² (n = 11) and 0% (95% CI: 0.0–45.9) in patients who received 33 mg/m² (n = 6) (Table 4).

In Dose-Optimization-part-A, ORR was 0% (95% CI: 0.0–70.8) in the 25 mg/m² D1 + steroid cohort (n = 3), 50.0% (95% CI: 6.8–93.2; 1 CR and 1 PR) in the 8 mg/m² D1/D8/D15 cohort (n = 4), and 0% (95% CI: 0.0–41.0) in the 12 mg/m² D1/D8 cohort (n = 7) (Table 4).

Details regarding PFS, OS, and DOR for both OC and EC are included in Table 4. Percentage change in sum of diameters of target lesions from baseline to postbaseline nadir is shown in Supplementary Fig. 1.

3.4. Pharmacokinetics

Pharmacokinetic data were evaluable in 25 patients (n = 13 for 0.9 mg/kg, n = 12 for 1.2 mg/kg) in Dose-Escalation and in 7 patients each in the 25 mg/m² (exposure comparable to 0.68 mg/kg) and 33 mg/m² (exposure comparable to 0.9 mg/kg) cohorts of Dose-Confirmation (Table 5). Following IV infusion Q3W of FZEC, maximum serum concentrations (C_{max}) of FZEC were observed near the end of infusion, occurring between 0.60 and 2.00 h (median) after infusion initiation in Dose-Escalation and approximately 1.02–1.72 h after initiation of infusion in Dose-Confirmation. Both C_{max} and AUC values increased with dose. Mean half-life was approximately 5–7 days in Dose-Escalation and 6–8 days in Dose-Confirmation. Clearance was consistent between doses (~20 mL/h) in Dose-Escalation, and the apparent volume

of distribution at steady state (V_{ss}) for FZEC was ~4 L, suggesting that distribution was limited to the vascular compartment. Similar results were seen in Dose-Confirmation. Accumulation ratio (R_{ss}) was close to 1 in both study parts, and the accumulation was minimal after repeated dosing.

Data regarding pharmacokinetics for Dose-Optimization-part-A are included in the Appendix (under Results).

3.5. FRA expression and tumor response: Dose-Escalation, Confirmation, and Optimization-part-A

Patients with OC had a median FRα expression of 80% (tumor proportion score [TPS; i.e., the percentage of tumor cells showing positive IHC staining at all intensity levels 1+, 2+, and 3+]). Patients with EC had a median FRα expression of 40% (TPS). No consistent relationships were noted between expression and antitumor activity (Supplementary Tables 6 and 7).

4. Discussion and conclusions

In this phase 1/2 study, we assessed the safety and preliminary anti-tumor activity of FZEC in patients with pretreated cancers, including OC and EC, across the Dose-Escalation-part, Dose-Confirmation-part, and Dose-Optimization-part-A. Prior preclinical and early clinical data of FZEC have shown promise in both OC and EC [10,20,24–27]. Safety and optimization of the FZEC dose were the main objectives of this study as evidenced by the changes made to the dose, dose methodology, and regimens during parts of this study based on accumulated data.

Given that ADCs have been associated with ILD/pneumonitis [34], and specifically with FZEC in the first-in-human Study-101 [10], this was an AESI in the current study. The high incidence and severity of ILD/pneumonitis across cohorts (incidence: 40%; grade ≥3: 16%) in the Dose-Escalation-part of the study necessitated mitigation measures. A separate modeling and pharmacokinetic analysis showed that BSA-based dosing may reduce excessive exposure associated with body

Table 3

TRAEs occurring in >10% of patients in any group.

