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Pegylated Liposomal Doxorubicin for Recurrent Ovarian Cancer with Platinum Resistance or Refractoriness: Results from a Prospective Single-Arm Study

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ABSTRACT

Therapeutic options remain limited for patients with ovarian cancer who experience recurrence or progression following platinum-based chemotherapy. This study investigated the antitumor activity and tolerability of pegylated liposomal doxorubicin (PLD) in individuals with varying degrees of platinum sensitivity, including partial sensitivity, resistance, and refractoriness. In this multicenter, prospective, open-label trial with a single treatment arm, patients diagnosed with partially platinum-resistant, platinum-sensitive, or platinum-refractory ovarian cancer were treated with PLD at a dose of 40 mg/m² administered every 28 days for up to six cycles. The primary outcome measure was time to disease progression. Secondary outcomes included overall survival, tumor response, disease stabilization, patient-reported quality of life, and treatment safety. Changes in serum CA125 levels and variations in the platinum-free interval were examined as exploratory parameters. Between June 2017 and November 2020, 167 patients met the eligibility criteria and were analyzed. Median time without disease progression was 6.8 months (95% CI, 4.4–9.3), while median overall survival reached 19.1 months (95% CI, 15.0–23.3). Objective tumor regression occurred in 32.3% of patients, and 60.5% achieved disease control. A decline in CA125 after the initial treatment cycle was strongly associated with improved treatment outcomes, with higher response and disease control rates compared with patients lacking an early biomarker reduction (all $P < .05$). Severe (grade ≥3) adverse events were observed in fewer than 10% of participants, and serious treatment-related events occurred in 3.9%. No fatalities attributable to PLD were recorded. PLD provided meaningful clinical benefit with a favorable safety profile in ovarian cancer patients who had limited responsiveness to platinum-based therapy, supporting its use as a therapeutic option in this difficult-to-treat population.

Keywords: Pegylated liposomal doxorubicin, Ovarian cancer, Platinum-resistant, Platinum-refractory, Partially platinum-sensitive

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Introduction

Patients and study design

A forward-looking clinical investigation with an open-label and non-randomized structure was conducted to evaluate treatment outcomes in ovarian cancer. The study involved a single therapeutic cohort and was implemented at 17 medical centers in China over a recruitment period spanning June 2017 to November 2020. Authorization for study conduct was granted by the institutional ethics committee of the Hospital, and all trial-related activities followed the requirements of Good Clinical Practice and the Declaration of Helsinki. Participation was voluntary, and written informed consent was obtained from all individuals prior to enrollment.

Target population and general requirements

The study population consisted exclusively of women aged 18–80 years with a confirmed pathological diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer. Candidates were required to

demonstrate failure of platinum-based first-line chemotherapy, defined either as disease recurrence within 12 months of treatment completion or as progression to a persistent or refractory disease state during or following platinum exposure. Patients were not permitted to have received any chemotherapy after relapse or after first-line treatment.

Eligibility further required the presence of assessable disease according to RECIST version 1.1 or Gynecologic Cancer Intergroup (GCIG) CA125 standards, an ECOG performance status between 0 and 2, and a projected survival duration of at least 3 months.

Patients were not considered eligible if they had undergone chemotherapy alone without surgical intervention, had received prior pelvic or abdominal radiotherapy, or had a history of another malignancy with a disease-free interval shorter than 5 years.

Detailed enrollment conditions

Patients were enrolled only when all mandatory conditions listed below were satisfied:

1. Women between the ages of 18 and 80 years.
2. Individuals with a confirmed histological diagnosis of epithelial-type ovarian, fallopian tube, or primary peritoneal carcinoma.
3. Cases of disease recurrence occurring less than 12 months after completing initial platinum-containing chemotherapy, where: (1) upfront cytoreductive surgery resulted in optimal debulking (complete removal of visible disease or residual lesions smaller than 1 cm); (2) complete clinical response was obtained using a single platinum-based regimen consisting of 3–6 cycles for early-stage cases or 6–8 cycles for advanced-stage cases, followed by recurrence within 12 months of ending treatment.
4. Evidence of disease that became refractory or progressed despite frontline platinum-based therapy, including: (1) failure to reach complete response after optimal initial surgery and subsequent chemotherapy, with ongoing elevated CA125 or tumor growth while on treatment; (2) initial complete response following suboptimal surgery and chemotherapy, but recurrence within 12 months after stopping therapy; (3) persistent disease advancement after suboptimal surgery and chemotherapy.
5. No exposure to any additional chemotherapeutic agents following recurrence or completion of first-line treatment.
6. Presence of at least one target lesion assessable by RECIST 1.1 imaging standards or evaluable disease based on GCIG CA125 guidelines.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
8. Anticipated survival duration of at least 3 months.
9. Left ventricular ejection fraction measuring 70% or greater.
10. Sufficient bone marrow, liver, and kidney function, defined as: absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelets $\geq 80 \times 10^9$/L; hemoglobin ≥ 80 g/L; serum creatinine not exceeding 1.5 times the upper limit of normal; ALT and AST up to 2.5 times the upper limit of normal (or up to 5 times if liver metastases are present); total bilirubin no more than 2.5 times the upper limit of normal.
11. Willing and able to sign an informed consent document.

