original article

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Trabectedin plus pegylated liposomal doxorubicin in relapsed ovarian cancer delays third-line chemotherapy and prolongs the platinum-free interval

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Background: OVA-301 is a large randomized trial that showed superiority of trabectedin plus pegylated liposomal doxorubicin (PLD; CentoCor Ortho Biotech Products L.P., Raritan, NJ, USA). over single-agent PLD in 672 patients with relapsed ovarian cancer, particularly in the partially platinum-sensitive subgroup [platinum-free interval (PFI) of 6–12 months]. This superiority has been suggested to be due to the differential impact of subsequent (platinum) therapy.
Patients and methods: A detailed analysis of subsequent therapies and survival outcomes in the overall population and in the subsets according to platinum sensitivity was therefore conducted.
Results: Similar proportions of patients received subsequent therapy in each arm (76% versus 77%), including further platinum-based regimens (49% versus 55%). Patients in the trabectedin/PLD arm received subsequent chemotherapy at a later time (median delay 2.5 months versus PLD arm). Overall survival from subsequent platinum was significantly prolonged in the partially platinum-sensitive disease subset (hazard ratio = 0.63; $P = 0.0357$).
Conclusion: The superiority of trabectedin/PLD over single-agent PLD in OVA-301 cannot be explained by differences in the extent or nature of subsequent therapies administered to these patients. On the other hand, these exploratory analyses support the hypothesis that the enhanced survival benefits in the partially platinum-sensitive subset might be due to an extended PFI leading to longer survival with subsequent platinum.
Key words: pegylated liposomal doxorubicin, platinum-free interval, relapsed ovarian cancer, trabectedin

introduction

Trabectedin is a marine-derived antineoplastic agent first isolated from the tunicate *Ecteinascidia turbinata* and currently produced synthetically, which has shown *in vitro* and *in vivo* activity in multiple tumor types, including soft tissue sarcoma (STS) [1–4] and ovarian cancer [5–7]. Trabectedin was first approved as a single agent in the European Union in 2007 and, subsequently, in many other countries worldwide for the treatment of STS patients after failure of standard-of-care chemotherapies. Trabectedin in combination with pegylated liposomal doxorubicin (PLD) was approved in the European Union in 2009 for the treatment of patients with relapsed, platinum-sensitive ovarian cancer [8].

The basis for the label extension in ovarian cancer was mainly the positive results of a large phase III trial (OVA-301), in which 672 patients in relapse after initial platinum-based chemotherapy were randomly assigned to receive either trabectedin/PLD or PLD alone. The trial was stratified by platinum sensitivity, with one-third of the patients having platinum-resistant disease [i.e. platinum-free interval (PFI) < 6 months] at baseline. Progression-free survival (PFS) by independent radiology review was the primary end point [9, 10]. When combined with PLD, trabectedin significantly prolonged PFS over PLD alone with acceptable tolerability, as reflected by short-lived, noncumulative and predictable toxicity, with no new or unexpected toxic effects. In the platinum-sensitive stratum (PFI ≥ 6 months), the risk reduction

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of disease progression or death was 27% [hazard ratio (HR) = 0.73; $P = 0.0170$; median PFS 9.2 versus 7.5 months]. A protocol-specified interim analysis of overall survival (OS) was conducted with 300 events (versus 520 required for the final OS analysis) showing a 15% reduction in the risk of death with the combination (HR = 0.85; $P = 0.1506$). An updated OS interim analysis was conducted, at the request of regulatory authorities, with an additional year of follow-up and 419 events, the results of which have been presented elsewhere [8, 11, 12]. The updated OS results confirmed and strengthened those reported previously in a more mature dataset (HR = 0.85; $P = 0.092$). A significant 41% decrease in the risk of death was found in the partially platinum subset (HR = 0.59; $P = 0.0015$) [12]. Median OS for the partially platinum-sensitive subset was 23.0 months in the trabectedin/PLD arm versus 17.1 months in the PLD arm (median difference of 5.9 months). Importantly, for this subgroup, this difference in median OS is greater than the difference in median PFS (1.9 months).