Category	Dose-Escalation		Dose-Confirmation		Dose-Optimization-Part-A			Total (N = 89)	
	All Patients ^a								
	0.9 mg/kg (n = 13)	1.2 mg/kg (n = 12)	25 mg/m ² (n = 17)	33 mg/m ² (n = 7)	25 mg/m ² D1 + steroid (n = 13)	8 mg/m ² D1/D8/D15 (n = 14)	12 mg/m ² D1/D8 (n = 13)		
TRAEs, n (%)	9 (69.2)	9 (75.0)	15 (88.2)	6 (85.7)	9 (69.2)	12 (85.7)	11 (84.6)	71 (79.8)	
General disorders and administration site conditions									
Fatigue	4 (30.8)	3 (25.0)	4 (23.5)	2 (28.6)	0 (0.0)	2 (14.3)	4 (30.8)	19 (21.3)	
Asthenia	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	4 (30.8)	2 (14.3)	2 (15.4)	9 (10.1)	
Noncardiac chest pain	1 (7.7)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.4)	
Blood and lymphatic system disorders									
Anemia	3 (23.1)	1 (8.3)	2 (11.8)	0 (0.0)	2 (15.4)	2 (14.3)	3 (23.1)	13 (14.6)	
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (23.1)	3 (3.4)	
Gastrointestinal disorders									
Nausea	1 (7.7)	3 (25.0)	3 (17.6)	0 (0.0)	1 (7.7)	2 (14.3)	1 (7.7)	11 (12.4)	
Diarrhea	1 (7.7)	2 (16.7)	3 (17.6)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (7.9)	
Vomiting	1 (7.7)	2 (16.7)	0 (0.0)	0 (0.0)	1 (7.7)	2 (14.3)	1 (7.7)	7 (7.9)	
Constipation	0 (0.0)	1 (8.3)	2 (11.8)	0 (0.0)	0 (0.0)	1 (7.1)	2 (15.4)	6 (6.7)	
Abdominal pain	1 (7.7)	0 (0.0)	1 (5.9)	1 (14.3)	0 (0.0)	0 (0.0)	1 (7.7)	4 (4.5)	
Dyspepsia	0 (0.0)	1 (8.3)	0 (0.0)	1 (14.3)	0 (0.0)	1 (7.1)	1 (7.7)	4 (4.5)	
Metabolism and nutrition disorders									
Decreased appetite	1 (7.7)	5 (41.7)	0 (0.0)	0 (0.0)	1 (7.7)	3 (21.4)	0 (0.0)	10 (11.2)	
Hypertriglyceridemia	1 (7.7)	1 (8.3)	2 (11.8)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.6)	
Hyperglycemia	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	3 (3.4)	
Respiratory, thoracic, and mediastinal disorders									
Pneumonitis ^b	2 (15.4)	2 (16.7)	2 (11.8)	1 (14.3)	2 (15.4)	0 (0.0)	1 (7.7)	10 (11.2)	
Interstitial lung disease ^b	2 (15.4)	2 (16.7)	2 (11.8)	2 (28.6)	1 (7.7)	0 (0.0)	0 (0.0)	9 (10.1)	
Dyspnea	2 (15.4)	3 (25.0)	1 (5.9)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	7 (7.9)	
Cough	1 (7.7)	1 (8.3)	1 (5.9)	0 (0.0)	0 (0.0)	1 (7.1)	2 (15.4)	6 (6.7)	
Hypoxia	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	
Investigations									
Lymphocyte count decreased	3 (23.1)	3 (25.0)	1 (5.9)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (9.0)	
Blood creatinine increased	2 (15.4)	1 (8.3)	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.6)	
Gamma glutamyl transferase increased	1 (7.7)	1 (8.3)	2 (11.8)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	5 (5.6)	
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	1 (5.9)	1 (14.3)	1 (7.7)	0 (0.0)	1 (7.7)	4 (4.5)	
Blood uric acid increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	
Nervous system disorders									
Headache	1 (7.7)	1 (8.3)	1 (5.9)	0 (0.0)	2 (15.4)	0 (0.0)	1 (7.7)	6 (6.7)	
Peripheral sensory neuropathy	2 (15.4)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (15.4)	5 (5.6)	
Musculoskeletal and connective tissue disorders									
Muscle spasms	0 (0.0)	2 (16.7)	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.7)	4 (4.5)	
Vascular disorders									
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	

D, day; TRAE treatment-related adverse event.

