Randomized Multicenter Phase II Trial Comparing Two Schedules of Etoposide Pegol (NKTR-102) in Women With Recurrent Platinum-Resistant/Refractory Epithelial Ovarian Cancer

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ABSTRACT

Purpose

Etoposide pegol (NKTR-102) is a unique, long-acting topoisomerase-I inhibitor with prolonged systemic exposure to SN38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of irinotecan. This randomized phase II trial investigated two dosing schedules of etoposide pegol in patients with platinum-resistant/refractory ovarian carcinoma.

Patients and Methods

A total of 71 eligible patients were randomly assigned to receive etoposide pegol 145 mg/m² every 14 or 21 days until progression or unacceptable adverse events (AEs). The primary end point was objective response rate (ORR) by RECIST (version 1.0). Secondary end points included response by Gynecologic Cancer Intergroup criteria, duration of ORR, progression-free survival (PFS), and overall survival (OS).

Results

The overall confirmed ORR was 20% (95% CI, 10% to 30%): 20% for once every 14 days, and 19% for once every 21 days. Median response duration was 4.1 months for once every 14 days and 4.0 months for once every 21 days. Median PFS for every 14 and every 21 days was 4.1 and 5.3 months, respectively, and median OS was 10.0 and 11.7 months, respectively. Etoposide pegol was well tolerated, with the most common grade 3 to 4 AEs being dehydration (24%) and diarrhea (23%). Diarrhea, dehydration, nausea, and neutropenia were less frequent with the schedule of once every 21 days than with that of once every 14 days.

Conclusion

Both schedules of etoposide pegol showed activity in patients with heavily pretreated ovarian cancer, with encouraging ORR and PFS rates. The schedule of once every 21 days was better tolerated and had slightly longer PFS and OS rates. The treatment schedule of etoposide pegol 145 mg/m² once every 21 days was selected for the expanded phase II study and is preferred for future phase III studies. These findings provide support to directly compare etoposide pegol versus one of the approved drugs (eg, pegylated liposomal doxorubicin or topotecan) in platinum-resistant ovarian cancer.

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INTRODUCTION

Ovarian cancer is the fifth leading cause of death among women in the United States and the most fatal of the gynecologic cancers.¹ At diagnosis, approximately 70% of women present with advanced disease.² Long-term survival rates for advanced epithelial ovarian cancer have changed only modestly over the past few decades. The standard treatment for advanced ovarian cancer is maximal surgical cy-

torreduction and systemic chemotherapy consisting of a platinum analog plus paclitaxel.³ Despite an objective response rate (ORR) > 60% to 70% to first-line platinum-based therapy, the majority of patients (up to 80%) will relapse and develop subsequent platinum-resistant disease. Furthermore, as many as one third of patients will not have any meaningful response to the initial platinum-based therapy (disease progression or stable disease) or will experience an early relapse at ≤ 3 months.⁴

Fig 1. CONSORT diagram. AE, adverse event; PD, progressive disease. (*) One patient was randomly assigned but did not receive the study drug as a result of not meeting inclusion criteria. The treatment assignment for this patient was missing in the database. Therefore, this patient was counted as a screen failure. Q14d, once every 14 days; Q21d, once every 21 days.

The treatment of patients with platinum-refractory or platinum-resistant ovarian cancer (defined as progression during a platinum-based regimen or recurrence within 6 months after last dose, respectively) is challenging because of the marginal benefit obtained with current treatment options.⁴ Outside of entry into a clinical trial, monotherapy with a number of agents, including pegylated liposomal doxorubicin (PLD), topotecan, taxanes, or gemcitabine, is commonly used in this setting.⁵ Phase II and III randomized trials in women with platinum-resistant ovarian cancer after one prior line of chemotherapy including a platinum-based regimen have demonstrated overall response rates in the range of 10% to 20%⁶⁻⁸ and median progression-free survival (PFS) rates of 3.7 to 4.0 months.⁹ In patients who experience progression within a 3-month timeframe after prior platinum-based therapies, response rates are < 10%.¹⁰ These data highlight the need for new treatment options for this disease.

