Role of pegylated liposomal doxorubicin (Caelyx) in the treatment of relapsing ovarian cancer

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The most significant factor predicting response to second-line chemotherapy is the time interval elapsed from the end of chemotherapy to relapse occurrence. Two types of situations may be considered: patients with platinum-sensitive relapse (relapse-free interval longer than 6 months) and patients with platinum-refractory relapse (progression during treatment or relapse-free interval under 6 months). Pegylated liposomal doxorubicin is a doxorubicin formulation. Encapsulation in liposomes confers it different pharmacokinetic characteristics and a more favorable toxicity profile. The following review examines the efficacy and safety of pegylated liposomal doxorubicin for the treatment of relapsing epithelial ovarian cancer. *Anti-Cancer Drugs* 18:611–617 © 2007 Lippincott Williams & Wilkins.

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Introduction

In the US, ovarian cancer is an infrequent tumor, with an approximate incidence of 3%. Despite its infrequency, however, it represents the fifth cause of cancer mortality in women [1].

The mean patient age at the time of diagnosis is around 65–70 years and 5-year survival is less than 30%. Survival is mainly determined by the stage of the disease at the time of diagnosis, the possibilities for optimum surgical management and the relapse-free interval. Other factors that have also been evaluated as prognostic indicators are patient age, performance status, histological type and grade, presence of ascites, and initial Ca 125 levels [2].

With the exception of disease stages IA and IB without adverse risk factors (undifferentiated tumors or with an unfavorable histology), the currently accepted approach is to provide complementary treatment after surgery. In the same way as in patients with nonresectable or metastatic disease, such treatment consists of combination carboplatin and paclitaxel [3].

Four different groups can be established on the basis of the course of the disease: healing (20–25%), long-term recurrence following good response or complete remission (40%), short-term relapse (20%) and patients who fail to respond to initial chemotherapy (20%). In other words, about 80% of all patients with ovarian cancer will require second-line chemotherapy. Once disease recurrence has been confirmed, the objectives of treatment are to avoid or control the symptoms, delay disease progression, improve patient quality of life and – if possible – prolong survival. The choice of drug or drugs to be used in second-line chemotherapy depend on the duration of patient response to the initial platinum-based treatment, the previously used agents, the toxicity observed, performance status, the existing comorbidity and cost-efficacy considerations [4].

The duration of patient response to initial therapy, i.e. the relapse-free interval, is an essential element in the decision-taking process. It is also an independent prognostic factor of survival and a predictive factor of response to chemotherapy. On the basis of clinical experience, as early as in 1991, Markman *et al.* [5] referred to two different patient groups in relation to relapsing ovarian cancer. At present, this concept remains valid and we know that platinum-sensitive patients are more likely to respond to second-line chemotherapy. This likelihood moreover increases as the treatment-free interval (TFI) prolongs. Thus, patients can be classified as follows [6]:

- Sensitive to platinum: patients with a TFI > 6 months. These include an 'intermediate sensitivity' subgroup with a TFI of 6–12 months [7].
- Not sensitive to platinum: patients with some form of initial response but who relapse after a TFI less than

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6 months (resistant), or who either do not respond or show disease progression during treatment (refractory).

Caelyx is pegylated liposomal doxorubicin (PLD). Drug encapsulation within liposomes avoids the plasma-free doxorubicin peak found with the nonliposomal presentation and which is responsible for the cardiotoxicity of the drug. Pegylation (polyethylene glycol coating) affords resistance to phagocytosis mediated by the reticuloendothelial system, thereby increasing the plasma half-life of the drug and simulating continuous perfusion. This formulation moreover affords a lower frequency of alopecia and hematological toxicity. In addition, as a result of their small size, the pegylated liposomes are able to cross the neovessel pores of the tumor tissue. Therefore, there is less plasma clearance and more drug concentration within the target tumor tissue [8,9].

Pegylated liposomal doxorubicin in recurrent ovarian cancer not sensitive to platinum

The efficacy of PLD in ovarian cancer has been confirmed in a number of phase II trials. Muggia *et al.* [10] conducted a phase II trial involving 35 advanced ovarian cancer patients that progressed to chemotherapy based on platinum and paclitaxel. The patients received PLD 50 mg/m^2 every 21 days. The objective response rate was 26% [95% confidence interval (CI) 11.2–40.8]. In turn, 37% (95% CI 21–53) of the patients developed grade 3–4 toxicity at skin and mucosal membrane level. The median progression-free survival was 5.7 months, with a median global survival of 11 months.