^a Patients may be counted in multiple categories.^b Please see Table 2 for further information about ILD/pneumonitis.

weight-based dosing in patients with higher body weights [30]. As a result, the dose methodology was changed to BSA-based dosing in the Dose-Confirmation-part and all subsequent parts. The protocol was updated to include additional pulmonary exclusion criteria, ILD/pneumonitis monitoring/management guidelines/training, and requirements for a pulmonary/radiology on-site study team.

In the Dose-Confirmation-part, the 25 mg/m² Q3W (exposure comparable to 0.68 mg/kg) regimen was considered tolerable; both incidence and severity of ILD/pneumonitis (23.5%, all grade-1/2) were decreased. Preliminary efficacy was also observed with this dosage (overall ORR, 17.6%). The incidence of ILD/pneumonitis in the 33 mg/m² Q3W cohort, however, was higher (57.1%), including 1 treatment-related death that occurred after the 28-day AE-reporting period. Given this, and the lack of efficacy observed in the 33 mg/m² Q3W cohort, evaluation of this dose was discontinued. Based on tolerability of the FZEC 25 mg/m² Q3W, this regimen was evaluated further in Dose-Optimization-part-A, where all cohorts were delivered a dose equivalent to 25 mg/m² Q3W during the study, along with either steroids, or as fractionated dosing (to mitigate ILD/pneumonitis).

Results from Dose-Optimization-part-A showed that fractionation reduced the risk of ILD/pneumonitis. The 8 mg/m² D1/D8/D15 cohort was of particular interest as patients on this regimen showed preliminary antitumor activity with no ILD/pneumonitis events observed,

although this data should be interpreted with caution given the small sample sizes. In this cohort, among patients with OC, 1 patient had a PR and among patients with EC, 1 patient each had a CR and a PR. Additionally, the 25 mg/m² D1 + steroid Q3W cohort showed disease stabilization (67–70% patients had stable disease across EC/OC). The onset of ILD/pneumonitis was also delayed compared with the 12 mg/m² D1/D8 cohort, which may have been influenced by the concomitant prophylactic use of steroids in this cohort.

The safety observed in the 8 mg/m² D1/D8/D15 cohort of Dose-Optimization-part-A aligns with pharmacokinetic analyses in this part of the study. The 8 mg/m² D1/D8/D15 (under equivalent AUC conditions) demonstrated the highest predose serum concentration (C_{trough}) and the lowest serum concentration of FZEC at the end of infusion on D1 (C_{max}), suggesting that C_{max} may be a key factor in predicting ILD/pneumonitis incidence with FZEC, a hypothesis that is being further investigated via modeling studies. The exact way FZEC causes ILD/pneumonitis is not fully understood and other studies involving farletuzumab (in combination with chemotherapy) [35] or eribulin alone [36] have shown very low rates of ILD/pneumonitis (≤5%).

Despite incidence of ILD/pneumonitis in this study, other AEs were manageable, and FZEC was well tolerated. The preliminary antitumor activity and safety profile of patients in Dose-Optimization-part-A who received FZEC 8 mg/m² in a fractionated regimen (D1/D8/D15) in

Table 4

Summary of tumor responses as assessed by investigator per RECIST v1.1.