Etinotecan pegol (NKTR-102) is a unique, long-acting topoisomerase-I inhibitor that provides prolonged systemic exposure to SN38 (7-ethyl-10-hydroxycamptothecin), the active metabolite of irinotecan.¹¹ Preclinical and clinical studies of etirinotecan pegol have provided encouraging evidence of enhanced antitumor activity with less hematopoietic toxicity compared with irinotecan.¹²⁻¹⁸ Etirinotecan pegol demonstrated superior activity compared with irinotecan in a platinum-resistant A2780 ovarian carcinoma animal model.¹⁸ A phase I study evaluated three schedules of etirinotecan pegol: once a week for 3 weeks in a 4-week cycle, once every 14 days, and once every 21 days. In this study, etirinotecan pegol demonstrated promising efficacy in patients with advanced heavily pretreated solid tumor malignancies, including ovarian cancer, with an overall response rate of

32.9% and confirmed partial response rate of 11%.¹⁹ Given the significant unmet medical need for the treatment of women with recurrent platinum-resistant or platinum-refractory advanced ovarian cancer, this phase II trial was conducted to evaluate the activity of etirinotecan pegol as a single agent in women with this disease.

PATIENTS AND METHODS

Study Design

This was a multicenter, open-label, two-arm, phase II study. Patients were randomly assigned at a ratio of one to one to one of two treatment arms (145 mg/m² once every 14 days or 145 mg/m² once every 21 days). For each arm of the study, patient enrollment occurred in two successive stages (two-stage design). Initially, 20 patients were enrolled and treated in each treatment arm. If $\geq$ one patient responded among 20 evaluable patients in a treatment arm, that arm progressed to stage two, at which time 15 more patients were enrolled. The primary efficacy threshold was met within a treatment arm if $\geq$ five of 35 patients responded (stages one and two combined). Each arm was evaluated independently (Fig 1).

The primary objective of the study for each treatment arm was to determine the ORR by RECIST (version 1.0).²⁰ Secondary objectives included response rate by Gynecologic Cancer Intergroup guidelines,²¹ progression-free survival (PFS), overall survival (OS), and incidence and duration of toxicities according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).²²

Patients

Women were eligible for study inclusion if they had a histologically or cytologically confirmed diagnosis of inoperable metastatic or locally advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer; had measurable disease (per RECIST version 1.0) in $\geq$ lesion not previously irradiated or

nonmeasurable disease; were at least 18 years of age; had disease resistant to the last platinum-based chemotherapy (ie, patient experienced progression during platinum-based therapy, progression after platinum-based therapy with platinum-free interval [PFI] ≤ 6 months, or stable disease documented as best response to prior platinum-based therapy); Eastern Cooperative Oncology Group performance status of 0 or 1; and adequate renal, hepatic, and hematologic functions. There was no upper limit to the number of prior lines of therapy a patient could have received. In the event of a patient having nonmeasurable disease, the cancer antigen 125 (CA-125) level had to have been twice the upper limit of normal within 2 weeks of starting study drug.

Patients were excluded from trial entry if they had received chemotherapy or radiotherapy within 4 weeks of study drug initiation; had associated National Cancer Institute Common Terminology Criteria for Adverse Events toxicity grade > 1 from previous treatments, irrespective of interval (any grade alopecia allowed; no grade diarrhea allowed); had received prior treatment with a camptothecin (eg, topotecan, irinotecan, or any SN38 investigational drug); had a history of hypersensitivity to other pegylated drugs; had received an investigational drug or biologic agent (eg, bevacizumab) within 28 days of study drug initiation; had known or suspected CNS metastases; were pregnant or lactating; or had other significant comorbid conditions the investigator believed would impair study participation or cooperation. Additionally, patients could not have received selected cytochrome P450 3A4 inhibitors or inducers within 2 weeks of study drug initiation or during the study. All patients provided signed informed consent before study-specific screening procedures. The study was conducted in accordance with and approved by local institutional review boards and/or ethics committees.