In vitro and clinical data suggest that extension of PFI by intercalation of a nonplatinum therapy before platinum rechallenge may provide clinical benefit, particularly in patients with partially platinum-sensitive relapsed ovarian cancer [13–17]. The current report evaluates the subsequent therapies administered to OVA-301 patients after discontinuation of protocol therapy and their potential effects on the OS of these patients. Furthermore, the current hypothesis-generating analyses evaluated whether enhanced survival benefits with trabectedin/PLD over PLD alone in this trial could be ascribed

Table 1. Summary of subsequent therapies (all randomized patients)

All randomized patients	PLD ($n = 335$), n (%)	Trabectedin/ PLD ($n = 337$), n (%)	Total ($N = 672$), n (%)
Any subsequent therapy[a]	259 (77)	257 (76)	516 (77)
Chemotherapy	244 (73)	236 (70)	480 (71)
Platinum based	183 (55)	164 (49)	347 (52)
Nonplatinum based	61 (18)	72 (21)	133 (20)
Surgery (major cytoreduction)	14 (4)	19 (6)	33 (5)
Biological/hormonal therapy	30 (9)	32 (9)	62 (9)
Radiation therapy	14 (4)	24 (7)	38 (6)
Miscellaneous[b]	9 (3)	6 (2)	15 (2)

Categories shown are not mutually exclusive (one patient could receive more than one type of subsequent therapy) except for chemotherapy. For example, 79% of patients who had surgery did also receive chemotherapy.
[a]A total of 156 patients did not receive subsequent therapy: 61 of them (28 in PLD arm and 33 in trabectedin/PLD arm) were alive at last follow-up.
[b]Mostly experimental drugs.
PLD, pegylated liposomal doxorubicin.

Table 2. Summary of subsequent therapies (per platinum sensitivity subset)

Platinum-resistant subset (PFI < 6 months)	PLD ($n = 123$), n (%)	Trabectedin/PLD ($n = 119$), n (%)	Total ($N = 242$), n (%)
Any subsequent therapy	90 (73)	85 (71)	175 (72)
Chemotherapy	80 (65)	79 (66)	159 (66)
Platinum based	47 (38)	39 (33)	86 (36)
Nonplatinum based	33 (27)	40 (34)	73 (30)
Surgery (major cytoreduction)	4 (3)	9 (8)	13 (5)
Biological/hormonal therapy	11 (9)	9 (8)	20 (8)
Radiation therapy	4 (3)	9 (8)	13 (5)
Partially platinum-sensitive subset (PFI 6–12 months)	**PLD ($n = 91$), n (%)**	**Trabectedin/PLD ($n = 123$), n (%)**	**Total ($N = 214$), n (%)**
Any subsequent therapy	73 (80)	99 (80)	172 (80)
Chemotherapy	71 (78)	91 (74)	162 (76)
Platinum based	52 (57)	69 (56)	121 (57)
Nonplatinum based	19 (21)	22 (18)	41 (19)
Surgery (major cytoreduction)	1 (1)	2 (2)	3 (1)
Biological/hormonal therapy	9 (10)	19 (15)	28 (13)
Radiation therapy	3 (3)	5 (4)	8 (4)
Platinum-sensitive subset (PFI >12 months)	**PLD ($n = 122$), n (%)**	**Trabectedin/PLD ($n = 95$), n (%)**	**Total ($N = 217$), n (%)**
Any subsequent therapy	97 (80)	74 (78)	171 (79)
Chemotherapy	94 (77)	67 (71)	161 (74)
Platinum based	84 (69)	55 (58)	139 (64)
Nonplatinum based	10 (8)	12 (13)	22 (10)
Surgery (major cytoreduction)	9 (7)	8 (8)	17 (8)
Biological/hormonal therapy	10 (8)	4 (4)	14 (6)
Radiation therapy	7 (6)	10 (11)	17 (8)

Categories shown are not mutually exclusive (one patient could receive more than one type of subsequent therapy) except for chemotherapy.
PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin.