Category	Dose-Escalation		Dose-Confirmation		Dose-Optimization-Part-A			Total (N = 89)
	All Patients							
	0.9 mg/kg (n = 13)	1.2 mg/kg (n = 12)	25 mg/m ² (n = 17)	33 mg/m ² (n = 7)	25 mg/m ² D1 + steroid (n = 13)	8 mg/m ² D1/D8/D15 (n = 14)	12 mg/m ² D1/D8 (n = 13)	
Best overall response, n (%)								
Complete response	0	1 (8.3)	0	0	0	1 (7.1)	0	2 (2.2)
Partial response	2 (15.4)	1 (8.3)	3 (17.6)	0	0	2 (14.3)	0	8 (9.0)
Stable disease	7 (53.8)	6 (50.0)	9 (52.9)	4 (57.1)	9 (69.2)	6 (42.9)	7 (53.8)	48 (53.9)
Progressive disease	3 (23.1)	2 (16.7)	5 (29.4)	3 (42.9)	4 (30.8)	5 (35.7)	6 (46.2)	28 (31.5)
Unknown/not evaluable	1 (7.7)	2 (16.7)	0	0	0	0	0	3 (3.4)
ORR (CR + PR), n (%), (95% CI) ^a	2 (15.4) (1.9–45.4)	2 (16.7) (2.1–48.4)	3 (17.6) (3.8–43.4)	0 (0.0–41.0)	0 (0.0–24.7)	3 (21.4) (4.7–50.8)	0 (0.0–24.7)	10 (11.2) (5.5–19.7)
DCR (CR + PR + SD), n (%), (95% CI) ^a	9 (69.2) (38.6–90.9)	8 (66.7) (34.9–90.1)	12 (70.6) (44.0–89.7)	4 (57.1) (18.4–90.1)	9 (69.2) (38.6–90.9)	9 (64.3) (35.1–87.2)	7 (53.8) (25.1–80.8)	58 (65.2) (54.3–75.0)
CBR (CR + PR + durable SD), n (%), (95% CI) ^a	3 (23.1) (5.0–53.8)	3 (25.0) (5.5–57.2)	3 (17.6) (3.8–43.4)	0 (0.0–41.0)	3 (23.1) (5.0–53.8)	5 (35.7) (12.8–64.9)	4 (30.8) (9.1–61.4)	21 (23.6) (15.2–33.8)
Median DOR, months, (95% CI) ^b	5.80 (4.67–NE)	8.44 (4.80–NE)	5.32 (3.94–NE)	–	–	NE (2.86–NE)	–	6.13 (2.86–NE)
Median PFS, months, (95% CI)	3.84 (1.41–4.14)	2.89 (1.28–5.55)	3.94 (1.25–4.17)	2.60 (0.72–4.17)	3.84 (1.38–4.21)	2.73 (1.35–6.74)	2.43 (1.35–5.36)	2.76 (2.43–3.94)
Median OS, months, (95% CI)	6.24 (2.69–16.10)	7.79 (1.91–15.61)	16.36 (5.65–NE)	NE (4.40–NE)	NE (5.68–NE)	NE (5.85–NE)	NE (NE–NE)	15.61 (11.04–16.85)
Patients with OC								
Category	0.9 mg/kg (n = 10)	1.2 mg/kg (n = 10)	25 mg/m ² (n = 6)	33 mg/m ² (n = 1)	25 mg/m ² D1 + Steroid (n = 10)	8 mg/m ² D1/D8/D15 (n = 10)	12 mg/m ² D1/D8 (n = 6)	Total (N = 53)
Best overall response, n (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	2 (20.0)	1 (10.0)	2 (33.3)	0	0	1 (10.0)	0	6 (11.3)
Stable disease	5 (50.0)	6 (60.0)	4 (66.7)	1 (100)	7 (70.0)	5 (50.0)	3 (50.0)	31 (58.5)
Durable stable disease	1 (10.0)	1 (10.0)	0	0	2 (20.0)	2 (20.0)	1 (16.7)	7 (13.2)
Progressive disease	2 (20.0)	2 (20.0)	0	0	3 (30.0)	4 (40.0)	3 (50.0)	14 (26.4)
Unknown/not evaluable	1 (10.0)	1 (10.0)	0	0	0	0	0	2 (3.8)
