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Randomized Trial of Single Agent Paclitaxel Given Weekly Versus Every Three Weeks and with Peroral Versus Intravenous Steroid Premedication to Patients with Ovarian Cancer Previously Treated with Platinum

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The aim of this study was to evaluate the efficacy and toxicity of paclitaxel given at the same dose intensity and administered weekly (arm A) or every 3 weeks (arm B), and to assess the safety of intravenous steroids versus standard peroral premedication. Two hundred and eight patients with advanced ovarian cancer previously treated with no more than one platinum-containing regimen were randomized to receive either a weekly infusion of paclitaxel or an infusion every 3 weeks. The median delivered dose intensity was 77.6 mg/m^2/week in the weekly arm, and 72.7 mg/m^2/week in the every 3 weeks arm. WHO grade 3–4 hematological and non-hematological toxicity occurred more frequently in arm B. No difference in number of severe events of hypersensitivity, response rate, time to progression or survival between arms was observed. Weekly paclitaxel at a dose of 67 mg/m^2/week was found to have a better safety profile and seemed to be as effective as the equivalently dosed schedule every 3 weeks. Intravenous steroids are a safe alternative to oral steroids.

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The current standard treatment for advanced ovarian cancer is paclitaxel in combination with a platinum-containing drug. This is an effective regimen, with a high clinical response rate and a prolonged progression-free and overall survival compared to regimens without paclitaxel (1, 2).

Paclitaxel is also an active agent in previously treated patients even when the tumor is platinum resistant (3–10). However, the adverse reactions can sometimes be troublesome. In most patients total, but reversible, alopecia is seen and the neurotoxicity can sometimes be disabling and long lasting, especially when paclitaxel is given in combination with cisplatin or to patients who had previously been treated with a platinum agent. Other common adverse reactions are arthralgia, myalgia and fatigue. Serious allergic reactions, frequently seen in earlier studies, are uncommon since the introduction of premedication.

Paclitaxel is usually given as a 3- or 24-h infusion every 3 weeks, but it cannot be ruled out that paclitaxel given with a shorter interval could have the same or better efficacy, with fewer side effects. In recent studies, paclitaxel has been given weekly, either alone or in combination with other drugs or radiation (11–15). In a pilot study, Andersson et al. (11) reported on 40 women with advanced, previously treated, ovarian carcinomas who were given up to 22 weekly treatments with paclitaxel. The initial dose of 67 mg/m^2 was increased in two steps up to 81 mg/m^2 in most patients. The clinical response rate was 28%–22% in patients with platinum-resistant disease compared with 42% in patients with platinum-sensitive tumors. The toxicity was acceptable and possibly less pronounced than that with the every 3 weeks schedule.

In general, patients receive premedication consisting of a corticosteroid administered orally 12 and 6 h before pacli-

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taxel, and cimetidine and clemastine (or diphenhydramine) intravenously just before the paclitaxel infusion.

Premedication with an oral steroid might impose some inconvenience for the patients and problems with compliance. At the time this study was designed, there were no reports evaluating intravenous steroids given immediately before paclitaxel administration.

In the present randomized multicenter study, paclitaxel-naïve women with recurrent or progressive ovarian cancer were treated with paclitaxel given either weekly or every 3 weeks. The primary purpose of this study was to compare the clinical response rate in the two groups. Response duration, progression-free and overall survival and adverse reactions were also studied. Furthermore, the patients were randomized between oral and intravenous steroids and the frequency and seriousness of hypersensitivity reactions were compared.

MATERIAL AND METHODS

Eligibility

Patients with a histologically proven diagnosis of epithelial ovarian carcinoma were eligible for enrollment in this study. Patients were required to be 18–75 years of age, and to provide informed consent that had been approved by the Ethics Committee.

No more than one prior platinum-containing regimen was allowed, and evidence of progression during or progression/relapse after administration of the last platinum course was to be documented prior to study entry. At entry, all patients were required to have measurable disease documented clinically and/or radiologically, and adequate physiologic function and status (absolute neutrophil count $\geq 2.0 \times 10^9$, platelet count $\geq 100 \times 10^9$, serum creatinine $\leq 1.25 \times$ upper limit of normal, total bilirubin $\leq 1.25 \times$ upper limit of normal, Karnofsky performance status ≥ 60, and an anticipated survival ≥ 12 weeks).