Table 3. Summary of any subsequent platinum-based chemotherapy (all randomized patients and per platinum sensitivity subset)

All randomized patients with subsequent platinum therapy	PLD (n = 183), n (%)	Trabectedin/PLD (n = 164), n (%)	Total (n = 347)
Platinum based[a]			
Single agent	36 (20)	29 (18)	65 (19)
Combination[b]	147 (80)	135 (82)	282 (81)
Platinum-resistant subset (PFI < 6 months)	**PLD (n = 47), n (%)**	**Trabectedin/PLD (n = 39), n (%)**	**Total (N = 86), n (%)**
Platinum based			
Single agent	9 (19)	4 (10)	13 (15)
Combination	38 (81)	35 (90)	73 (85)
Partially platinum-sensitive subset (PFI 6–12 months)	**PLD (n = 52)**	**Trabectedin/PLD (n = 69)**	**Total (N = 121),**
Platinum based			
Single agent	14 (27)	16 (23)	30 (25)
Combination	38 (73)	53 (77)	91 (75)
Platinum-sensitive subset (PFI >12 months)	**PLD (n = 84)**	**Trabectedin/PLD (n = 55)**	**Total (N = 139)**
Platinum-based			
Single agent	13 (15)	9 (16)	22 (16)
Combination	71 (85)	46 (84)	117 (84)

[a]Patients with subsequent platinum at different times (i.e., as first, second or further lines) (see also Figure 1).
[b]Carboplatin/gemcitabine and carboplatin/paclitaxel were the most common.
PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin.

to an extended PFI leading to longer survival with subsequent platinum-based chemotherapy.

patients and methods

study design

Full details of OVA-301 trial and the key baseline characteristics of the overall study population have been previously described in detail [10]. Briefly, OVA-301 was an open-label, multicenter, randomized phase III clinical trial that investigated the efficacy and safety of PLD 30 mg/m^2 followed by trabectedin 1.1 mg/m^2 every 3 weeks compared with PLD 50 mg/m^2 every 4 weeks. Eligible patients were women ≥ 18 years old with histologically proven epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in relapse or progression after one platinum-based chemotherapy regimen. Patients with platinum-resistant (PFI < 6 months) or platinum-sensitive disease (PFI ≥ 6 months) were eligible (the trial was stratified on this basis). The primary end point was PFS by independent radiology assessment. Secondary analyses of PFS were based on independent oncologist and investigator's assessments, and the trial was also powered for OS. From April 2005 to May 2007, 672 patients (335 for PLD and 337 for trabectedin/PLD) were randomized. The final PFS analysis was conducted with 389 events assessed by independent radiology review in patients with radiologically measurable disease with a predetermined data cut-off (15 May 2008) [10]. Cut-off for current analysis of subsequent therapies was 31 May 2009.

evaluation of subsequent therapies

Information on subsequent therapies administered to patients after discontinuing protocol treatment included type and date of therapy. For surgery, information on the procedure was collected. For subsequent chemotherapy and other treatments, the agents' or the procedure's names and dates of occurrence, but not the response or date of clinical/radiological progression, were recorded. Therefore, this report is focused on the description of subsequent therapies. An exploratory analysis of OS from the beginning of subsequent treatment is also provided. Data are shown for the overall population, for the protocol strata of patients with platinum-resistant and platinum-sensitive disease, as well as for the clinically important subset of patients with partially platinum-sensitive disease (i.e. those with PFI 6–12 months), which represents an area of intense controversy for the optimal treatment options and research [18, 19].