ORR, n (%), (95% CI) ^a	2 (20.0) (2.5–55.6)	1 (10.0) (0.3–44.5)	2 (33.3) (4.3–77.7)	0 (0.0–97.5)	0 (0.0–30.8)	1 (10.0) (0.3–44.5)	0 (0.0–45.9)	6 (11.3) (4.3–23.0)
DCR, n (%), (95% CI) ^a	7 (70.0) (34.8–93.3)	7 (70.0) (34.8–93.3)	6 (100) (54.1–100.0)	1 (100) (2.5–100.0)	7 (70.0) (34.8–93.3)	6 (60.0) (26.2–87.8)	3 (50.0) (11.8–88.2)	37 (69.8) (55.7–81.7)
CBR, n (%), (95% CI) ^a	3 (30.0) (6.7–65.2)	2 (20.0) (2.5–55.6)	2 (33.3) (4.3–77.7)	0 (0.0–97.5)	2 (20.0) (2.5–55.6)	3 (30.0) (6.7–65.2)	1 (16.7) (0.4–64.1)	13 (24.5) (13.8–38.3)
Median DOR, months, (95% CI) ^b	5.80 (4.67–NE)	12.09 (NE–NE)	6.24 (5.32–NE)	–	–	NE (NE–NE)	–	7.05 (4.67–NE)
Median PFS, months, (95% CI)	3.40 (1.28–7.39)	2.89 (1.28–5.55)	4.06 (2.37–NE)	3.75 (NE–NE)	3.30 (1.22–4.21)	2.56 (1.18–6.83)	1.91 (1.18–NE)	2.76 (2.40–4.11)
Median OS, months, (95% CI)	6.13 (1.28–17.22)	11.04 (1.91–15.61)	NE (15.34–NE)	NE (NE–NE)	NE (2.40–NE)	NE (4.47–NE)	NE (NE–NE)	15.61 (7.79–16.85)
Patients with EC								
Category	0.9 mg/kg (n = 1)	1.2 mg/kg (n = 2)	25 mg/m ² (n = 11)	33 mg/m ² (n = 6)	25 mg/m ² D1 + steroid (n = 3)	8 mg/m ² D1/D8/D15 (n = 4)	12 mg/m ² D1/D8 (n = 7)	Total (N = 34)
Best overall response, n (%)								
Complete response	0	1 (50.0)	0	0	0	1 (25.0)	0	2 (5.9)
Partial response	0	0	1 (9.1)	0	0	1 (25.0)	0	2 (5.9)
Stable disease	1 (100)	0	5 (45.5)	3 (50.0)	2 (66.7)	1 (25.0)	4 (57.1)	16 (47.1)
Durable stable disease	0	0	0	0	1 (33.3)	0	3 (42.9)	4 (11.8)
Progressive disease	0	0	5 (45.5)	3 (50.0)	1 (33.3)	1 (25.0)	3 (42.9)	13 (38.2)
Unknown/not evaluable	0	1 (50.0)	0	0	0	0	0	1 (2.9)
ORR, n (%), (95% CI) ^a	0 (0.0–97.5)	1 (50.0) (1.3–98.7)	1 (9.1) (0.2–41.3)	0 (0.0–45.9)	0 (0.0–70.8)	2 (50.0) (6.8–93.2)	0 (0.0–41.0)	4 (11.8) (3.3–27.5)
DCR, n (%), (95% CI) ^a	1 (100) (2.5–100.0)	1 (50.0) (1.3–98.7)	6 (54.5) (23.4–83.3)	3 (50.0) (11.8–88.2)	2 (66.7) (9.4–99.2)	3 (75.0) (19.4–99.4)	4 (57.1) (18.4–90.1)	20 (58.8) (40.7–75.4)
CBR, n (%), (95% CI) ^a	0 (0.0–97.5)	1 (50.0) (1.3–98.7)	1 (9.1) (0.2–41.3)	0 (0.0–45.9)	1 (33.3) (0.8–90.6)	2 (50.0) (6.8–93.2)	3 (42.9) (9.9–81.6)	8 (23.5) (10.7–41.2)
Median DOR, months, (95% CI) ^b	0	4.80 (NE–NE)	3.94 (NE–NE)	–	–	NE (2.86–NE)	–	4.37 (2.86–NE)
Median PFS, months, (95% CI)	3.84 (NE–NE)	3.33 (0.85–NE)	2.73 (1.18–4.21)	1.94 (0.72–NE)	4.04 (1.38–NE)	3.37 (1.35–NE)	2.76 (0.95–5.65)	2.74 (1.38–4.17)
Median OS, months, (95% CI)	16.10 (NE–NE)	3.33 (0.85–NE)	7.03 (4.50–19.52)	NE (4.40–NE)	NE (NE–NE)	NE (7.82–NE)	NE (2.07–NE)	19.52 (7.82–NE)