Treatment

A total of 71 patients were randomly assigned and received $\geq$ one dose of etirinotecan pegol. Ten of these patients were randomly assigned (at a ratio of one to one) to one of two treatment arms: 170 mg/m² once every 14 days or 170 mg/m² once every 21 days. After study initiation, an amendment was implemented to reduce the dose to 145 mg/m² based on the lower incidence of grade 3 diarrhea at the 145 mg/m² dose level compared with the 170 mg/m² dose level in the phase I study.^{19,23} An additional 61 patients were initiated at the 145 mg/m² dose. Etirinotecan pegol was administered as a 90-minute intravenous infusion without premedications. Treatment was continued until disease progression, unacceptable toxicity, completion of 12 months of therapy, or discontinuation criteria were met (ie, death, withdrawal of consent by patient, or investigator decision). Etirinotecan pegol dose modifications were recommended based on hematologic parameters and/or the development of diarrhea. To reinstate treatment, recovery to an absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, hemoglobin value ≥ 9.0 mg/dL, and fully resolved diarrhea was required. Because diarrhea is an expected toxicity of etirinotecan pegol, investigators were instructed to ensure all patients received optimal antidiarrheal therapy after the first episode of loose stools, regardless of severity.

Assessments

Tumor measurements were appropriately documented during screening by radiologic imaging (computed tomography [CT] scans or magnetic resonance imaging [MRI]) and approximately every 6 weeks during the treatment period through the end-of-treatment visit (if not assessed within previous 28 days). The same radiologic method (CT or MRI) and technique for acquisition of data were used each time to characterize each lesion. Radiologic imaging included the pelvis, abdomen, and chest. CA-125 levels were measured at screening, each treatment visit, and end of treatment. For patients with measurable disease, response was assessed per RECIST (version 1.0) by the principal investigator.

Approximately every 3 months after the end-of-treatment visit, patients were contacted to assess disease progression (if not determined during study treatment), survival, receipt of subsequent anticancer therapy, and resolution of any toxicities attributable to study drug. Quarterly follow-up continued until the patient died, withdrew from the study, or was lost to follow-up; ended at the discretion of the principal investigator; or study termination by the sponsor.

Statistical Analysis

The design of this study was based on Simon's two-stage design. Sample sizes for the first and second stages of the study were determined based on the null hypothesis of $P \leq .050$ and the alternative hypothesis of $P \geq .200$, where P was the proportion of response in each treatment arm. The type I error was 0.029 (target for this value is 0.050), and the type II error was 0.145 (target for this value is 0.20). Power analysis and sample size (PASS version 2008; Statistical Solutions, Saugus, MA) software was used to calculate sample sizes and critical numbers. Analysis results reflect data obtained from the clinical database as of November 14, 2011. Demographics, baseline characteristics, and safety data were summarized for patients who received any dose of etirinotecan pegol.

The efficacy analyses were performed among a modified intent-to-treat (MITT) population (patients who received any study drug, had measurable disease at baseline, and also met inclusion criteria for platinum-resistant disease). The ORR was defined as the number of patients with a confirmed complete response (CR) or partial response (PR) per RECIST (version 1.0) expressed as a percentage of the patients with measurable disease in the MITT population, including 95% CIs calculated using Clopper-Pearson (exact) methodology. Duration of response and median time of PFS and OS were calculated from the date of first etirinotecan pegol dose and estimated using the Kaplan-Meier method. For PFS, patients who were alive without disease progression were censored at the time of last tumor assessment or at the onset of subsequent antitumor therapy. For OS, patients who were alive through the November 14, 2011, data cutoff were censored at the time of last contact.