In a similar patient population, Gordon *et al.* [9] conducted a phase II study to evaluate the efficacy and safety of PLD at a dose of 50 mg/m^2 every 28 days. The study included 90 patients, of which 89 were evaluated for efficacy and safety. The response rate was 17% (95% CI 9.1–24.6).

These studies served as the basis for the designing of a phase III trial in patients with disease relapse or progression after a line of treatment with platinum, comparing the efficacy and safety of PLD (50 mg/m^2 every 4 weeks) versus topotecan (1.5 mg/m^2/day for 5 days every 3 weeks) [11].

The study comprised a total of 474 patients with ovarian cancer that had relapsed after platinum-based first-line chemotherapy and patients who had failed to respond to such therapy. The patients were stratified according to their response to initial treatment with platinum and the presence or not of voluminous disease (above 5 cm). The principal study endpoint was progression-free survival, whereas secondary endpoints comprised global survival, response rate, safety and patient quality of life. The results of the preliminary analysis revealed no significant differences in progression-free survival (PLD 16.1 versus 17 weeks para topotecan), global survival (PLD 60 versus 56.7 weeks for topotecan) or percentage response (PLD 19.7 versus 17% for topotecan). In the subgroup of platinum-sensitive patients, however, different results were recorded in relation to median progression-free survival (PLD 28.9 versus 23.3 weeks for topotecan, $P = 0.037$) and median global survival (PLD 108 versus 71.1 weeks for topotecan, $P = 0.008$), in favor of the PLD treatment arm.

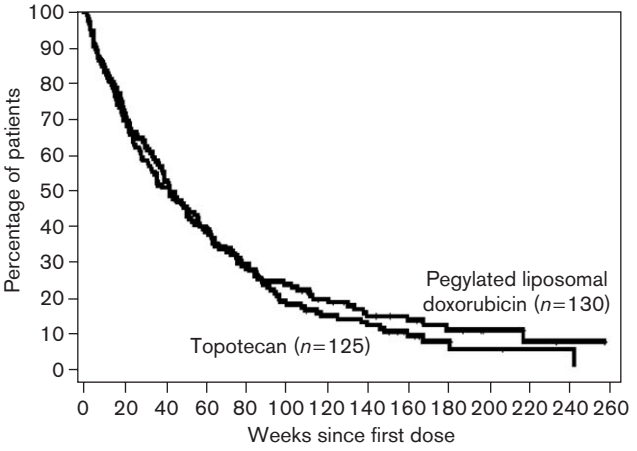
PLD was also seen to be superior on analyzing patient quality of life, as assessed by the EORTC quality of life questionnaire (QLQ-C30).

The updating of the data of this study on occasion of the European Cancer Conference in 2003 showed greater global survival in the PLD arm, with a hazard ratio of 1.216 ($P = 0.05$), implying a mortality risk reduction of over 20%. The significant difference in global survival among the platinum-sensitive patients was maintained, with 35 weeks more than in the case of topotecan (median global survival 112 versus 77 weeks). Survival proved similar for both regimens in the platinum-refractory group, however, with overlapping of the entire course of the respective survival curves (Fig. 1).

In the previous publication on this clinical trial [12], and with an 87% mortality rate among the included patients, the above conclusions were confirmed.

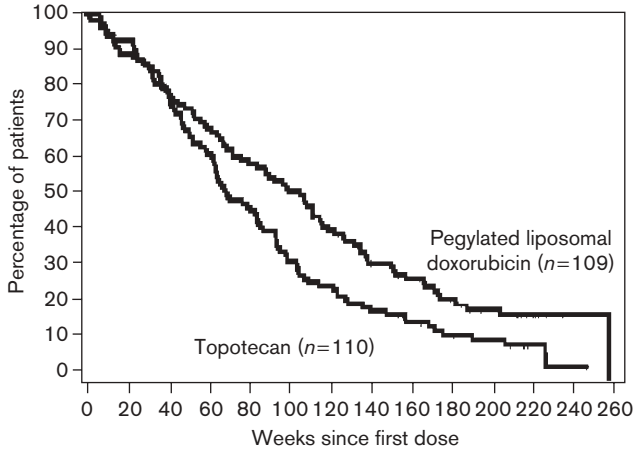
Overall, the median survival improved from 59.7 weeks for topotecan to 62.7 weeks for PLD, the survival rates after 3 years being 13.2 and 20.2%, respectively.