SD must be ≥5 weeks after first dose. Durable SD is a subset of SD with a duration of SD ≥23 weeks from first dose.

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; EC, endometrial cancer; NE, not evaluable; ORR, objective response rate; OC, ovarian cancer; OS, overall survival; PR, partial response; PD, progressive disease; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

^a 95% CI is constructed using the method of Clopper and Pearson.^b Medians are provided where more than 1 patient was a responder; if only 1 patient was evaluable, duration of response of that patient is provided. Medians are estimated by Kaplan-Meier method, and the 95% CIs are estimated with a generalized Brookmeyer and Crowley method

Table 5
Pharmacokinetic analysis of FZEC: Dose-Escalation and Dose-Confirmation parts.

FZEC	Dose-Escalation				Dose-Confirmation			
	0.9 mg/kg (n = 13)		1.2 mg/kg (n = 12)		25 mg/m ² (n = 7)		33 mg/m ² (n = 7)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2	Cycle 1	Cycle 2
C _{max} (μg/mL) ^a	25.9 (25.2)	28.2 (21.8) ^d	28.8 (25.3)	33.8 (28.1) ^e	14.4 (16.8)	15.8 (19.4)	19.8 (8.25)	22.2 (11.1) ^f
AUC (μg·h/mL) ^{a,b}	2890 (37.9) ^d	3380 (28.5) ^d	3420 (30.9) ^e	3480 (29.3) ^g	2060 (19.5)	2310 (21.2)	2840 (18.5)	3170 (14.3) ^f
T _{max} (h) ^c	1.58 (1.00–5.08)	2.00 (0.50–5.12) ^d	1.62 (1.00–25.27)	0.60 (0.50–4.50) ^e	1.53 (1.07–25.50)	1.50 (0.65–4.50)	1.72 (1.00–3.03)	1.02 (0.57–2.50) ^f
t _{1/2} (day) ^a	5.61 (31.3) ^d	6.55 (24.9) ^d	5.50 (29.1)	5.29 (29.8) ^e	6.59 (22.5)	7.98 (12.9)	7.03 (33.9)	7.11 (24.6) ^f
CL (mL/h) ^a	21.3 (32.8) ^d	17.9 (24.2) ^d	24.4 (36.9) ^e	23.2 (31.7) ^g	21.0 (22.8)	18.7 (28.9)	20.8 (12.7)	19.3 (14.7) ^f
V _{ss} (L) ^a	3.63 (18.6) ^d	3.82 (20.9) ^d	4.29 (24.5) ^e	3.98 (16.5) ^g	4.55 (12.6)	4.76 (30.0)	4.65 (20.9)	4.59 (14.5) ^f
R _{ss}	–	1.15 (18.0) ^e	–	1.08 (17.2) ^g	–	1.12 (17.2)	–	1.05 (11.7) ^f

AUC, area under the concentration–time curve; AUC_(0–inf), AUC from 0 h to infinity; AUC_(0–τ), AUC over the dosing interval; CL, drug clearance; C_{max}, maximum serum concentration; CV, coefficient of variation; FZEC, farletuzumab eteribulin; R_{ss}, accumulation ratio; t_{max}, time at which C_{max} was achieved; t_{1/2}, terminal phase elimination half-life; V_{ss}, apparent volume of distribution at steady-state.

^a Geometric mean (%CV).

^b AUC_(0–inf) for cycle 1 and AUC_(0–τ) for cycle 2.

^c Median (min–max); ^dn = 12; ^en = 11; ^fn = 6; ^gn = 10.

pretreated patients warrants further evaluation. FRα expression thresholds differed between OC and EC, reflecting the respective median expression levels in each disease. The limited sample size and exploratory nature of the analysis preclude firm conclusions regarding the impact of FRα expression on antitumor activity. The RP2D was not determined in the presented parts and further dose optimization is being pursued in the ongoing part B of the study.