Conditions precluding participation

Enrollment was not permitted for patients meeting any of the following criteria:

1. Presence of another malignant disease with remission lasting less than 5 years;
2. Receipt of systemic chemotherapy without accompanying surgical management during first-line treatment;
3. Existing or prior cardiac dysfunction meeting New York Heart Association class ≥ 2;
4. Previous anthracycline exposure reaching or exceeding 300 mg/m² for doxorubicin or 550 mg/m² for epirubicin, or evidence of anthracycline-induced cardiac injury;
5. History of pelvic or abdominal radiotherapy;
6. Active, uncontrolled infection necessitating systemic anti-infective therapy;
7. Known hypersensitivity to the investigational product or its formulation components;
8. Documented involvement of the central nervous system, including metastases;
9. Administration of any chemotherapy agents within 28 days before initiation of study treatment;
10. Any additional medical or clinical condition that, in the investigator's judgment, rendered the patient unsuitable for participation.

Treatment delivery and monitoring

Treatment consisted of pegylated liposomal doxorubicin (Duomeisu, CSPC Pharmaceutical Co., Ltd.), administered intravenously at a dose of 40 mg/m² on day 1 of a repeating 28-day cycle. Although continuation of therapy was encouraged for a minimum of 4 cycles, treatment duration ultimately depended on clinical circumstances. Therapy could be discontinued earlier if radiographic progression occurred, toxicity was deemed unacceptable by the site investigator, or the patient chose to withdraw consent. Conversely, continuation beyond 6 cycles was permitted when clinical benefit was observed and tolerability remained acceptable. Adjustments to dosing, including temporary interruption, dose reduction, or permanent discontinuation, were allowed for toxicity management; however, patients requiring more than 2 dose modifications were withdrawn from the study.

Assessments

Clinical status was documented prior to treatment initiation within a 7-day window and included physical examination, vital sign assessment, serum CA125 determination, imaging by computed tomography or magnetic resonance imaging, ECOG performance status, quality-of-life evaluation, and laboratory testing. Tumor burden was reassessed at intervals of 2 cycles using RECIST version 1.1 or Gynecologic Cancer Intergroup CA125 criteria. Adverse events were actively monitored throughout treatment, reassessed on Day 30 following the final dose, and recorded at all follow-up visits, with severity graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patient-reported quality of life was measured using the EORTC QLQ-C30 questionnaire prior to cycles 3 and 5, while serum CA125 levels were quantified at each treatment cycle using enzyme immunoassay methodology.

Outcome measures

Clinical efficacy was primarily evaluated through progression-free survival, defined as the interval from study enrollment to either objective disease progression or death. Additional outcomes included overall survival, calculated from enrollment to death from any cause; objective response rate, representing the proportion of patients whose best response was complete or partial remission; and disease control rate, encompassing patients with complete response, partial response, or stable disease. Safety and quality-of-life outcomes were also assessed. Exploratory analyses focused on changes in CA125 values between baseline and completion of the first treatment cycle, as well as the platinum-free interval, defined as the time from the final administration of first-line platinum chemotherapy to initiation of a subsequent platinum-based regimen following PLD therapy.

Analytical strategy

No statistical power calculation was performed for patients categorized as partially platinum-sensitive. For those with platinum-resistant or platinum-refractory disease, trial efficiency was assessed using a Simon's two-stage design with a 2-sided type I error of 5% and 80% statistical power. Historical data reporting response rates between 15% and 40.4% for PLD monotherapy informed the assumption of an expected response rate of 30%. Accordingly, the null and alternative hypotheses were defined as $P_0 = 15\%$ and $P_1 = 30\%$, respectively. The first stage required treatment of 23 patients, with progression to the second stage contingent upon observation of at least 3 responses. An additional 48 patients were then enrolled, yielding a total of 71 patients, with 11 or more responses required to define therapeutic success. Allowing for an anticipated 10% attrition rate, the final sample size for this subgroup was 78 patients. Overall enrollment planning targeted 200 patients across all platinum-sensitivity categories.

Efficacy outcomes were evaluated in both the full analysis set, which included all patients receiving at least 1 dose of study drug, and the per-protocol set, restricted to patients without major protocol deviations and with at least 1 post-baseline efficacy assessment. Safety analyses incorporated all patients exposed to at least 1 dose of PLD who completed at least 1 safety evaluation. Continuous variables were summarized using mean ± standard deviation, whereas categorical variables were expressed as frequencies and percentages. Time-to-event endpoints, including progression-free survival, overall survival, and duration of response, were estimated using Kaplan–Meier methodology and compared using the log-rank test. Differences in objective response rate and disease control rate were examined using the χ^2 test or Fisher's exact test, as appropriate. Prognostic associations with progression-free survival were explored through univariate and multivariate Cox proportional hazards models, with effect estimates reported as hazard ratios and 95% confidence intervals. All hypothesis testing was two-sided, with statistical significance defined as $P < .05$. Analyses were conducted using SPSS version 25 (IBM, Armonk, NY) and Prism 7 (GraphPad Software, San Diego, CA).

Table 1. Drug Information

Category	Details
Manufacturer	CSPC Pharmaceutical Co., Ltd.
Drug Name (Generic/Brand)	Pegylated liposomal doxorubicin (Duomeisu®)
Drug Classification	Anthracycline cytotoxic agent
Therapeutic Category	Cytotoxic agent
Dosage Unit	mg/m²
Dosage Strength	40 mg/m²
Dosing Schedule	Given on day 1 of each 28-day treatment cycle
Administration Route	Intravenous infusion (IV)

Table 2. Patient Characteristics

Number of patients, Female	**167**
Number of patients, Male	0
Number of prior systemic therapies	None
Median (range), age (years)	54.0 (21.0-74.0)
Stage	
	I-II: 7 (4.2)
	III: 130 (77.8)
	IV: 23 (13.8)
	Unknown: 7 (4.2)
Performance status: ECOG	
	0: 77 (46.1%)
	1: 81 (48.5%)
	2: 9 (5.4%)
	3: 0
	4: 0