Fig. 1



Survival among platinum-refractory patients [12]. Curves are virtually superimposable in both treatment arms.

Fig. 2



Survival among platinum-sensitive patients [12].

In the platinum-sensitive group, the patients treated with PLD showed benefit, with a hazard ratio of 1.432 ($P = 0.017$) and a mortality risk reduction of over 40% (Fig. 2). Superior gain in survival was recorded among those women with a TFI of below 12 months and separation of the survival curves was observed fundamentally after the first year. Here the median survival was 25.1 months for PLD and 16.3 months for topotecan. A multivariate analysis of global survival was made with the purpose of assessing the influence of possible prognostic factors upon the effect of treatment (platinum sensitivity, performance status, voluminous disease, TFI and ascites); the survival results were not seen to be influenced by such factors.

The two agents presented different toxicity profiles: palmoplantar erythrodystesthesia (PPE) or hand and foot syndrome and stomatitis in the case of PLD, and hematological toxicity (requiring increased supportive treatment and variations in administration) and alopecia in the topotecan treatment arm. The need for dose modification was significantly less frequent in the PLD arm. There was no evidence of any direct relationship between the cumulative dose above 300 mg/m^2 and changes in ventricular ejection fraction, and no patient suffered symptomatic congestive heart failure. Only 3.8% of the patients developed PPE requiring treatment suspension.

The cost–efficacy relationship was likewise favorable to PLD in both this study and in other series [13], mainly owing to the need for supportive therapy for the hematological adverse events recorded in the topoisomerase inhibitor treatment arm (use of erythropoietin, platelet transfusions and colony-stimulating factors).

To summarize, the study published by Gordon *et al.* [12] is the only series to report improvement in survival among platinum-sensitive patients, comparing two nonplatinum agents (PLD and topotecan). Having established efficacy in monotherapy, the next step will be the evaluation of treatment behavior in combination with other drugs in platinum-sensitive patients.

Pegylated liposomal doxorubicin in platinum-sensitive recurrent ovarian cancer

As noted in the Introduction, platinum-sensitive disease relapse presents a better prognosis [5,6] and it is recommended that such cases should again be treated with a platinum drug. The response rate is related to the TFI (Table 1).

Up until a few years ago, the subject of debate was whether to treat these women with monochemotherapy or polychemotherapy. From studies such as the ICON 4, AGO OVAR 2.2 [14] and GEICO 0199 surveys [15], we now know the superiority of the combination carboplatin-paclitaxel versus carboplatin as monotherapy in the treatment of women with platinum-sensitive disease relapse. These studies included over 800 platinum-sensitive patients, in whom an increase in median survival was recorded of 29 versus 24 months, as well as an increase in the proportion of women alive after 2 years (57 versus 50%), in favor of the combination therapeutic approach (Table 2).

In contraposition, there was increased neurotoxicity (23%), alopecia (86%) and hematological toxicity in the combination treatment arm; however, the latter (in grade III–IV) was similar in both arms.

These results open the possibility of conducting trials with other schemes in combination with carboplatin. Drugs such as gemcitabine [16,17] and PLD appear optimum to this effect, as they offer a good toxicity profile and efficacy.

Phase II trial of the combination pegylated liposomal doxorubicin plus carboplatin

Consensus is lacking on the PLD dose to be administered with carboplatin. The literature reports different experiences with carboplatin area under curve 5 day 1 plus PLD at doses of 30, 40 and 50 mg/m^2/day 1 every 28 days. In most studies, grade 3–4 mucocutaneous toxicity,

Table 1 Platinum-free interval and response to platinum [5]

Platinum-free interval (months)	Response rate (%)
5–12	27
13–24	33
>24	59

Response rates obtained with platinum therapy following relapse depending on the time elapsed since the end of previous cytostatic treatment.