Patients with a history of atrial or ventricular arrhythmias or congestive heart failure, even if medically controlled, or documented myocardial infarction within 6 months or a history of 2nd or 3rd degree heart block were not eligible. Patients with pre-existing motor or sensory neurotoxicity $>$ grade 2 according to the WHO criteria were also not eligible.

Prior to study entry, patients were stratified according to platinum resistance (i.e. relapse ≤ 6 months and > 6 months after primary platinum-based therapy). Stratification and randomization was performed at the Bristol-Myers-Squibb office in Stockholm.

Patient demographic and clinical characteristics are listed in Table 1.

Table 1

Patients' characteristics

	Paclitaxel 67 mg/m^2/week n = 105 A1/A2	Paclitaxel 200 mg/m^2/3 weeks n = 103 B1/B2
Age (years)		
Median	59	60
Range	37–74	40–76
Performance status (WHO)		
0	57	56
1	40	33
2	8	14
Platinum-resistant tumor (relapse $\pm$ 6 months after primary chemotherapy)		
Yes	57	51
No	48	52
Tumor size at inclusion		
≤ 2 cm	7	11
2–5 cm	34	26
5–10 cm	30	26
≥ 10 cm	33	40
Unknown	1	0
Paresthesia at inclusion (WHO)		
Grade 0	92	91
Grade 1	13	12

Treatment plan

Patients received treatment randomly according to a bifactorial design (Table 2). Group A1/A2 received paclitaxel 67 mg/m^2/week over a time period of 3 h. One course was defined as 3 weeks of therapy. Group B1/B2 received 200 mg/m^2 every 3 weeks over a 3-h period. Cycles were to be given as planned, i.e. it was not permissible to prolong the treatment-free interval. Dose modifications were allowed. If no hematological toxicity occurred, the dose was escalated maximally by two steps (Table 3). Dose reduction was performed in the case of severe cytopenia. Patients who could not tolerate the lowest dose level were taken off the study treatment. No dose escalation was allowed once a dose reduction had been made. If the infusion was interrupted due to a hypersensitivity reaction, patients could be retreated at the investigator's discretion. A decision on whether or not to continue treatment with paclitaxel was made on the basis of tumor reassessments every 6 weeks. Patients with disease progression (PD) were taken off the study.

Patients with stable disease (SD) received treatment until either progression or unacceptable toxicity occurred. Pa-

Table 2

Study design (bifactorial randomization)

	Oral steroids 12 and 6 h prior to paclitaxel	Parenteral steroids 30 min prior to paclitaxel
Arm A Paclitaxel given 67 mg/m^2/week	A1	A2
Arm B Paclitaxel given 200 mg/m^2/3 weeks	B1	B2

Table 3

Dose modifications (treatment started at dose level 0)

A1/A2 dose level	−2	−1	0	+1	+2
Paclitaxel mg/m^2/week	48	57	67	75	81
B1/B2 dose level	−2	−1	0	+1	+2
Paclitaxel mg/m^2/3 weeks	145	170	200	225	242

tients who achieved a complete response (CR) or partial response (PR) continued the study treatment for a minimum of 6 weeks and thereafter at the investigator's discretion to tumor progression/relapse or unacceptable toxicity, whichever came first.

Premedication consisted of oral dexamethasone 20 mg or its equivalent administered 12 and 6 h before paclitaxel administration, total dose 40 mg (arms A1/B1), or dexamethasone 20 mg given intravenously 30 min prior to paclitaxel (arms A2/B2). Premedication with clemastine 2 mg and cimetidine 300 mg (or ranitidine 50 mg) was given intravenously to all patients 30 min before treatment with paclitaxel.

With the exception of the study medication given, all patients were treated in a similar way.