Table 3. Cancer Types or Histologic Subtypes

Histological Subtype	Number of Patients (n = 167)
Mucinous	3 (1.8%)
Serous	148 (88.6%)
Clear cell	5 (3.0%)
Endometrioid	2 (1.2%)
Mixed epithelial	1 (0.6%)
Unknown	8 (4.8%)

Table 4. Primary Assessment Method

Parameter	Details
Patients Enrolled	167
Patients Screened	171
Patients Evaluable for Efficacy	137
Patients Evaluable for Toxicity	152
Efficacy Evaluation Criteria	RECIST version 1.1
Duration Outcomes (median)	
Overall Survival (OS)	19.1 months (95% CI: 15.0–23.3)
Progression-Free Survival (PFS)	6.8 months (95% CI: 4.4–9.3)
Duration of Treatment	4 cycles (range: 1–8 cycles)
Tumor Response (n = 167)	
Partial Response (PR)	49 (29.3%)
Complete Response (CR)	5 (3.0%)
Progressive Disease (PD)	36 (21.6%)
Stable Disease (SD)	47 (28.1%)

Outcome notes

Figure 1 shows the trial profile.

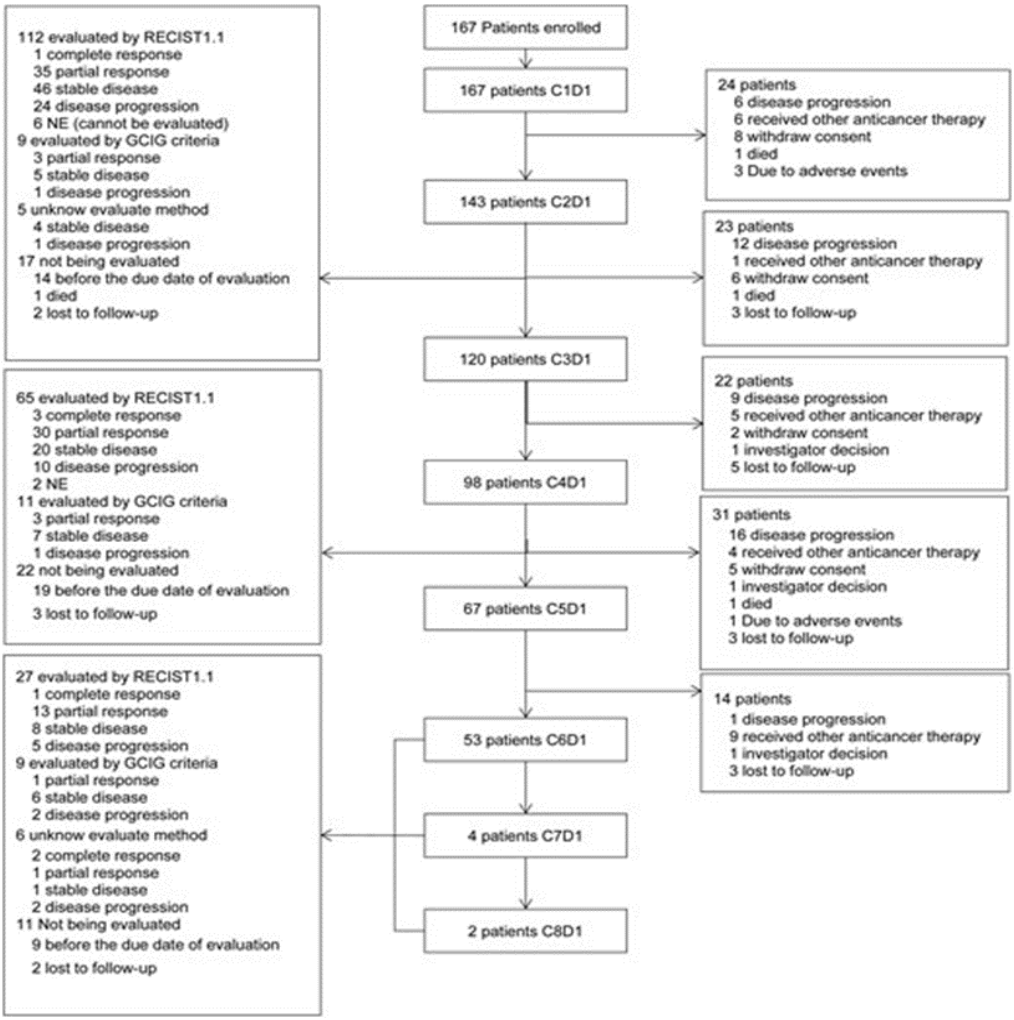


Figure 1. Schematic representation of patient disposition throughout the study. Abbreviations: RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; NE, not evaluable; GCIG, Gynecologic Cancer InterGroup; C, cycle; D, day.

Figure 2 depicts time-to-event outcomes using Kaplan–Meier methodology in both the full analysis population and the per-protocol population, including analyses by platinum response category. At the point of data lock, progression or death had occurred in approximately two-thirds of patients in the FAS (116/167) and nearly three-quarters of those in the PPS (102/137). Across the entire cohort, median progression-free survival was estimated at 6.8 months in the FAS and 7.4 months in the PPS, with overlapping confidence intervals. Clear differences in PFS emerged after stratification by platinum sensitivity. Patients classified as partially platinum-sensitive consistently demonstrated longer disease control than those with platinum-refractory disease in both analysis sets (FAS: 8.8 vs 4.2 months, P = .04; PPS: 8.8 vs 3.9 months, P = .006). Outcomes for the platinum-resistant group were intermediate, with a median PFS of 4.9 months in both the FAS and PPS. Overall survival analyses showed that slightly more than half of the study population had died by the cutoff date (FAS: 51.5%; PPS: 52.6%). Median OS for the overall population was approximately 19 months in the FAS and 21 months in the PPS. Survival outcomes also varied by platinum response. Median OS among platinum-resistant patients was 16.8 months in the FAS and 18.3 months in the PPS. In contrast, patients with partially platinum-sensitive disease experienced significantly prolonged survival compared with those with platinum-refractory disease in both populations (FAS: 27.7 vs 15.2 months, P = .02; PPS: 29.2 vs 15.2 months, P = .01).