Table 2 Response and survival data corresponding to two studies [14,15]

	ICON 4		GEICO 0199	
	Platinum	Paclitaxel–platinum	CARBO	Paclitaxel–carboplatin
N	410	392	40	41
RR (%)	54	66	50	75.6
PFS months	9	12[a]	8.4	12.2[a]
OS months	24	29[a]	18	NR[a]

NR, not yet reached; OS, overall survival; PFS, progression-free survival.
[a]Statistically significant.

Table 3 Phase II studies of the PLD and carboplatin combination

Author	PLD dose (mg/m^2)	Carboplatin dose	Response (%)	Grade 3–4 toxicity
González-Billalabeitia [19]	20	AUC 5	68 (95% CI 50–86)	0
	30			Thrombopenia
	35			Thrombopenia/mucositis
	40			Thrombopenia
Vorobiof [20]	50	AUC 5	55 (95% CI 37–73)	Anemia 3%
				Neutropenia 37.9%
				Thrombopenia 27.5%
				Erythrodysthesia 6%
				Stomatitis 6%
PFS months	9	12[a]	8.4	12.2[a]
OS months	24	29[a]	18	NR[a]

Response rate and dose-limiting toxicities reported in different trials with the combination of carboplatin and PLD.
OS, overall survival; PFS, progression free survival; PLD, pegylated liposomal doxorubicin; CI, confidence interval.
[a]Statistically significant.

neutropenia and grade 3–4 thrombopenia were the dose-limiting problems [18–20] (Table 3).

On occasion of ASCO 2002 and 2004, Ferrero [21] presented the results of a multicenter study analyzing the efficacy of the combination PLD–carboplatin in patients with platinum-sensitive relapsing ovarian cancer. This phase II trial with 104 patients documented a 63% global response rate (95% CI 53.6–72.4) and a 38% complete remission rate (95% CI 28.6–47.4). The median survival was 32 months, with a range of 21–36 months according to whether the TFI was 6–12 more than or 12 months, respectively. No serious grade 3–4 toxicities were documented, the most common problems being mucositis and PPE. and the percentage of neurotoxicity and alopecia was low versus the combination carboplatin–paclitaxel (Table 4).

A Canadian trial was presented on occasion of the European Cancer Conference 2005 [7], analyzing the efficacy and safety of PLD–carboplatin at the same doses as in the GINECO trial (30 mg/m^2 and area under curve

Table 4 Toxicity of both combinations with carboplatin

	PLD–carboplatin GINECO (%)	Paclitaxel–carboplatin GEICO 0199 (%)
G3–4 neutropenia	23 (cycles)	18.4 (patients)
G3–4 thrombopenia	8 (cycles)	2.6 (patients)
G3–4 anemia	4 (cycles)	5.3 (patients)
G2–3 neuropathy	–	23.7 (patients)
Alopecia	12 (cycles)	86.8 (patients)
Mucositis	12 (cycles)	18.4 (patients)
Palmoplantar erythrodysthesia	11 (cycles)	–

Toxicity of the carboplatin and PLD combination reported by Ferrero *et al.* (GINECO), as compared to the toxicity reported in the GEICO 0199 study.
PLD, pegylated liposomal doxorubicin.

5, respectively, every 4 weeks) in patients with relapsing ovarian cancer considered to be intermediately sensitive, that is, with a TFI of 6–12 months. Of the 63 predicted patients, a total of 34 were included – with a 40% global response rate (95% CI 24–56). The authors reported a 10% incidence of grade 3–4 adverse effects (anemia, abdominal pain, allergic reactions).

Pegylated liposomal doxorubicin in combination with other drugs (combinations without platinum)

Different authors have explored the activity of PLD in combination with different cytostatic substances other than platinum compounds (Table 5).

Verhaar-Langerais *et al.* [22] have published the results of a phase II study involving the combination of PLD and topotecan. The study included 27 patients with epithelial ovarian cancer that progressed either during treatment or within 6 months after concluding platinum therapy.

The treatment scheme used was: PLD 30 mg/m^2 on day 1 and topotecan 1 mg/m^2 on days 1–5. The treatment was repeated every 21 days.

The analysis of toxicity in the first 12 patients revealed 82% grade 3–4 neutropenia and 18% grade 3–4 thrombopenia – these problems leading to a delay in dose in 45% of the patients. The investigators decided to amend the protocol, reducing the topotecan dose to 0.75 mg/m^2 and increasing the PLD dose to 40 mg/m^2.