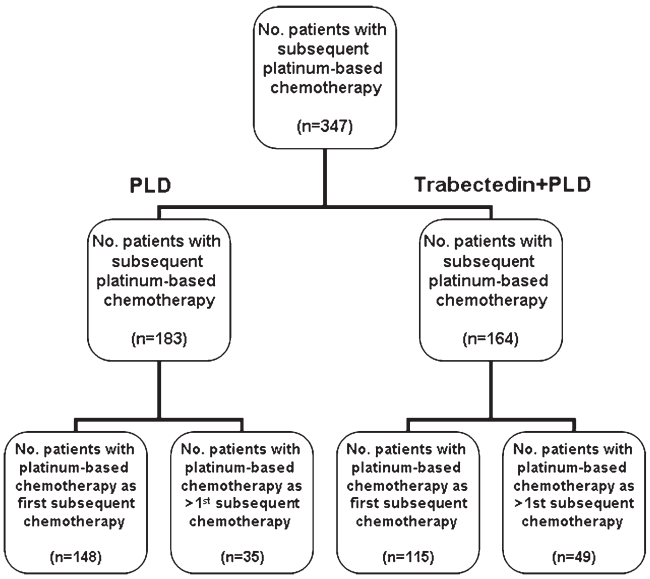

Figure 1. Flow chart of patients receiving platinum as further chemotherapy. PLD, pegylated liposomal doxorubicin.

statistical methods

All randomized (intent-to-treat) patients were included in the different analyses: overall population, platinum sensitivity strata per investigator (platinum resistant and platinum sensitive), and by PFI subsets in the platinum-sensitive stratum (6–12 months and >12 months). The variable 'PFI' at baseline was calculated as time between last dose of prior platinum and progression before the start of protocol therapy (either PLD or trabectedin/PLD). Therefore, a minor discrepancy can be found in the total number of patients versus the investigator-based allocation to protocol

Table 4. Summary of first subsequent chemotherapy (all randomized patients and per platinum sensitivity subset)

All randomized patients	PLD (n = 335), n (%)	Trabectedin/PLD (n = 337), n (%)	Total (N = 672), n (%)
Platinum based[a]			
Single agent	26 (8)	15 (4)	41 (6)
Combination[b]	122 (36)	100 (30)	222 (33)
Nonplatinum based			
Single agent	72 (21)	82 (24)	154 (23)
Combination[c]	6 (2)	7 (2)	13 (2)
Platinum-resistant subset (PFI < 6 months)	**PLD (n = 123), n (%)**	**Trabectedin/PLD (n = 119), n (%)**	**Total (N = 242), n (%)**
Platinum based			
Single agent	5 (4)	1 (1)	6 (2)
Combination	31 (25)	26 (22)	57 (24)
Nonplatinum based			
Single agent	33 (27)	36 (30)	69 (29)
Combination	4 (3)	5 (4)	9 (4)
Partially platinum-sensitive subset (PFI 6–12 months)	**PLD (n = 91), n (%)**	**Trabectedin/PLD (n = 123), n (%)**	**Total (N = 214), n (%)**
Platinum based			
Single agent	11 (12)	9 (7)	20 (9)
Combination	34 (37)	40 (33)	74 (35)
Nonplatinum based			
Single agent	24 (26)	32 (26)	56 (26)
Combination	—	2 (2)	2 (1)
Platinum-sensitive subset (PFI >12 months)	**PLD (n = 122), n (%)**	**Trabectedin/PLD (n = 95), n (%)**	**Total (N = 217), n (%)**
Platinum based			
Single agent	10 (8)	5 (5)	15 (7)
Combination	58 (48)	34 (36)	92 (42)
Nonplatinum based			
Single agent	16 (13)	16 (17)	32 (15)
Combination	1 (1)	—	1 (<1)

[a]Patients with subsequent platinum as first line (see also Figure 1).
[b]Carboplatin/gemcitabine and carboplatin/paclitaxel were the most common regimens.
[c]Taxanes (docetaxel and paclitaxel) and topotecan were the most frequent agents in nonplatinum-based combinations
PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin.