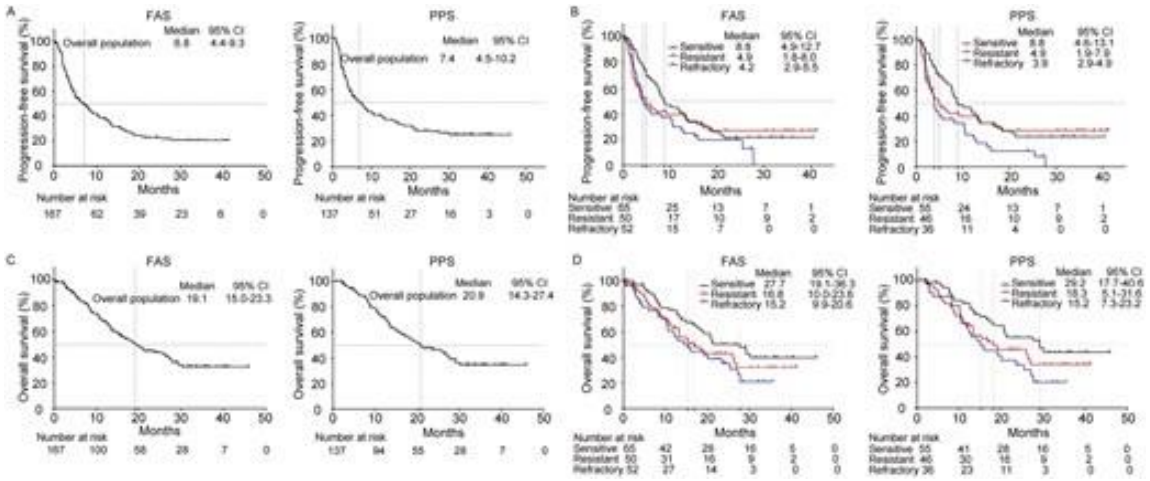


Figure 2. Survival outcomes, including progression-free survival and overall survival, were evaluated in the full analysis set and the per-protocol set, both for the entire cohort and according to platinum sensitivity. Panels display PFS for the overall population and for platinum-defined subgroups, as well as corresponding OS results across these analysis populations. Abbreviations: PFS, progression-free survival; OS, overall survival; FAS, full analysis set; PPS, per-protocol set.

Figure 3 presents a swimmer plot summarizing treatment duration and response among patients who achieved an objective tumor response. Disease stabilization or response was observed in 101 patients, corresponding to 60.5% (95% CI, 52.6–68.0%) of the FAS cohort and 73.7% (95% CI, 65.5–80.9%) of the PPS cohort. Among the 54 patients who experienced an objective response, the median duration of response (DOR) was 16.6 months (95% CI, 3.2–29.9 months). When analyzed by platinum sensitivity, median DOR was 11.3 months (95% CI, 4.9–17.7 months) in the partially platinum-sensitive group, had not been reached in the platinum-resistant group, and was 10.2 months (95% CI, 0.0–26.7 months) in the platinum-refractory group.

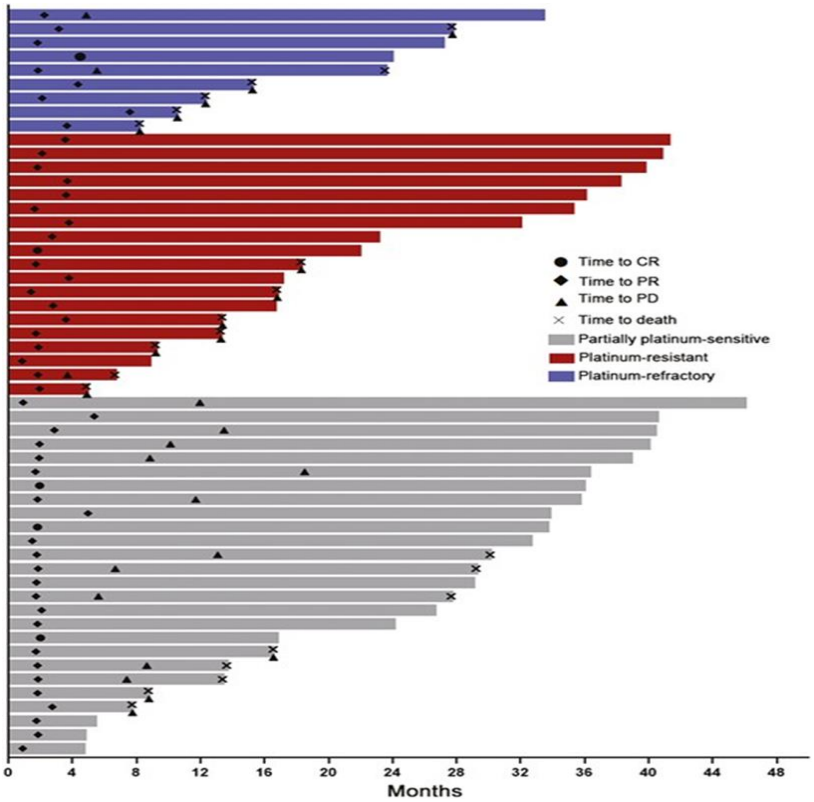


Figure 3. Graphical depiction of treatment exposure and response duration among patients who achieved a measurable antitumor response. Abbreviations: PR, partial response; CR, complete response; PD, progressive disease.