RESULTS

Enrollment and Demographics

Seventy-one patients from 18 medical centers were enrolled, were randomly assigned, and received $\geq$ one dose of etirinotecan pegol. Demographic and baseline characteristics for the randomly assigned population are listed in Table 1. The median age of patients was 61 years, with 39% of patients age ≥ 65 years; 52% of the patients had Eastern Cooperative Oncology Group performance status of 0; 96% of patients were deemed to have measurable disease by RECIST (version 1.0). The median PFI was 13.6 weeks; 22% of patients had a PFI of ≤ 4 weeks (classified as platinum refractory), whereas 69 patients (97%) were platinum resistant (including platinum-refractory patients). Sixty-nine patients were evaluated for efficacy. Patients in both arms had received a median of three prior cancer therapies and a median of two prior platinum-based cancer therapies, with 25% of patients having received $\geq$ three previous lines of platinum-based therapies. All had received a prior taxane, 47% of patients had received prior PLD, and 44% had undergone prior gemcitabine therapy.

Efficacy

A total of 69 patients were included in the MITT population. Two patients, one in each treatment arm, did not meet the platinum-resistant criteria at study entry (PFIs were 184 and 510 days, respectively) and were excluded from the MITT population.

Response data are summarized in Table 2. Thirteen patients (20%; 95% CI, 10% to 30%) achieved a confirmed PR per RECIST (version 1.0) criteria (20% for once-every-14-days schedule, and 19% for once-every-21-days schedule); median duration of response was 4.1 months (4.1 months, once every 14 days; 4.0 months, once every 21 days). Fifty-eight percent of patients had stable disease (63%, once every 14 days; 52%, once every 21 days). Clinical benefit (patients with confirmed objective response plus those with stable disease ≥ 3 months) was observed in approximately half the patients enrolled

Table 1. Clinical Characteristics of Randomly Assigned Population

Characteristic	Etinotecan Pegol Every 14 Days (n = 36)		Etinotecan Pegol Every 21 Days (n = 35)		Total (N = 71)	
	No.	%	No.	%	No.	%
Age, years						
Median	60		63		61	
Range	42-83		26-80		26-83	
≥ 65	12	33	16	46	28	39
ECOG PS						
0	18	50	19	54	37	52
1	18	50	16	46	34	48
Measureable disease by RECIST	36	100	32	91	68	96
CA-125 evaluable disease by GCIG	31	86	29	83	60	85
Histologic subtype						
Serous	28	78	26	74	54	76
Clear cell	2	6	0	0	2	3
Mucinous	0	0	1	3	1	1
Squamous cell	1	3	0	0	1	1
Mixed epithelial	0	0	1	3	1	1
Other	5	14	7	20	12	17
PFI, weeks*						
Median	15.3		10.4		13.6	
≤ 4 (platinum refractory)	7	19	9	26	16	23
> 4 (platinum resistant)	29	81	26	74	55	78
Prior lines of therapy, No.						
Median	3		3		3	
Range	1-8		1-19		1-19	
Previous platinum regimens, No.						
Median	2		2		2	
Range	1-5		1-7		1-7	
1	12	33	11	31	23	32
2	16	44	14	40	30	42
≥ 3	8	22	10	29	18	25
Prior therapies						
PLD	16	44	17	49	33	46
Gemcitabine	15	42	16	46	31	44
Taxane	36	100	35	100	71	100
Bevacizumab	4	11.1	5	14.3	9	12.7

NOTE. Ten patients started receiving study treatment drug at a dose level of 170 mg/m² (once every 14 days, n = 4; once every 21 days, n = 6) were included according to dose schedule.

Abbreviations: CA-125, cancer antigen 125; ECOG PS, Eastern Cooperative Oncology Group performance status; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; GCIG, Gynecologic Cancer Intergroup.

*PFI was determined from date of last dose of platinum to disease progression.