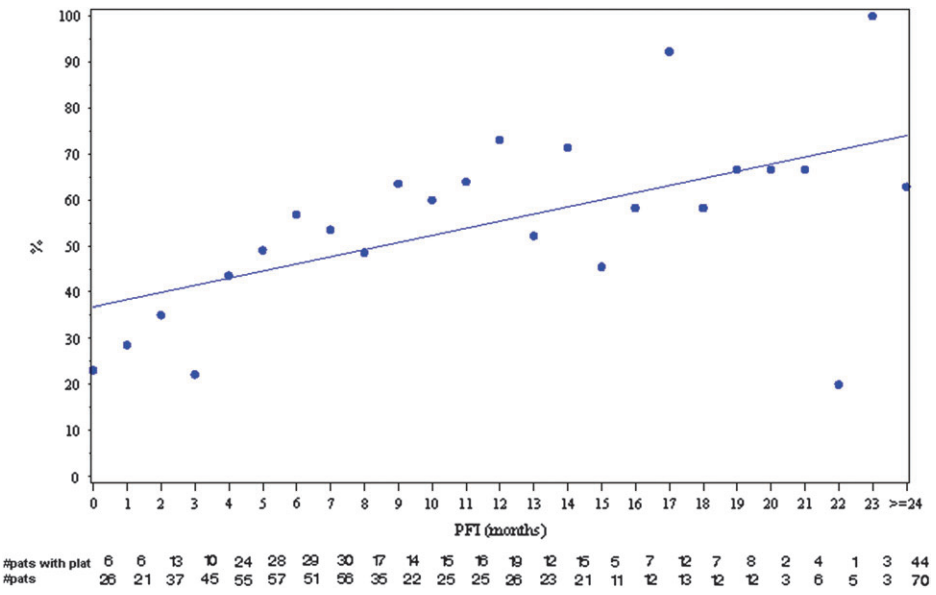

Figure 2. Percentage of patients receiving subsequent platinum therapies per platinum-free interval. PFI, platinum-free interval (P < 0.0001).

strata. Time to subsequent therapy and OS were estimated using the Kaplan–Meier method. Hazard ratios from Cox regressions and treatment arms were compared by the log-rank test. A linear regression was performed to calculate the slope for the percentage of patients receiving platinum therapy according to their PFI at baseline.

results

subsequent therapies

all randomized patients. As of the 31 May 2009 cut-off, 77% of patients treated in OVA-301 had received subsequent therapy after completing either PLD alone or trabectedin/PLD (Table 1). At the time of this analysis, subsequent chemotherapy was received by 71% of patients, which included subsequent platinum-based chemotherapy for 52% of patients.

Similar proportions of patients received subsequent therapy in each treatment arm (77% PLD versus 76% trabectedin/PLD), although platinum-based regimens were slightly less common in the trabectedin/PLD arm (49% versus 55%: Table 1). Details for all first subsequent therapies and for first subsequent platinum-based chemotherapy are given in Tables 2 and 3, respectively. A flow chart of patients who received platinum as first or further subsequent chemotherapy is provided in Figure 1. A platinum-based combination regimen was the first choice as