Figure 4 summarizes patient-reported quality-of-life outcomes over the course of therapy. Among the 167 enrolled patients, questionnaire completion rates were 62.3% at study entry (104 patients), 60.0% prior to the third treatment cycle (72 patients), and 58.2% before the fifth cycle (39 patients). Across all 15 assessed domains, quality-of-life scores remained stable over time, with no statistically significant changes observed when post-treatment assessments were compared with baseline values (all P values > .05).

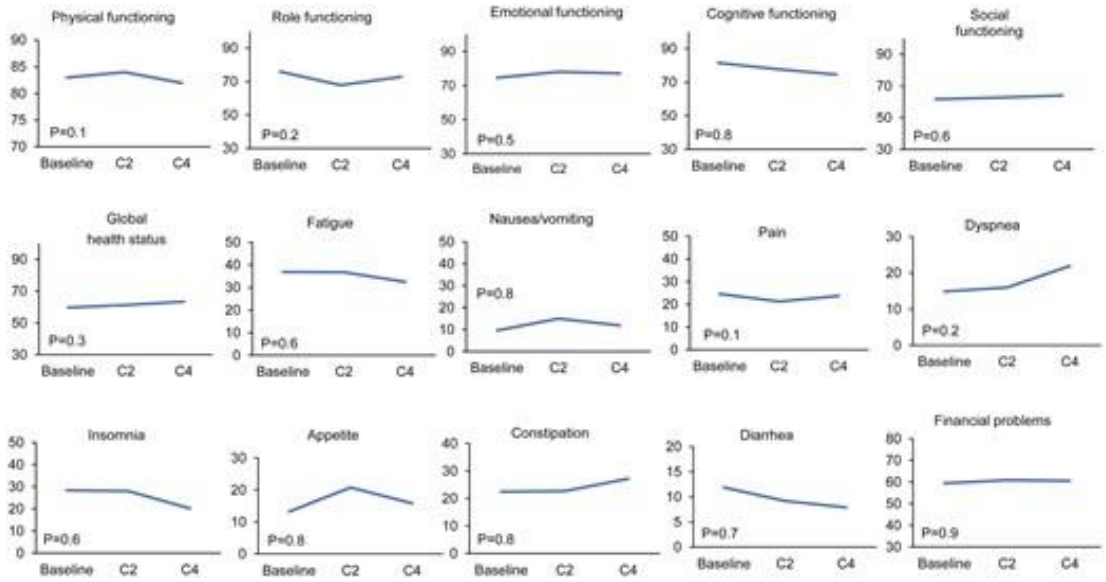
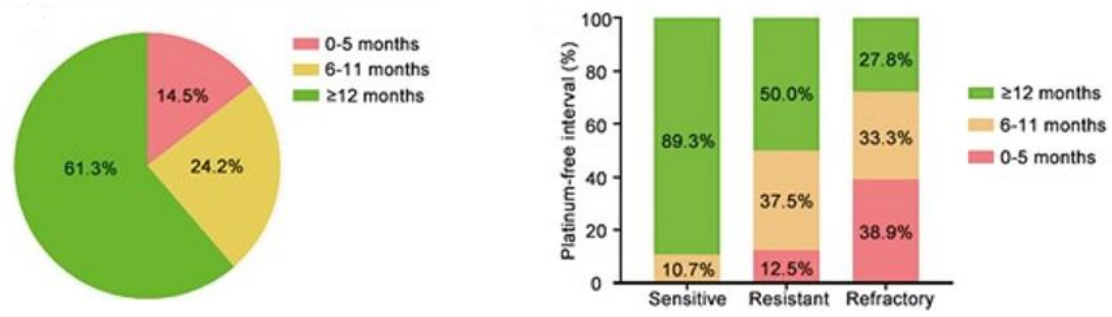


Figure 4. Patient-reported quality-of-life outcomes assessed across treatment cycles.
Abbreviation: C, cycle.

Figure 5 illustrates the distribution of platinum-free intervals following PLD therapy in a subset of 62 evaluable patients. After treatment, 9 patients (14.5%) experienced a PFI of up to 5 months, 15 patients (24.2%) had a PFI between 6 and 11 months, and the majority—38 patients (61.3%)—remained platinum free for at least 12 months. The median PFI for the entire group was 13.0 months, with observed values ranging from 3.0 to 48.0 months. When examined by platinum sensitivity, prolonged PFIs (≥12 months) were most frequently observed in the partially platinum-sensitive group (25 of 28 patients; 89.3%), followed by the platinum-resistant group (8 of 16 patients; 50.0%) and the platinum-refractory group (5 of 18 patients; 27.8%). Corresponding median PFIs were 17.0 months (range, 9.0–48.0 months) for partially platinum-sensitive patients, 11.5 months (range, 3.0–25.0 months) for platinum-resistant patients, and 6.5 months (range, 3.0–15.0 months) for platinum-refractory patients.



a) b)

Figure 5. Duration of the platinum-free interval following treatment. Panel A presents results for the entire evaluable cohort (n = 62), while Panel B displays outcomes stratified by platinum sensitivity, including partially platinum-sensitive (n = 28), platinum-resistant (n = 16), and platinum-refractory (n = 18) subgroups.