The relationship of tumor responses and FRα expression will also be further evaluated in Dose-Optimization-part-B of this study, which will utilize all data from the presented cohorts (including safety [ILD rate], efficacy, pharmacokinetics, and other available data). Dose-Optimization-part-B will aim to test regimens of FZEC (alone/in combination with lenvatinib) using the weekly schedule with concomitant steroid use, to optimize antitumor activity in patients with advanced PROC while maintaining a low ILD/pneumonitis rate through dose fractionation [37]. Further, future studies exploring FZEC in combination with other therapeutic modalities (e.g., anti-VEGF therapy, immunotherapy, or PARP inhibitors) may represent a potentially synergistic strategy to enhance its antitumor activity and overcome resistance mechanisms, especially given FZEC's bystander effects and its influence on the tumor microenvironment.

Declaration of generative AI use and Ethics approval

No AI was used in drafting this manuscript.

The protocol, informed consent form, and related documents were reviewed and approved by an Institutional Review Board or Independent Ethics Committee constituted and functioning in accordance with Good Clinical Practice (GCP). This study was conducted in accordance with standard operating procedures of the sponsor, which are designed to ensure adherence to guidelines as required by Principles of the World Medical Association Declaration of Helsinki and GCP.

CRedit authorship contribution statement

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Declaration of competing interest

Robert M. Wenham: Received consultation or advisory fees from Merck, Genentech, Mural Oncology, GSK/Tesaro, AstraZeneca, AbbVie, Legend Biotech, Regeneron, Seagen, Genmab, Shattuck Labs, Eisai; equity and stock ownership from Ovation Diagnostics; funding or grants from Merck, Sonnet Biotherapeutics, Anixa Bio, Tapimmune (Marker Therapeutics); speaking and lecture fees from CurioScience, OncoLive, Pfizer; travel reimbursement from Eisai.

Isabelle Ray-Coquard: Received research funding from MSD Oncology, GSK, BMS, Amgen; consultation or advisory fees from AstraZeneca, Agenus, AbbVie, Amgen, Clovis Oncology, Corcept, Daiichi Sankyo, Genmab, GSK, Immunogen, Immune adapt, MSD, Novocure, Seagen, Pfizer, BMS, Regeneron, Incyte, MSD, Novartis, PharmaMar, Roche, Scorpion Therapeutics, Corcept Therapeutics, Sutro Biopharma; governing board member for GINECO, GCI, and ENGOT (Chair).

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Daniela Matei: Received consultation or advisory fees from CVS Health, Corcept, GSK; funding or grants from PinotBio; travel reimbursement from Corcept.

Sharad Ghamande: Received consultation or advisory fees from GSK; grants (institutional) from NCI, GSK, Eisai, Merck, A2, PharmaMar.

Ana Oaknin: Received consultation or advisory fees from AbbVie, Agenesis, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Daiichi Sankyo, Debiopharm International, Eisai, Exelixis, F. Hoffmann-La Roche, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncoXerna Therapeutics, Inc., PharmaMar, Regeneron, Sattuck Labs, Seagen/Pfizer, Stemline Therapeutics, Sutro Biopharma, TORL Therapeutics, Zentaris, Zymeworks; speaking and lecture fees from AstraZeneca, GSK, Roche, MSD, Immunogen; travel reimbursement from AstraZeneca, PharmaMar, Roche.

Jonathan S. Berek: Received consultation or advisory fees from Merck, DSMB; funding or grants from Immunogen, Eisai, Karyopharm.

J. Alejandro Perez-Fidalgo: Received consultation or advisory fees from AstraZeneca, Clovis Oncology, GSK, Eisai, Karyopharm Therapeutics, Regeneron, AbbVie, Deciphera, MSD, Pharma&; received research grants from GSK, PharmaMar, AstraZeneca; speakers' bureau for AstraZeneca, PharmaMar, GSK, Clovis Oncology, Seagen, MSD Oncology, Eisai; travel reimbursement from Roche, Pfizer, AstraZeneca, GSK.