The median follow-up duration was 30 months (range 11–48). The complete response rate was 4%, with 24% of partial responses, 44% of patients with stable disease and 28% with disease progression. The median time to progression was 30 weeks (range 4–108 +), whereas the median survival was 41 weeks (1–141 +).

Bourgeois H *et al.* [23] reported the results of a phase I dose-searching study involving the combination of DLP and ifosfamide. The survey included patients with

Table 5 PLD combinations with drugs that are different from platinum

Combination	Response (%)	Grade 3–4 toxicity
PLD–topotecan [22]	28	Leukopenia/neutropenia Anemia Thrombopenia
PLD–ifosfamide [23]	22.9	Leukopenia/neutropenia Anemia Thrombopenia Mucositis Diarrhea Emesis
PLD–gemcitabine [24]	34	Leukopenia/neutropenia Anemia Thrombopenia Palmoplantar erythrodys-testhesia Mucositis Diarrhea Nausea
PLD–gemcitabine [25]	22	Leukopenia/neutropenia Anemia Thrombopenia Esophagitis-stomatitis Alopecia Cutaneous Pulmonary palmoplantar erythrodys-testhesia Allergia
PLD–gemcitabine [26]	33	Leukopenia/neutropenia Anemia Thrombopenia Mucositis/Estomatitis Estreñimiento Emesis Palmoplantar erythrodys-testhesia Edema Dyspnea
PLD–vinorelbine [27]	20.7	Leukopenia/neutropenia Anemia Thrombopenia Neutropenic fever Palmoplantar erythrodys-testhesia Constipation

PLD, pegylated liposomal doxorubicin.

advanced ovarian cancer in progression with one or more chemotherapy lines; the patients had received at least one treatment with platinum salts.

The management plan consisted of the administration of PLD on day 1, and ifosfamide 1700 mg/m^2/day on days 1–3 every 28 days. The starting dose of PLD was 25 mg/m^2, which was increased in 5-mg steps in the following patient cohorts until the maximum tolerated dose was defined.

A total of 51 patients were included, of which 48 were eligible and received the treatment as programmed. Fifteen patients had platinum-sensitive disease, whereas 33 patients had platinum-resistant disease.

The maximum tolerated dose was 45 mg/m^2, although the dose recommended for future studies was DLP 40 mg/m^2 on day 1 and ifosfamide 1700 mg/m^2 on days 1 and 3, every 28 days. The most relevant side effects were grade 3–4 neutropenia in 55.7% of the cycles, febrile neutropenia in 4%, grade 3–4 anemia in 12.5%, grade 3–4 thrombopenia in 6%, emesis in 23% and diarrhea in 6%. Although a secondary objective, the authors reported a 22.9% objective response rate.

D'Agostino *et al.* [28] conducted a phase II trial combining PLD and gemcitabine. The study included women with advanced recurrent ovarian cancer following at least one first-line of chemotherapy with platinum–taxane. The patients were administered PLD at a dose of 30 mg/m^2 on day 1, and gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days.

A total of 70 patients were included, of which 67 were evaluable to the effects of treatment response.

The most relevant toxicity was grade 3–4 neutropenia in 35.6% of the patients, grade 3–4 anemia in 7%, grade 3–4 thrombopenia in 8.5%, grade 2–3 PPE in 25.7%, grade 2–3 stomatitis in 25.7%, grade 2–3 paresthesias in 4.2% and grade 2–3 diarrhea in 5.6% of the cases.

The efficacy data were: 34.3% of responses (95% CI 23–45.6), 38.8% of patients with stable disease (95% CI 27.1–50.5) and 26.9% with disease progression (95% CI 16.3–47.5). The median time to progression was 28 weeks (range 4–97).

Of the 67 patients, 36 presented criteria of resistance to platinum, whereas 31 were classified as platinum-sensitive. The patients with platinum-sensitive disease showed a 45% response rate (95% CI 27.7–62.7), whereas 41.9% presented stable disease (95% CI 24.5–59.3).