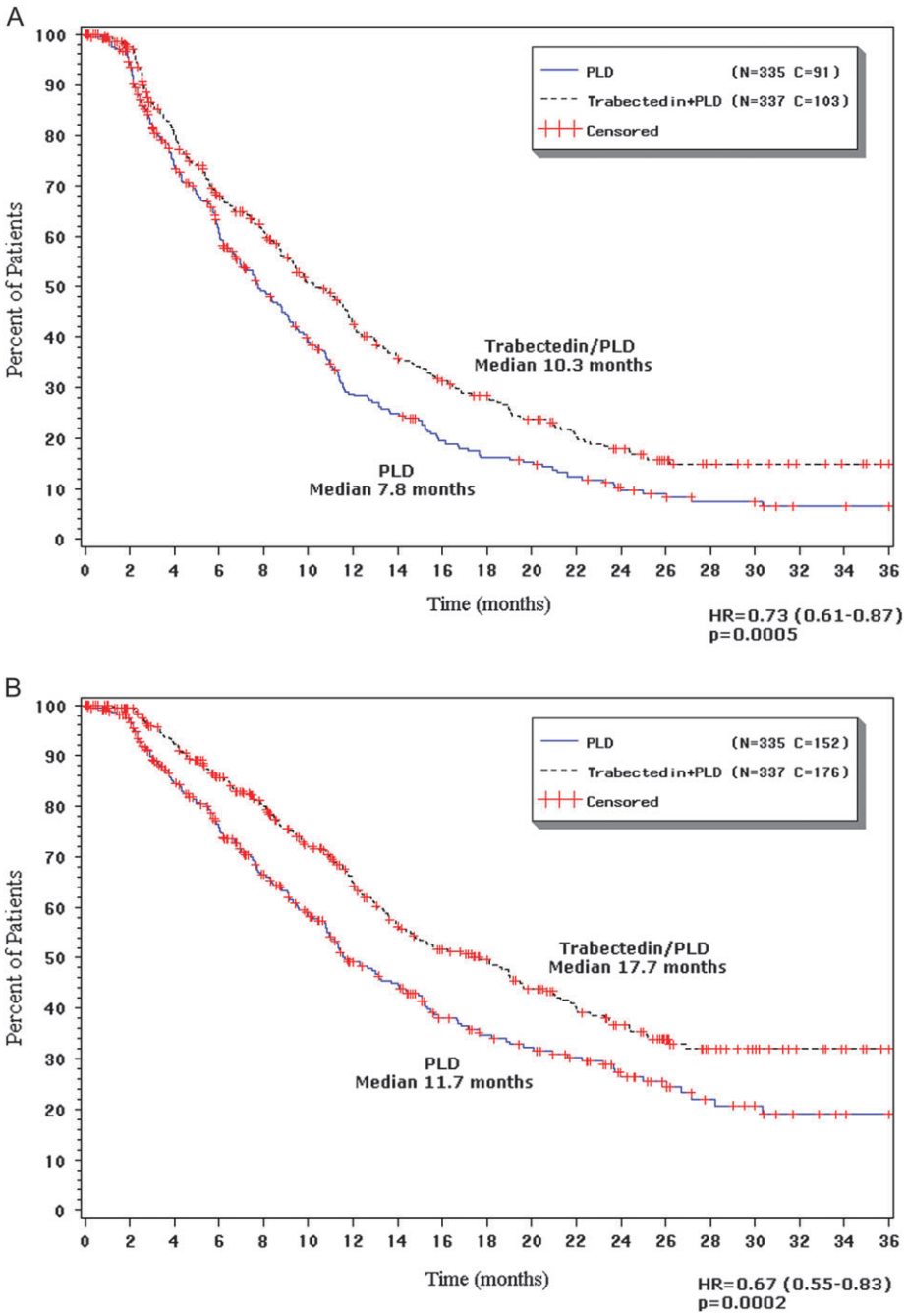

Figure 3. Time to subsequent chemotherapy in the overall population ($N = 672$ patients). (A) All chemotherapy regimens. (B) Platinum-based regimens. C, number of censored patients; HR, hazard ratio; *N*, number of patients; *P*, log-rank test *P* value; PLD, pegylated liposomal doxorubicin.

subsequent therapy in 33% of patients, followed by a nonplatinum single-agent regimen in 23% (Table 4). Most of first subsequent platinum (81%) was given in combination.

Major subsequent surgery with cytoreductive intent was performed in 4% PLD versus 6% trabectedin/PLD of the patients and OS after subsequent surgery was not different (P = 0.4122) by study arm. Subsequent radiation therapy was slightly more common in the trabectedin/PLD arm (7% versus 4%), although the types and intent of subsequent radiation therapy were not consistently collected.

analysis per platinum-sensitivity subsets. Subsequent therapy and the breakdown of first subsequent chemotherapy per platinum sensitivity subsets are provided in Tables 2 and 4, respectively. Subsequent platinum-based chemotherapy was administered to 36% of patients in the stratum of patients with platinum-resistant disease versus 57% in the partially platinum-sensitive subset and 64% in the platinum-sensitive stratum. The proportion of patients treated with subsequent platinum was similar in the commonly described, discrete categories of PFI 6–12 versus PFI >12 months, but it showed a significantly increasing trend when PFI was plotted as a continuous variable (Figure 2).

time to subsequent chemotherapy and survival

all randomized patients. Time to subsequent chemotherapy was delayed by a median of 2.5 months for patients in the trabectedin/PLD arm versus those in the PLD arm in the overall population (Figure 3A). The corresponding median delay was 6 months for subsequent platinum-based chemotherapy (Figure 3B). When only patients who received platinum as subsequent chemotherapy are analyzed, the difference in median time to subsequent platinum, i.e. subsequent PFI (sPFI), was 2.7 months: 10.3 months in trabectedin/PLD arm versus 7.6 months in PLD arm; HR = 0.80 (95% confidence interval, 0.64–0.99 P = 0.0361).