Pau Guillén Sentís: Nothing to disclose.

Eva M. Guerra Alia: Received consultation or advisory fees from AstraZeneca, MSD, Clovis Oncology, GSK, PharmaMar, Roche, Pharma&, AbbVie; paid expert testimony for AstraZeneca, MSD, PharmaMar, Pharma&, Roche, GSK, Clovis, Eisai, AbbVie; travel reimbursement from Roche, GSK, AstraZeneca.

June Hou: Nothing to disclose.

Phillipe Follana: Received speaking and lecture fees from AbbVie, GSK; travel reimbursement from AbbVie, Novartis, GSK, Daiichi Sankyo.

Lauriane Eberst: Received honoraria from AstraZeneca, MSD, GSK, AbbVie; travel reimbursement from AstraZeneca, MSD, GSK, AbbVie.

Andrew Clamp: Received funding or grants from AstraZeneca, Verastem, MSG, Lilly, Genmab; speaking and lecture fees from AbbVie, GSK, Pharma&.

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Patricia Roxburgh: Nothing to disclose.

Robert H. Jones: Nothing to disclose.

Patricia Pautier: Board membership for AbbVie, AstraZeneca, MSD; speaking and lecture fees from GenMab; travel reimbursement from AbbVie.

Amanda L. Jackson: Board membership for Mid Atlantic Gyn Oncology Society; consultation or advisory fees from Ethicon and Faeth.

Deborah K. Armstrong: Board membership for UpToDate (ovarian cancer), NCCN Ovarian Cancer Committee, ABIM LKA (question writing committee), OCRA Strategic Advisory Committee, NIH Gynecologic Cancer Steering Committee; research funding from AstraZeneca (paid to institution).

Tingting Song: Employee of Eisai.

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Rachael Scott: Employee of Eisai.

Vicky Makker: Received consultation or advisory fees from Eisai, Merck, Karyopharm Therapeutics, Takeda, ArQule, IBM, GSK, Clovis Oncology, Faeth Therapeutics, Novartis, DualityBio, iTeos Therapeutics, Kartos Therapeutics, Lilly; research funding from Lilly, AstraZeneca,

Eisai, Merck, BMS, Karyopharm Therapeutics, Takeda, Clovis Oncology, Bayer, Zymeworks, DualityBio, Faeth Therapeutics; travel reimbursement from Eisai, Merck, AstraZeneca, ESMO.

Acknowledgments

This study was sponsored by Eisai Inc., Nutley, NJ, USA. Medical writing support was provided by Oxford PharmaGenesis Inc., Wilmington, DE, USA, and was funded by Eisai Inc., Nutley, NJ, USA.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2026.08.023>.

Data availability

The data will not be available for sharing at this time as the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

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Glossary

ADC: antibody-drug conjugate
 AE: adverse event
 AESI: adverse event of special interest
 BSA: body surface area
 CBR: clinical benefit rate
 CR: complete response
 DCR: disease control rate
 DOR: duration of response
 EC: endometrial cancer
 ECOG PS: Eastern Cooperative Oncology Group performance status
 EMA: European Medicines Agency
 FR α : folate receptor alpha
 FZEC: farletuzumab ecteribulin
 IHC: immunohistochemistry
 ILD: interstitial lung disease
 NE: not estimable
 NSCLC: non-small cell lung cancer
 OC: ovarian cancer
 ORR: objective response rate
 OS: overall survival
 PARP: poly(ADP-ribose) polymerase
 PD: progressive disease
 PFS: progression-free survival
 PCR: polymerase chain reaction
 PR: partial response
 PROC: platinum-resistant ovarian cancer
 RECIST: Response Evaluation Criteria in Solid Tumors
 RP2D: recommended phase 2 dose
 SD: stable disease
 TEAE: treatment-emergent adverse event
 TNBC: triple-negative breast cancer
 TPS: tumor proportion score
 TRAE: treatment-related adverse event