Efficacy and safety evaluations

Hematological evaluation was performed at baseline and then weekly during the treatment period. Serum creatinine, alkaline phosphatases, bilirubin and liver enzymes were measured at baseline and every 3 weeks during treatment. Performance status (Karnofsky) was assessed at baseline and at the start of each treatment cycle. Subjective toxicity (WHO) was recorded before every treatment. Tumor evaluations were performed at baseline and every 6 weeks with physical examinations and appropriate radiological investigations. The image technique used at baseline to measure a given tumor lesion was repeated throughout the study period. WHO tumor response criteria were used (16). In the case of two observations being missing, not less than 4 weeks apart, tumor response was judged as not confirmed. Time to progression (TTP) was calculated from the first day of study treatment to the day of documented tumor progression (PD) or censored observation. Response duration for patients who obtained CR was calculated from the day of first observation of complete response to the day of documented PD or censored observation. For patients who obtained PR, duration was calculated from the first day of the study treatment to the day of documented PD or censored observation. Overall survival was calculated from the date of randomization to death or censored observation. Survival distributions were estimated by the Kaplan–Meier method and survival differences between groups were analyzed using the log-rank test. Toxicity was tabulated and differences between groups were analyzed using the Fisher exact test or the χ^2 test. All analyzed data were validated by a monitoring procedure of study sites throughout the study period.

Quality of life was not recorded in a protocolized manner.

Statistics

The sample size was determined to detect a $\geq 15\%$ total difference in objective response rate (CR + PR) between patients receiving weekly paclitaxel and those receiving paclitaxel every third week (i.e. A1, A2 vs. B1, B2). From the Nordic Ovarian Taxol Study (052 + 802) the frequency of objective response in a similar population when paclitaxel was given every 3rd week was estimated to 28%. Assuming a 43% higher response rate in the experimental arm and using a two-sided $\alpha = 0.05$ level test, a total of 318 patients (159/arm) were needed to detect a relative difference of $\geq 54\%$ with 80% power in terms of response rate. To ensure a sufficient number of evaluable patients, we planned to include 350 patients.

The incidence of hypersensitivity reactions (all grades) with oral steroids was estimated to be 34%. A projected number of 350 patients would allow a detection rate of approximately 30% relative difference or greater between patients with oral and parenteral steroid premedication.

RESULTS

A total of 208 patients from 10 different centers (Table 4) were randomized between February 1995 and June 1998. At the date of analysis the median observation time was 27 months (range 7–47$^+$ months).

Intent-to-treat analysis was performed in 208 patients for efficacy analysis. A total of 205 patients who actually received paclitaxel were considered for safety evaluation. Three patients never received treatment. In addition, a per-protocol analysis was performed to assess the response rate for those 177 patients who were treated for at least 9 weeks.

Two patients were non-eligible, one patient in the every 3 weeks group was 76 years of age, and one patient in the weekly group had non-measurable disease at inclusion. The different arms were well balanced and there were no statistically significant differences between the two treatment groups at inclusion.

Table 4

Participating centers and number of patients included

Hospital	No. of patients included
Gothenburg (Swe)	89
Linköping (Swe)	19
Lund (Swe)	27
Örebro (Swe)	12
Umeå (Swe)	48
Kuopio (Fin)	2
Oulu (Fin)	5
Turku (Fin)	2
Joensuu (Fin)	1
Tampere (Fin)	3
Total	208

Table 5

Hematological toxicity (lowest value per patient)

	Paclitaxel 67 mg/m^2/week n = 104 A1/A2	Paclitaxel 200 mg/m^2/3 wks n = 101 B1/B2	p-value (Fisher's exact test)
Grade 1–4			
Hemoglobin	81 (78%)	65 (64%)	0.04
WBC	74 (71%)	79 (78%)	0.27
Neutrophils	63 (61%)	80 (79%)	<0.01
Platelets	1 (1%)	5 (5%)	0.12
Grade 3–4			
Hemoglobin	4 (4%)	4 (4%)	1.0
W.B.C.	17 (16%)	17 (17%)	1.0
Neutrophils	19 (18%)	45 (45%)	<0.001
Platelets	0	1 (1%)	0.49

Treatment

Of the 205 patients treated, 104 were randomized to the weekly arm and 101 to the every 3 weeks arm. The weekly group received 1694 treatments, i.e. 565 courses, equivalent to a 3-weekly schedule, compared with 717 courses for the every 3 weeks group. The median number of courses was 5.7 (range: 1–16) and 7 (range: 1–17), in the weekly and every three weeks groups, respectively ($p = 0.002$). One patient in the weekly arm received 48 treatments (48 weeks or 16 courses). The total median dose given was lower in the weekly arm, 1 330 mg/m^2 versus 1 618 mg/m^2 in the every 3 weeks arm.