The delay in the administration of subsequent platinum does not appear to have exerted an influence on OS. Median OS counted from the administration of subsequent platinum was identical at 14.9 months in each arm (Figure 4), and 1-year survival rates were 58% (PLD arm) and 60% (trabectedin/PLD arm).

Time to subsequent nonplatinum-based chemotherapy (in patients who only received this type of chemotherapy) as well as OS counted from the administration of subsequent nonplatinum-based chemotherapy were similar in each arm (HR = 0.99 and 0.98, respectively).

analysis per platinum-sensitivity subsets. Subsequent platinum-based chemotherapy was delayed by a median of 1.9 months (HR = 0.64; P = 0.0167) for the subset of patients with PFI 6–12 months who were randomly allocated to the trabectedin/PLD arm. OS counted from the administration of subsequent platinum was significantly extended in these patients, with a 37% reduction in the risk of death (HR = 0.63; P = 0.0357) and a 3.5 months longer median OS (13.3 months versus 9.8 months; Figure 5B).

Differences were larger in the PFI 6–12 months subset when only data of patients who received platinum as first subsequent therapy are analyzed (Figure 6A and B). In this subpopulation, platinum was delayed a median of 4 months (HR = 0.61; P = 0.0203) and OS from first platinum was significantly extended by a median of 8.7 months (HR = 0.54; P = 0.0169).

Delays in the administration of subsequent platinum therapy for patients randomized to trabectedin/PLD arm versus PLD alone were shorter in the platinum-resistant stratum (PFI < 6 months; HR = 0.86; P = 0.4854) and in the platinum-sensitive subset (PFI >12 months; HR = 0.83; P = 0.3017),

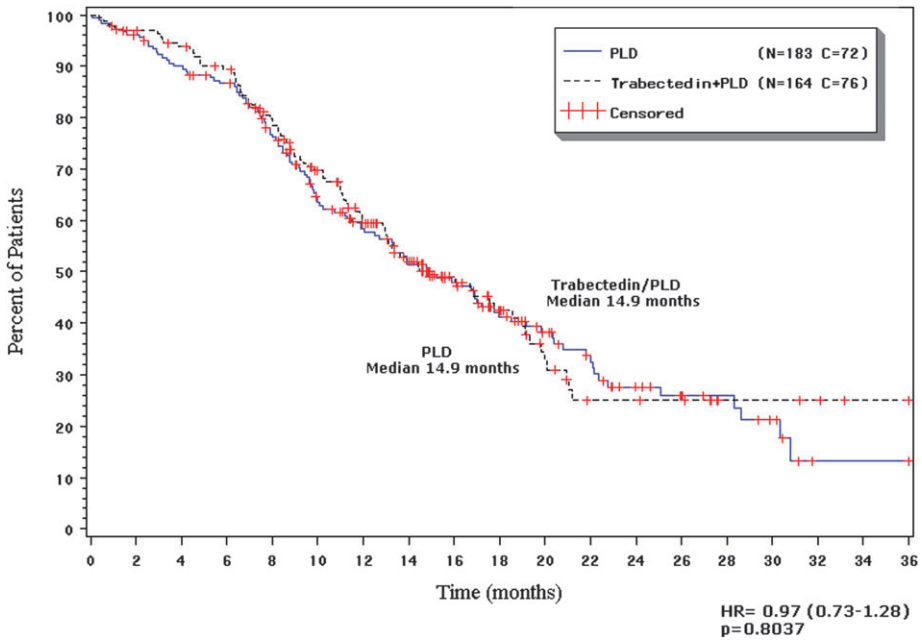

Figure 4. Median overall survival from the administration of subsequent platinum-based therapy (all patients who received further platinum; n = 347). C, number of censored patients; HR, hazard ratio; N, number of patients; P, log-rank test P value; PLD, pegylated liposomal doxorubicin.