Table 2. Etinotecan Pegol Response Rates in MITT Population

Response	Etinotecan Pegol Every 14 Days (n = 35)		Etinotecan Pegol Every 21 Days (n = 34)		Total (n = 69)	
	No.	%	No.	%	No.	%
RECIST						
No. evaluable	35		31		66	
Confirmed ORR	7	20	6	19	13	20
GCIG						
No. evaluable	35		34		69	
Confirmed ORR	11	31	12	35	23	33
CA-125						
No. evaluable	30		28		58	
Confirmed ORR	12	40	11	39	23	40
CR	3	10	4	14	7	12
PR	9	30	7	25	16	28
Prior lines of platinum						
RECIST						
Confirmed ORR						
1	2 of 11	18	2 of 10	20	4 of 21	19
2	3 of 16	19	2 of 12	17	5 of 28	18
≥ 3	2 of 8	25	2 of 9	22	4 of 17	24
Received prior PLD						
RECIST						
No. evaluable	16		14		30	
Confirmed ORR	3	19	3	21	6	20
No prior PLD						
RECIST						
No. evaluable	19		17		36	
Confirmed ORR	4	21	3	18	7	19
PFI confirmed ORR						
≤ 4 weeks (refractory)*	0 of 7	0	1 of 8	13	1 of 15	7
> 4 weeks (resistant)*	7 of 28	25	5 of 23	22	12 of 51	24

Abbreviations: CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer Intergroup; MITT, modified intent to treat; ORR, objective response rate; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PR, partial response.

*PFI was calculated based on date of progression of last platinum therapy.

onto this study (54%, once every 14 days; 48%, once every 21 days). Among the MITT population (n = 69), the confirmed response rate using Gynecologic Cancer Intergroup criteria was 33%, with one CR. In those patients with evaluable levels of CA-125 (at least twice the upper limit of normal) at baseline, the CR and PR rates per CA-125 guidelines were 12% and 28%, respectively (Fig 2; Appendix Fig A1, online only).

ORR was also examined for different baseline disease characteristics. As shown in Table 2, patients who had received prior PLD (alone or in combination) achieved ORRs similar to those of the overall population. When the data were analyzed based on PFI, objective responses were lower in platinum-refractory patients (defined as PFI ≤ 4 weeks) compared with those who were platinum resistant

(PFI > 4 weeks to 6 months) to the last platinum-based chemotherapy (7% and 24%, respectively; Table 2).

Among the 69 patients, median PFS was 4.1 months (95% CI, 2.8 to 5.5 months), and OS was 11.1 months (95% CI, 9.2 to 13.9 months; Table 3; Appendix Figs A2 and A3, online only). The median PFS and OS were slightly longer in the once-every-21-days arm (PFS and OS: 5.3 and 11.7 months, respectively) than the once-every-14-days arm (PFS and OS: 4.1 and 10.0 months, respectively) but not statistically significant. Patients who were less platinum resistant also had a slightly longer but not statistically significant PFS and OS (PFS and OS: 4.1 and 11.7 months, respectively) compared with those who were platinum refractory (PFS and OS: 3.8 and 10.2 months, respectively).

Safety

The most common toxicity was diarrhea, observed in 82% of patients (86%, once every 14 days; 77%, once every 21 days). Grade 3 or 4 diarrhea occurred in 31% (once every 14 days) and 14% (once every 21 days) of patients (Table 4). Overall, the median onset time for grade ≥ 3 diarrhea was 62 days (range, 8 to 169 days). Similarly, fewer patients in the once-every-21-days arm experienced grade 3 or 4

Fig 2. Maximum decline by (A) RECIST (version 1.0) and (B) cancer antigen 125 (CA-125). Each bar represents an individual patient in the study.

dehydration, nausea, hypokalemia, and hyponatremia compared with those in the once-every-14-days arm (Table 4). However, grade 3 or 4 vomiting was equal in both treatment arms (Table 4). Grade 3 or 4 hematologic toxicity reported in the once-every-14-days and once-every-21-days arms included neutropenia (14% and 9%), anemia (9% and 6%), and febrile neutropenia (11% and 0%, respectively). Overall, the median onset time for grade ≥ 3 neutropenia was 86 days (range, 8 to 147 days). Study drug-related grade ≥ 4 toxicities occurred in

16% of patients (17%, once every 14 days; 14%, once every 21 days), with a single patient having diarrhea, febrile neutropenia, hyperglycemia, hypocalcaemia, hypokalemia, hyponatremia, neutropenia, pelvic hemorrhage, and respiratory tract infection and two patients having pulmonary embolism and renal failure (one in each arm).