At 9 weeks, 32 patients in the weekly group had been withdrawn from the study for the following reasons: disease progression (14 patients), prolongation of treatment-free interval (8 patients), patient request (4 patients), investigator decision (2 patients), study drug toxicity (1 patient) and other reasons (3 patients), compared with 20 patients in the every 3 weeks group: disease progression (9 patients), study drug toxicity (4 patients), prolongation of treatment-free interval (3 patients), patient request (2 patients), death (1 patient), and other reasons (1 patient).

The median dose intensity (mg/m^2/week) was higher in the weekly arm, 77.6 and 72.7, respectively ($p < 0.0001$). The paclitaxel dose given in the weekly schedule was increased more often than the paclitaxel dose given every 3 weeks. Patients in the weekly arm received a dose level of +2 in 61% of the treatments, compared with 28% in the every 3 weeks schedule.

Safety

The safety analysis was based on 205 patients who received at least one dose of paclitaxel. Most of the treatment cycles were administrated in an outpatient setting. Overall, therapy was well tolerated and no treatment-related deaths were reported.

Hematological toxicity. Severe hematological toxicity was uncommon (Table 5). Significantly more patients in the every three weeks group experienced grade 3 or 4 neutropenia, 45/101 (45%), compared to 19/104 (18%) in the weekly group. This difference was statistically significant ($p < 0.001$). Thrombocytopenia was uncommon in both groups.

Non-hematological toxicity. Non-hematological toxicity such as neuropathy, arthralgia, myalgia were frequently seen in both groups, mainly of grade 1–2 intensity (Table 6). No grade 4 events were reported. A statistically significant difference in severe toxicity (grade 3) between the groups was found for neuropathy and alopecia, favoring the weekly schedule, whereas grade 3 nail changes (discolored nails and/or loosening from the nail bed) were observed only in this group. Grade 1–3 arthralgia and myalgia were reported more frequently in the every 3 weeks group (84%) than in the weekly group (59%). This difference was statistically significant ($p < 0.001$). No statistical difference was found in nausea and vomiting between the groups.

Hypersensitivity reactions. Number and severity of hypersensitivity reactions were compared between the 106 patients who received the standard premedication schedule, i.e. oral steroids 12 and 6 h prior to paclitaxel, and the 99 patients who received parenteral steroids 30 min prior to paclitaxel (Table 7). There were no statistically significant differences between the two groups, either overall or for grade 3–4 reactions. The paclitaxel infusion was discontinued in about 3% of patients in both arms because of hypersensitivity reactions.

Response rate

Of 205 patients randomized, 37 patients in the weekly group and 38 patients in the every 3 weeks group responded to treatment (Table 8), which is not statistically significant ($p = 0.89$).

Neither was there any statistical difference between the two groups regarding overall response rates in platinum-resistant patients (19% in the weekly group and 26% in the

Table 6

Non-hematological toxicity (worst value per patient)

	Paclitaxel 67 mg/m^2/week n = 104 A1/A2	Paclitaxel 200 mg/m^2/3 wks n = 101 B1/B2	p-value (Fisher's exact test)
Grade 1–3			
Neuropathy	84 (81%)	86 (85%)	0.72
Alopecia	85 (82%)	91 (90%)	0.11
Arthralgia/Myalgia	61 (59%)	85 (84%)	<0.001
Nausea/Vomiting	48 (46%)	42 (42%)	0.57
Nails	37 (36%)	2 (2%)	<0.001
Grade 3			
Neuropathy	11 (11%)	29 (29%)	<0.001
Alopecia	48 (46%)	80 (79%)	<0.001
Arthralgia/Myalgia	5 (5%)	8 (8%)	0.40
Nausea/Vomiting	4 (4%)	3 (3%)	1.0
Nails	9 (9%)	0	<0.01

every 3 weeks group), although there was a difference regarding number of complete responders among these patients favoring the every 3 weeks schedule (14% versus 6%).

Response duration and time to progression

The overall median response duration was 9.4 months (95% confidence interval, 6.2–13.9) for the weekly group, and 12.4 months (95% confidence interval, 9.1–14.3) for the every 3 weeks group ($p = 0.57$). Complete response duration was shorter in the weekly group with 4.5 months (95% confidence interval, 3.6–10.7) compared with 7.8 months (95% confidence interval, 4.2–10.2) in the every 3 weeks group ($p = 0.84$). Median time to progression (Fig. 1) was 6.1 months (95% confidence interval, 5.0–8.0) in the weekly group, and 8.1 months (95% confidence interval, 6.4–9.7) for the every 3 weeks group ($p = 0.85$).