These authors have published an update of the study data [24]. Inclusion was extended to 111 patients, of whom 106 could be evaluated for the effect of response. The complete response rate was 8.5% (95% CI 3.2–13.8), with 25.5% partial responses (95% CI 17.3–33.7) and stable disease in 34% (95% CI 24.9–42.9). The median duration of the responses was 22 weeks (range 3–122).

The patients with platinum-sensitive disease showed a 53.7% objective response rate (95% CI 38.4–69), with stable disease in 36.6% (95% CI 21.9–51.3).

With a median follow-up of 46.5 weeks, the survival data were as follows: progression-free survival (median) 28 weeks, global survival (median) 60 weeks.

By subgroups, the results in the platinum-sensitive patients were as follows: progression-free survival (median) 35 weeks, global survival (median) 92 weeks. In turn,

among the platinum-resistant patients, the results were as follows: progression-free survival (median) 20 weeks, global survival (median) 50 weeks.

With this same combination of gemcitabine and PLD, the Swiss cooperative group conducted a phase II study [25] including 37 patients with platinum-resistant advanced ovarian cancer.

The treatment scheme was gemcitabine 650 mg/m^2 on days 1 and 8, plus PLD 25 mg/m^2 on day 1, every 28 days.

The reported grade 3–4 side effects were as follows: anemia 13.5%, neutropenia 19%, thrombopenia 3%, PPE 3% and allergic reaction 3%.

As to efficacy, the objective response rate was 22% (95% CI 10–39) and 5.5% presented stable disease (95% CI 0.7–18.7). With a median follow-up of 16.2 months, the median survival was 8.4 months.

Investigators of the AGO group have published their experiences with this same combination. [26]. The PLD dose administered was 30 mg/m^2 on day 1, whereas the gemcitabine dose was 650 mg/m^2 on days 1 and 8, every 28 days. The study included 30 patients with criteria of refractory or platinum-resistant disease. The response rate was seen to be 33% (95% CI 17–49). The most relevant grade 3–4 toxicity was hematological (leukopenia, neutropenia).

Comparative trials with pegylated liposomal doxorubicin

After completing patient recruitment, the SWOG 200 trial compares carboplatin with or without PLD, in platinum-sensitive recurrent disease, on the basis of improvement in global survival. In this same situation and in the open phase we have the CALYPSO study, which compares paclitaxel–carboplatin versus PLD–carboplatin.

On occasion of ASCO in May 2005, Pignata *et al.* [29] reported the preliminary results of a multicenter study (MIT0-2) comparing carboplatin and paclitaxel versus carboplatin and PLD in patients with previously untreated, advanced-stage ovarian cancer. The primary endpoint is progression-free survival. The data corresponding to the 96 patients registered up until July 2004 were presented. No deaths owing to toxicity were documented in the PLD–carboplatin treatment arm, whereas one toxic death was recorded in the paclitaxel–carboplatin arm. Regarding hematological toxicity, grade 3 anemia was observed in 17 (PLD) versus 10% (paclitaxel), grade 3 neutropenia in 34 (PLD) versus 24% (paclitaxel), grade 4 neutropenia in 11 (PLD) versus 24% (paclitaxel) and grade 3 thrombopenia in 19 versus 10%. Alopecia was recorded in 6% of the patients administered PLD–carboplatin and in 81% of those receiving paclitaxel–carboplatin. In turn, peripheral neuropathy was more common in the patients administered paclitaxel: grade 1 in 33% and grade 2 in 8%. In contrast, PPE was only reported in the patients treated with PLD: grade 1 in 13% and grade 2 in 2% [29].

Conclusions

PLD is effective in the treatment of women with relapsing ovarian cancer. If offers better results compared with topotecan in patients with relapsing disease considered to be nonsensitive to platinum drugs. The latest data recorded indicate improved survival in platinum-sensitive patients versus other nonplatinum drugs.

In the context of platinum-sensitive recurrent malignancy, phase II trials in combination with platinum have yielded a percentage response (63%) similar to that afforded by the classical combination of paclitaxel–carboplatin (66%), though with a superior complete response rate (38%). The drug should be taken into account in the treatment of patients when it is not possible to use taxanes or platinum derivatives.

The studies in course will confirm its use in first-line treatment for advanced ovarian cancer, as part of sequential therapies, triplets or in substitution of the classical combination of taxane and platinum.

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