For the 10 patients with starting dose of 170 mg/m², no higher incidences of grade ≥ 3 treatment-emergent adverse events were observed compared with overall patients treated in the randomized portion of the study (Appendix Table A1, online only). In the once-every-21-days schedule, dose reductions and delays resulting from adverse events occurred in 17.1% and 11.4% of patients, respectively, compared with 27.8% and 16.7%, respectively, in the once-every-14-days schedule (Table 5). Overall, eleven patients (19%, once every 14 days; 11%, once every 21 days) discontinued from the study drug because of drug-related adverse events. Reasons included diarrhea in five patients (grade 1, $n = 1$; grade 2, $n = 1$; grade 3, $n = 3$); asthenia/fatigue in two patients; and dehydration, febrile neutropenia, neutropenia, and decreased performance status in one patient each. Two

Table 3. PFS and OS in MITT Population

Survival	Etirinotecan Pegol Every 14 Days (n = 35)	Etirinotecan Pegol Every 21 Days (n = 34)	Total (n = 69)
Overall patients			
No.	35	32	67
PFS, months			
Median	4.1	5.3	4.1
95% CI	2.2 to 5.5	2.5 to 5.7	2.8 to 5.5
OS, months			
Median	10.0	11.7	11.1
95% CI	8.8 to 14.4	7.4 to 15.3	9.2 to 13.9
Patients with prior PLD			
No.	16	17	33
PFS, months			
Median	5.4	5.5	5.4
95% CI	2.2 to 6.4	1.6 to 6.8	2.8 to 5.5
OS, months			
Median	12.2	14.4	13.9
95% CI	8.8 to 16.7	5.3 to 23.3	10.0 to 16.7
Platinum refractory			
No.	7	9	16
PFS, months			
Median	3.8	2.1	3.8
95% CI	0.7 to 14.9	0.8 to 13.9	1.3 to 14.9
OS, months			
Median	11.1	4.3	10.2
95% CI	3.8 to 21.6	0.8 to NE	2.7 to 14.9

Abbreviations: MITT, modified intent to treat; NE, not estimable; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin.

Table 4. Most Common ($\geq 10\%$) Grade 3 or 4 AEs

AE	Etirinotecan Pegol Every 14 Days (n = 36)		Etirinotecan Pegol Every 21 Days (n = 35)		Total (N = 71)	
	No.	%	No.	%	No.	%
Patients with $\geq$ one TEAE	25	69.4	25	71.4	50	70.4
Dehydration	10	27.8	7	20.0	17	23.9
Diarrhea	11	30.6	5	14.3	16	22.5
Hypokalemia	9	25.0	5	14.3	14	19.7
Fatigue	5	13.9	8	22.9	13	18.3
Nausea	9	25.0	4	11.4	13	18.3
Abdominal pain	5	13.9	7	20.0	12	16.9
Decreased appetite	4	11.1	5	14.3	9	12.7
Neutropenia	5	13.9	3	8.6	8	11.3
Vomiting	4	11.1	4	11.4	8	11.3
Hyponatremia	5	13.9	2	5.7	7	9.9

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Table 5. Dose Reductions and Delays Resulting From AEs