Baseline demographic and clinical features, along with antitumor response data, are summarized in **Tables 5** through 3. Safety findings related to treatment exposure are detailed in **Table 8**. Among 152 patients assessed for safety, the adverse events most frequently observed at any severity level were neutropenia (42.8%), oral mucositis

(15.1%), anemia (13.2%), nausea (13.2%), and palmar-plantar erythrodysesthesia (12.5%). Mild to moderate toxicities (grade 1–2) occurred in just over half of patients (53.9%), whereas severe events (grade 3–4) were less common, affecting 9.9% of the cohort. Neutropenia represented the most frequent high-grade toxicity (3.3%), with grade 3–4 oral mucositis and hand-foot syndrome each reported in 2.0% of patients. Serious adverse events were documented in six individuals (3.9%), including febrile episodes (n = 2), ascites (n = 2), pulmonary infection (n = 1), and intestinal obstruction (n = 1). Importantly, no treatment-related fatalities were recorded.

Table 5. Baseline characteristics.

Patient Characteristic	Overall (n = 167)	Partially Platinum-Sensitive (n = 65)	Platinum-Refractory (n = 52)	Platinum-Resistant (n = 50)	P Value
Median CA-125 level, U/mL (range)	195.5 (5.9–7135.0)	226.2 (9.0–7135.0)	105.8 (7.3–4386.0)	221.4 (5.9–7045.0)	.3
Median age, years (range)	54.0 (21.0–74.0)	52 (38.0–74.0)	55 (21.0–68.0)	55 (41.0–73.0)	.3
FIGO stage at diagnosis, n (%)					.4
I–II	7 (4.2)	2 (3.1)	2 (3.9)	3 (6.0)	
III	130 (77.8)	52 (80.0)	37 (71.2)	41 (82.0)	
IV	23 (13.8)	10 (15.4)	8 (15.4)	5 (10.0)	
Unknown	7 (4.2)	1 (1.5)	5 (9.6)	1 (2.0)	
Site of primary tumor, n (%)					.2
Fallopian tube	7 (4.2)	3 (4.6)	0	4 (8.0)	
Primary peritoneal	2 (1.2)	0	1 (1.9)	1 (2.0)	
Ovarian	155 (92.8)	61 (93.9)	49 (94.2)	45 (90.0)	
Unknown	3 (1.8)	1 (1.5)	2 (3.9)	0	
Type of cytoreductive surgery, n (%)					.7
Interval cytoreduction	88 (52.7)	36 (55.4)	25 (48.1)	27 (54.0)	
Upfront (primary) cytoreduction	79 (47.3)	29 (44.6)	27 (51.9)	23 (46.0)	
Tumor histology, n (%)					.3
Mucinous	3 (1.8)	1 (1.5)	2 (3.9)	0	
Serous	148 (88.6)	60 (92.3)	42 (80.8)	46 (92.0)	
Clear cell	5 (3.0)	1 (1.5)	3 (5.8)	1 (2.0)	
Mixed epithelial	1 (0.6)	1 (1.5)	0	0	
Endometrioid	2 (1.2)	1 (1.5)	0	1 (2.0)	
Unknown	8 (4.8)	1 (1.5)	5 (9.6)	2 (4.0)	
Residual disease after interval surgery[b], n (%)					.9
Complete (no gross residual, R0)	36 (40.9)	15 (23.1)	8 (15.4)	13 (26.0)	
Optimal (<1 cm residual, R1)	29 (33.0)	12 (18.5)	9 (17.3)	8 (16.0)	
Suboptimal (R2)	9 (10.2)	3 (4.6)	4 (7.7)	2 (4.0)	
Unknown	14 (15.9)	6 (9.2)	4 (7.7)	4 (8.0)	
Residual disease after upfront primary surgery[a], n (%)					.05
Complete (no gross residual, R0)	32 (40.5)	12 (18.5)	11 (21.2)	9 (18.0)	
Optimal (<1 cm residual, R1)	28 (35.4)	13 (20.0)	6 (11.5)	9 (18.0)	
Suboptimal (R2)	8 (10.1)	1 (1.5)	7 (13.5)	0	
Unknown	11 (13.9)	3 (4.6)	3 (5.8)	5 (10.0)	
ECOG performance status, n (%)					.2
0	77 (46.1)	37 (56.9)	22 (42.3)	18 (36.0)	
1	81 (48.5)	24 (36.9)	28 (53.9)	29 (58.0)	
2	9 (5.4)	4 (6.2)	2 (3.9)	3 (6.0)	

[a] $n = 79$.

[b] $n = 88$.

Abbreviations: PS, performance status; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Obstetrics and Gynecology.

Table 6. Tumor response.

Response Category	FAS – All Patients(n = 167)	FAS – Partially Platinum-Sensitive(n = 65)	FAS – Platinum-Resistant(n = 50)	FAS – Platinum-Refractory(n = 52)	PPS – All Patients(n = 137)	PPS – Partially Platinum-Sensitive(n = 55)	PPS – Platinum-Resistant(n = 46)	PPS – Platinum-Refractory(n = 36)
Partial response, n (%)	49 (29.3)	23 (35.4)	18 (36.0)	8 (15.4)	49 (35.8)	23 (41.8)	18 (39.1)	8 (22.2)
Complete response, n (%)	5 (3.0)	3 (4.6)	1 (2.0)	1 (1.9)	5 (3.7)	3 (5.5)	1 (2.2)	1 (2.8)
Progressive disease, n (%)	36 (21.6)	9 (13.9)	17 (34.0)	10 (19.2)	36 (26.3)	9 (16.4)	17 (37.0)	10 (27.8)
Objective response rate, %	32.3	40.0	38.0	17.3	39.4	47.3	41.3	25.0
Not evaluable, n (%)	30 (18.0)	10 (15.4)	4 (8.0)	16 (30.8)	–	–	–	–
Disease control rate, %	60.5	70.8	58.0	50.0	73.7	83.6	63.0	72.2
Stable disease, n (%)	47 (28.1)	20 (30.8)	10 (20.0)	17 (32.7)	47 (34.3)	20 (36.4)	10 (21.7)	17 (47.2)