Survival

The median survival (Fig. 2) for the weekly group was 13.6 months (10.5–18.7), and 14.7 months (12.3–19.1) for the every 3 weeks group ($p = 0.98$).

Table 7

Hypersensitivity reactions (number of events)

	Oral steroids 12 and 6 h prior to paclitaxel n = 106 A1/B1	Parenteral steroids 30 min prior to paclitaxel n = 99 A2/B2
Grade 1–4		
Skin	17 (16.0%)	18 (18.2%)
Generalized urticaria	1 (0.9%)	0
Dyspnea	4 (3.8%)	4 (4.0%)
Respiratory distress requiring treatment	1 (0.9%)	1 (1.0%)
Hypotension	1 (0.9%)	1 (1.0%)
Grade 3–4		
Skin	3 (2.8%)	4 (4.0%)
Generalized urticaria	1 (0.9%)	0
Dyspnea	0	1 (1.0%)
Respiratory distress requiring treatment	1 (0.9%)	0

DISCUSSION

Although paclitaxel has proven activity in taxane-naïve ovarian cancer patients, the optimal dose and schedule has not been defined. Hitherto, most studies have focused on 3- or 24-h infusion every 3 week (17). However, in vitro studies indicate that the duration of exposure might be an important factor in the cytotoxic activity of this group of drugs (18). This thought is further supported by the observed activity of prolonged 96-h infusion of paclitaxel to patients whose tumors had progressed during shorter infusions of the drug (19, 20).

Table 8

Response rate

	Paclitaxel 67 mg/m^2/week n = 105 A1/A2	Paclitaxel 200 mg/m^2/3 wks n = 103 B1/B2
Intent-to-treat analysis		
CR[1]	13 (12.4%)	17 (16.5%)
PR[3]	24 (22.8%)	21 (20.4%)
Overall response rate	37 (35.2%)	38 (36.9%)
SD	43 (41.0%)	33 (32.0%)
PD	15 (14.3%)	19 (18.5%)
NE	9 (8.6%)	11 (10.7%)
Not treated	1 (0.9%)	2 (1.9%)
Per-protocol analysis	n = 87	n = 90
CR[2]	12 (13.8%)	16 (17.8%)
PR[3]	24 (27.6%)	21 (23.3%)
Overall response rate	36 (41.4%)	37 (41.1%)
SD	36 (41.4%)	34 (37.8%)
PD	15 (17.2%)	19 (21.1%)

[1] Three patients in each group had unconfirmed complete response.
[2] Three and two patients in the weekly and every three week group respectively had unconfirmed complete response.
[3] Seven and six patients in the weekly and every three week group respectively had unconfirmed partial response.

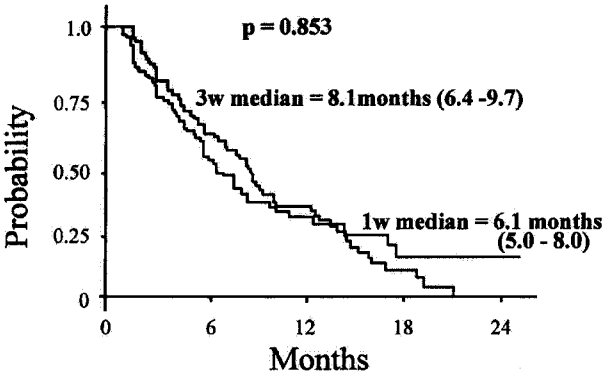

Fig. 1. Time to progression: intention to treat analysis.

Such a long infusion time is, however, often considered impractical by both the patient and the hospital staff. Weekly dosing of paclitaxel is a method mimicking prolonged drug exposure.

This schedule has resulted in promising overall response rates ($\geq 50\%$) seen in small phase I–II studies. Doses up to 80 mg/m^2 administered during one hour have resulted in a mild toxicity (12, 21).

The purpose of this study was to investigate the efficacy and safety of two different time schedules, while the dose intensity was planned to be the same in the two arms.