Reduction/Delay	Etirinotecan Pegol Every 14 Days (n = 36)		Etirinotecan Pegol Every 21 Days (n = 35)		Total (N = 71)	
	No.	%	No.	%	No.	%
Patients with dose reduction	10	27.8	6	17.1	16	22.5
Patients with dose stopped temporarily	6	16.7	4	11.4	10	14.1
Patients with dose delay	16	44.4	11	31.4	27	38.0
Duration of dose delay, days						
No.	11		9		20	
Mean	7.9		6.1		7.1	
SD	4.8		2.7		4.0	
Median	7.0		7.0		7.0	
Minimum to maximum	0-14		1-11		0-14	

Abbreviations: AE, adverse event; SD, standard deviation.

deaths (one in each treatment arm) were considered to be partially attributable to etirinotecan pegol (acute renal failure, once every 14 days; sepsis, once every 21 days). However, both deaths were complicated by intestinal obstruction (likely secondary to underlying malignancy), vomiting, and prerenal azotemia.

DISCUSSION

Our study showed that etirinotecan pegol has activity in patients with advanced ovarian cancer who have been heavily pretreated. Although the response rate was similar in both schedules (ie, 20%, once every 14 days; 19%, once every 21 days), PFS and OS were slightly higher but not statistically significant in the once-every-21-days schedule (5.3 and 11.7 months, respectively) than in the once-every-14-days schedule (4.1 and 10.0 months, respectively). Although few studies have looked at treatment in patients with recurrent ovarian cancer receiving $\geq$ third-line therapy,^{7,24,25} making direct comparisons of response rates difficult, the response rate of 20% in this study is slightly higher than the response rate of 18.3% reported by Gordon et al⁷ in platinum- and paclitaxel-resistant patients treated with PLD who had received $\leq$ three prior regimens. Shapiro et al²⁵ reported a response rate of only 13% with gemcitabine in a patient population (16% had received $\geq$ four prior regimens) similar to the one in our study. The overall median PFS of 4.1 months and OS of 11.1 months in our study are similar to PFS (4.2 months) and OS (10.8 months) for patients treated with topotecan in the third line after PLD in the second line.²⁴ Etirinotecan pegol also showed activity in patients who had received prior PLD (n = 33), with an ORR of 20% and median PFS and OS (5.4 and 14 months, respectively) longer than the PFS and OS observed with topotecan in third-line therapy after PLD reported by Vergote et al.²⁴

Although most patients had previously received multiple prior chemotherapy regimens, treatment with etirinotecan pegol was generally well tolerated when dosed on a 21-day schedule. The most common grade 3 or 4 adverse events were dehydration, nausea, diarrhea, hypokalemia, fatigue, and abdominal pain, the majority of which seemed to occur at a lower frequency when the drug was dosed at 21-day intervals. Additionally, toxicities that might influence a patient's decision to undergo continued therapy (such as alopecia and/or neuropathy) were notably absent with

etirinotecan pegol. Unlike typical chemotherapies with much shorter half-lives relative to etirinotecan pegol (SN38 $T_{1/2}$, 50 days), dose delays of subsequent cycles to ensure recovery from adverse events when necessary allows patients who benefit from treatment with etirinotecan pegol to continue therapy.

In conclusion, single-agent etirinotecan pegol provided encouraging response rates and PFS, with a favorable toxicity profile in patients with platinum-resistant disease and a median of three prior lines of therapy. On the basis of better tolerability, a trend toward improved PFS and OS, and the convenience of less frequent dosing, the treatment schedule of etirinotecan pegol 145 mg/m² once every 21 days was selected for the additional phase II and III studies.