Abbreviations: DCR, disease control rate; ORR, objective response rate; PPS, per-protocol set; FAS, full analysis set; NE, not evaluable; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 7. Tumor Response Evaluated According to Changes in CA125 Levels from Baseline to the Completion of the Initial Treatment Cycle

CA125 reduction following the first cycle	No (n = 89)	Yes (n = 53)	P value
Partial response (PR), n (%)	19 (21.4)	29 (54.7)	<.001
Complete response (CR), n (%)	1 (1.1)	4 (7.6)	.07
Progressive disease (PD), n (%)	23 (25.8)	5 (9.4)	.03
Stable disease (SD), n (%)	34 (38.2)	12 (22.6)	.07
Objective response rate (ORR) (%)	22.5	62.3	<.001
Not evaluable (NE), n (%)	12 (13.5)	3 (5.7)	.2
Disease control rate (DCR) (%)	60.7	84.9	.002

Abbreviations: NE, not evaluable; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response.

Table 8. Adverse events

Adverse Event	Any Grade, n (%)	Grade 3–4, n (%)	Grade 1–2, n (%)
Any adverse event	97 (63.8)	15 (9.9)	82 (53.9)
Non-hematological toxicity			
Nausea	20 (13.2)	0	20 (13.2)
Oral mucositis	23 (15.1)	3 (2.0)	20 (13.2)
Fatigue	11 (7.2)	0	11 (7.2)
Hand-foot syndrome	19 (12.5)	3 (2.0)	16 (10.5)
Increased ALT	7 (4.6)	0	7 (4.6)
Increased AST	8 (5.3)	0	8 (5.3)
Diarrhea	4 (2.6)	1 (0.7)	3 (2.0)
Alopecia	3 (2.0)	0	3 (2.0)
Increased blood bilirubin	4 (2.6)	0	4 (2.6)
Increased creatinine	2 (1.3)	0	2 (1.3)

Fever	3 (2.0)	0	3 (2.0)
Hematological toxicity			
Neutropenia	65 (42.8)	5 (3.3)	60 (39.5)
Thrombocytopenia	6 (4.0)	2 (1.3)	4 (2.6)
Anemia	20 (13.2)	1 (0.7)	19 (12.5)

Data were expressed as n (%).

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; AEs, adverse events.

Analysis, Assessment, and Discussion

Assessment by investigator	**Ongoing activity, but findings superseded by later advancements**
Study completion	Completed

The present work provides the final analysis of a prospective, multicenter, single-arm trial investigating pegylated liposomal doxorubicin (PLD) in ovarian cancer patients classified as partially platinum-sensitive, platinum-resistant, or platinum-refractory. The results indicate that PLD offers meaningful clinical activity, demonstrated by durable progression control, prolonged overall survival, and favorable tumor response metrics. Taken together with its tolerable toxicity profile, these findings support the use of PLD as a viable therapeutic option for Chinese patients across these platinum-resistance categories.

Multiple chemotherapeutic agents have historically been used in the recurrent or refractory ovarian cancer setting, including topotecan, gemcitabine, paclitaxel administered on weekly or three-weekly schedules, and PLD, all of which have shown varying degrees of antitumor efficacy [1, 2]. In a randomized phase III comparison, topotecan and PLD (50 mg/m²) yielded comparable survival outcomes, with median OS values of 14.9 and 15.7 months, respectively [3]. Similarly, another phase III multicenter trial reported median OS of 12.8 months for gemcitabine and 14.0 months for PLD (40 mg/m²) when used as salvage therapy [4]. Weekly paclitaxel demonstrated a median PFS of 4.3 months in patients with recurrent or persistent disease in an NRG Oncology/GOG study [5]. Against this backdrop, PLD treatment in our study achieved a median PFS of 6.8 months and a median OS of 19.1 months in the FAS population, suggesting superior outcomes relative to those historically reported with these alternative agents [3–5]. Variations in platinum sensitivity and baseline CA125 status may partially account for cross-trial differences in PFS; nonetheless, the observed outcomes reinforce the therapeutic relevance of PLD in this clinical context.

CA125 has long been recognized as a prognostic and predictive biomarker in ovarian cancer [6, 7]. Dynamic changes in CA125 during treatment are commonly interpreted as indicators of therapeutic efficacy or resistance, with declining levels reflecting response and rising levels signaling progression [8]. In line with these principles, patients who exhibited an early decrease in CA125 after the first treatment cycle in our study achieved superior response outcomes, including higher ORR, DCR, and PR rates, along with a reduced incidence of PD, compared with patients without an early CA125 decline.

The platinum-free interval (PFI) remains a cornerstone metric in ovarian cancer management, guiding treatment selection and providing prognostic insight [9]. Accumulating evidence suggests that the strategic use of nonplatinum therapies to extend the PFI may allow re-sensitization to platinum agents, ultimately translating into survival benefit [10]. In this study, PLD extended the PFI to at least 12 months in over 60% of patients with recurrent or refractory disease, with particularly high rates observed among those with partially platinum-sensitive tumors. This substantial prolongation of PFI implies that PLD may facilitate the recovery of platinum sensitivity across a spectrum of resistance states, further underscoring its clinical value.