The dose of 200 mg/m^2 in the control arm was chosen in order to be able to give a reasonably high dose in the weekly schedule, i.e. 67 mg/m^2. Dose escalation up to 81 mg/m^2 was allowed in those patients where no hematological toxicity was encountered. As patients in the weekly arm received 61% of the cycles at dose level +2 (81 mg/m^2) compared with only 28% of the cycles for the every 3 weeks patients, the median dose intensity turned out to be almost 7% higher in the weekly arm. In contrast, the median total dose in the weekly arm was 22% lower than the total dose given in the every 3 weeks schedule. This is explained by the fact that more patients in the weekly arm (32 patients vs. 20) were taken off the study early, i.e.

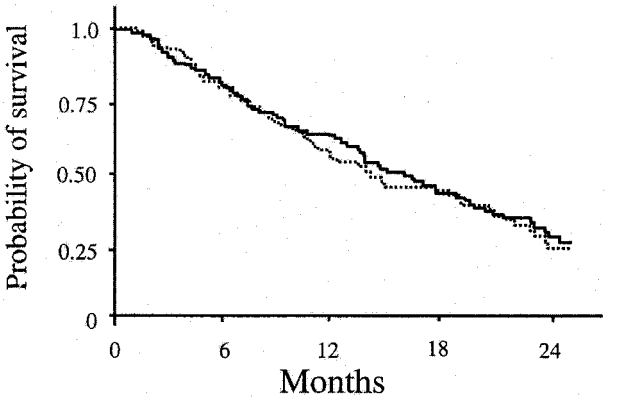

Fig. 2. Survival: intention to treat. — 3w median = 14.7 months (12.3–19.1); .... 1 w median = 13.6 months (10.5–18.7); p = 0.980.

within 9 weeks, due to either early progression or for administrative reasons. The difference between the arms regarding number of early progressions may be because of a low initial weekly dose and because some patients may have had a more aggressive tumor biology.

Owing to an increasing lack of recurring taxane-naïve patients during the study period, we were forced to close the inclusion when 208 patients were randomized. Although we could not detect any statistically significant difference between the arms regarding response rate, time to progression and survival, there is still a possibility that a true difference exists, given the limited number of patients.

Prophylactic intravenous steroids given immediately before the paclitaxel infusion did not imply any statistically detectable increase in the risk of hypersensitivity reactions compared to the conventional peroral intake of steroids 12 and 6 h before each treatment. Although there still is a possibility that with a larger sample size a difference would have been detected, we do not think that the observed frequency of clinically relevant reactions motivates the abandonment of steroids given intravenously. Recently, two reports have been published which substantiate this opinion (22, 23).

Weekly administration of paclitaxel may impose some inconvenience compared to the every 3 weeks schedule, but the toxicity profile favored the weekly administration. In addition, the overall response rate of 36% compares well with the results from other studies in which second-line paclitaxel was administered in conventional doses every 3 weeks to taxane-naïve, ovarian cancer patients (3–10). The higher actual dose intensity also indicates that a higher weekly dose than the present is feasible. This is also supported by others. Fenelly et al. (12) administered weekly paclitaxel to women with relapsed ovarian cancer in a phase I study. All had been treated before with paclitaxel and cisplatin. The drug was given as a 1-h infusion and at the highest dose level (100[PR1] mg/m^2) the dose intensity was 90.75 mg/m^2. The response rate was 30%. Two of the responding women had previously mad progress on the standard 3 weeks schedule. In a retrospective study, weekly paclitaxel doses between 80 and 100 mg given to 45 heavily pretreated women with ovarian carcinoma resulted in an overall response rate of 29%, with a low frequency of hematological and non-hematological toxicity (21).

Although a high proportion of patients (60–80%) with advanced ovarian cancer respond to modern, taxane and platinum-containing first-line therapy, about 70% will later experience progress and ultimately succumb to their disease. There is still a considerable lack of knowledge about the impact of salvage chemotherapy in terms of survival and quality of life (24).

In our opinion, the efficacy data and the significantly lower toxicity, excluding nail toxicity, regarding neuropathy, arthralgia/myalgia, alopecia and neutropenia with weekly treatments make this an interesting alternative to the conventional schedule of every 3 weeks both in the first-line setting and as salvage therapy.

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