This study confirms the activity and safety of etirinotecan pegol in platinum-resistant ovarian cancer. Continued development in phase III is warranted in this population, and it may be appropriate to investigate etirinotecan pegol earlier in treatment in a less heavily pretreated population. These findings suggest that etirinotecan pegol should be compared with one of the approved drugs (eg, PLD or topotecan) in patients with platinum-resistant ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

The initial schedule of once per week for 3 weeks in a 4-week cycle was chosen based on prior clinical experience with irinotecan. Subsequent expansions of the schedule to once every 14 days and once every 21 days were driven by clinical observations at each dose/schedule combination and by initial pharmacokinetic (PK) data suggesting that disposition and elimination in humans were notably slower than those observed in animals.²³ PK modeling and simulation using results from the phase I study showed some accumulation of SN-38, as would be expected after once-every-21-days administration of a drug with a terminal disposition half-life of approximately 50 days. SN-38 area under the curve (AUC) after four cycles was approximately 80% of the predicted steady-state AUC; therefore, neither rapid nor extensive additional accumulation is expected when the recommended once-every-21-days schedule is used.²³

Assessments

Clinical benefit (either an objective response or stable disease ≥ 3 months) was also assessed. Laboratory testing was performed at the beginning of every treatment cycle and included complete blood count with differential, serum chemistries, and coagulation parameters. Additionally, patients were assessed for adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events grading system. The end-of-treatment visit occurred within 30 (± 3 days) after last dose of study drug.

Efficacy

Waterfall plots for maximum decrease of tumor based on RECIST (version 1.0) and cancer antigen 125 (CA-125) for both treatment arms combined are depicted in Figure 2. The majority of patients (80%) achieved a decrease in tumor response measurements (by RECIST [version 1.0] or CA-125 level). A decrease $\geq 30\%$ in tumor response by RECIST (version 1.0) was documented in 17 patients, whereas 26 patients had $\geq 50\%$ decrease in CA-125 level. The median time of decrease of the CA-125 level to 50% in responders (confirmed plus unconfirmed) occurred at week 4 in the once-every-14-days arm and at week 3 in the once-every-21-days arm (Appendix Fig A1).

Safety

A total of 71 patients were included in the safety population. The median number of etirinotecan pegol cycles received was five (range, one to 12; five in once-every-14-days arm, and four in once-every-21-days arm), with a median exposure of 84 days (80 days, once every 14 days; 84 days, once every 21 days). At the time of data cutoff, all patients had discontinued study drug treatment. The most common reason for study drug discontinuation was disease progression, occurring in 42% of patients.

Table A1. Grade 3 or 4 AEs in Patients With Starting Dose of 170 mg/m²

System Organ Class/Preferred Term	Etinotecan Pegol Every 14 Days (n = 4)		Etinotecan Pegol Every 21 Days (n = 6)		Total (n = 10)	
	No.	%	No.	%	No.	%
Patients with $\geq$ one TEAE	2	50.0	2	33.3	4	40.0
Febrile neutropenia	1	25.0	0	0.0	1	10.0
Neutropenia	1	25.0	0	0.0	1	10.0
Diarrhea	0	0.0	1	16.7	1	10.0
Ileus	0	0.0	1	16.7	1	10.0
Nausea	0	0.0	1	16.7	1	10.0
Asthenia	0	0.0	1	16.7	1	10.0
Fatigue	1	25.0	1	16.7	2	20.0
Weight decrease	1	25.0	0	0.0	1	10.0
Decreased appetite	0	0.0	1	16.7	1	10.0
Dehydration	0	0.0	1	16.7	1	10.0
Hypokalemia	1	25.0	0	0.0	1	10.0
Syncope	0	0.0	1	16.7	1	10.0
Pelvic hemorrhage	0	0.0	1	16.7	1	10.0
Deep vein thrombosis	0	0.0	1	16.7	1	10.0

Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

Fig A1. Cancer antigen 125 (CA-125) response with the once-every-14-days treatment schedule. The bottom and top edges of the box correspond to the sample 25th (Q1) and 75th (Q3) percentiles. The box length is one interquartile range (Q3 to Q1). The center horizontal line corresponds to the sample median.

Fig A2. Kaplan-Meier curves for progression-free survival. Q14d, once every 14 days; Q21d, once every 21 days.

Fig A3. Kaplan-Meier curves for overall survival. Q14d, once every 14 days; Q21d, once every 21 days.