Therapeutic strategies for partially platinum-sensitive ovarian cancer typically involve either platinum-based combinations or nonplatinum regimens administered alone or in combination [11]. In a phase III trial, carboplatin combined with PLD achieved a median PFS of 9.4 months, compared with 8.8 months for carboplatin plus paclitaxel [12]. In our cohort, PLD monotherapy produced a median PFS of 8.8 months and a median OS of 27.7 months in patients with partially platinum-sensitive disease, indicating that a nonplatinum approach can yield outcomes comparable to those achieved with platinum-based combinations.

For patients with platinum-resistant recurrent ovarian cancer, treatment options remain limited and outcomes poor, with median PFS typically ranging from 3.0 to 4.0 months and median OS rarely exceeding 16.0 months [9, 13, 14]. The efficacy observed with PLD in our platinum-resistant subgroup—median PFS of 4.9 months and median OS of 16.8 months—aligns with these expectations and supports its role as an active agent in this difficult-to-treat

population. In contrast, platinum-refractory ovarian cancer lacks an established standard of care [15], and published survival outcomes are particularly unfavorable, often falling below one year [16–18]. Notably, patients with platinum-refractory disease in our study achieved a median OS of 15.2 months following PLD treatment, suggesting a potential improvement over historical benchmarks. However, given the small size of this subgroup, these findings should be interpreted with caution and require confirmation in larger, dedicated studies.

From a safety perspective, treatment-related adverse events were observed in approximately two-thirds of patients. The most frequently reported toxicities included neutropenia, oral mucositis, anemia, nausea, and hand-foot syndrome. This toxicity pattern is consistent with previously published safety data for PLD across ovarian cancer and other malignancies [19–21]. Most adverse events were low grade and manageable with supportive care, and no unexpected safety signals were identified. Importantly, no deaths attributable to PLD occurred, confirming the acceptable tolerability of this regimen.

Several study limitations merit consideration. Patient enrollment was terminated early after 171 participants due to slow accrual, largely driven by disruptions associated with the COVID-19 pandemic. The single-arm, open-label design without a comparator group may also introduce bias, particularly in subjective endpoints such as quality-of-life assessments. Additionally, quality-of-life data were collected only during the initial four treatment cycles because of declining patient compliance over time. These limitations highlight the need for future large-scale, randomized controlled trials to more definitively establish the role of PLD in patients with partially platinum-sensitive, platinum-resistant, and platinum-refractory ovarian cancer.

Management of ovarian cancer that recurs or fails to respond to platinum-based chemotherapy remains particularly challenging, and effective therapeutic alternatives are limited. Pegylated liposomal doxorubicin (PLD) was developed as an advanced formulation of doxorubicin to enhance pharmacokinetic properties and reduce toxicity. Multiple phase III randomized studies have established that PLD (Caelyx) confers survival benefits compared with commonly used agents such as topotecan or gemcitabine in patients with recurrent or refractory ovarian cancer. Duomeisu, a domestically produced PLD formulation developed by CSPC Pharmaceutical Group Limited, has previously demonstrated antitumor efficacy comparable to conventional doxorubicin while exhibiting reduced cardiotoxic effects in advanced breast cancer. Nevertheless, clinical evidence supporting the use of PLD in Chinese patients with recurrent or refractory ovarian cancer remains scarce.

An interim evaluation of the current trial has been reported previously, focusing on patients with partially platinum-sensitive disease as well as those with platinum resistance or refractoriness. A distinctive aspect of this study is the PLD dose of 40 mg/m², a regimen that has not been adequately examined in Chinese ovarian cancer populations. The present analysis therefore provides the final results of this prospective, multicenter, single-arm study and addresses an important gap in existing clinical data.

Between June 2017 and November 2020, 167 patients meeting the eligibility criteria were enrolled and constituted the full analysis set **(Table 9)**. All participants had discontinued study treatment by the time of data cutoff. With a median follow-up duration of 13.3 months (95% CI, 10.6–16.0 months), median progression-free survival was 6.8 months (95% CI, 4.4–9.3 months), while median overall survival was 19.1 months (95% CI, 15.0–23.3 months). Treatment with PLD resulted in an objective response rate of 32.3% and a disease control rate of 60.5%, including complete tumor regression in five patients.

Changes in the tumor marker CA125 appeared to have prognostic relevance. Patients who exhibited a decline in CA125 levels after the first treatment cycle achieved substantially better outcomes than those without an early decrease, with significantly higher objective response rates (62.3% vs 22.5%) and disease control rates (84.9% vs 60.7%) (all $P < .05$).

In terms of tolerability, adverse events of any severity were reported in 63.8% of the 152 patients evaluated for safety. Hematologic toxicity, particularly neutropenia (42.8%), was the most common adverse event, followed by oral mucositis (15.1%), anemia (13.2%), nausea (13.2%), and hand–foot syndrome (12.5%). Severe (grade ≥3) toxicities occurred in fewer than 10% of patients, and serious adverse events were observed in 3.9%. No deaths attributable to PLD treatment were documented.

Table 9. Trial Information

Category	Details
Disease Stage / Treatment	Stages I-IV, involving pegylated liposomal doxorubicin (PLD)
Disease	Ovarian cancer that is partially platinum-sensitive, platinum-resistant, or platinum-refractory

Study Type	Prospective, open-label, single-arm, multicenter clinical trial
Prior Therapy	Initial platinum-based chemotherapy regimen
Secondary Endpoints	Overall survival (OS), objective response rate (ORR), disease control rate (DCR), quality of life (QOL), and safety profile
Primary Endpoint	Progression-free survival (PFS)

Study Framework and Eligibility Specifications

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Conflict of Interest: None

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