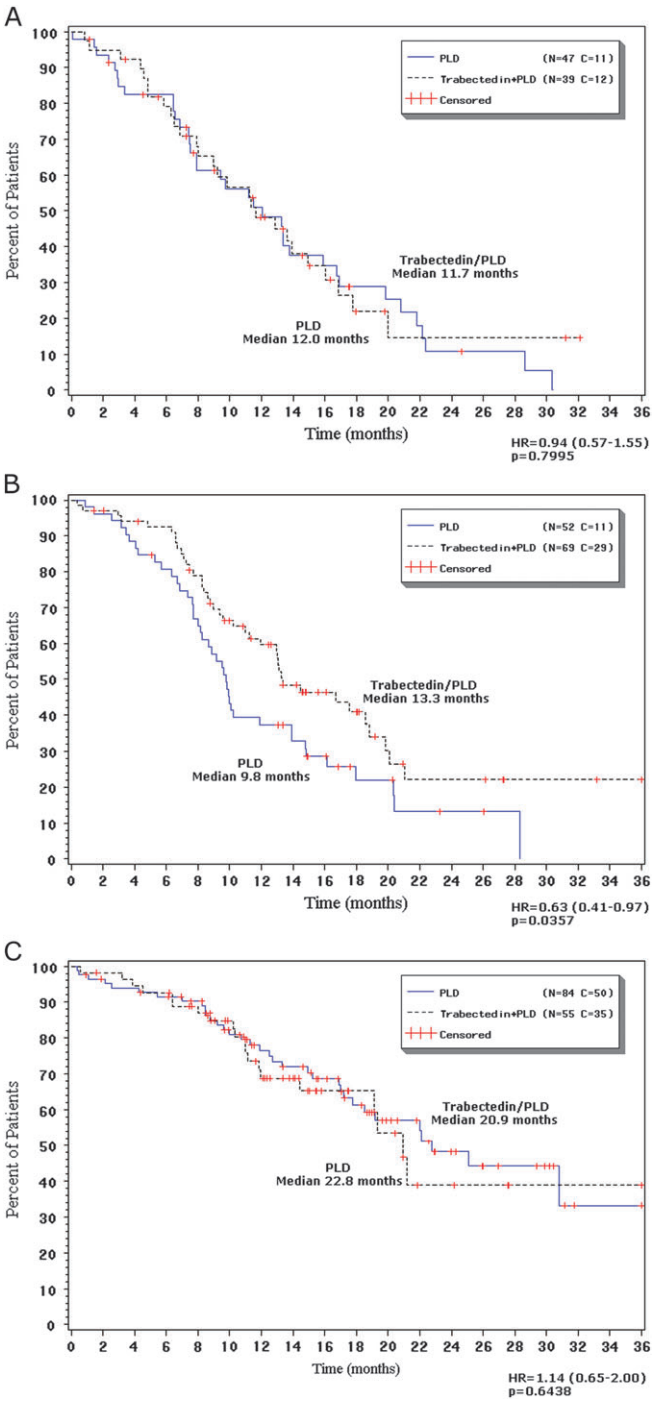

Figure 5. Median overall survival from the administration of subsequent platinum-based therapy per platinum sensitivity subset (all patients who received further platinum). (A) Platinum-resistant (PFI < 6 months; $n = 86$); (B) Partially platinum sensitive (PFI 6–12 months; $n = 121$); (C) Platinum sensitive (PFI > 12 months; $n = 139$). C, number of censored patients; HR, hazard ratio; *P*, log-rank test *P* value; PLD, pegylated liposomal doxorubicin.

although these did not translate into a worsening in OS counted from the administration of subsequent platinum in either subset (Figure 5A and C).

The observed differences by study arm in time to subsequent platinum-based chemotherapy (sPFI) and OS outcomes with subsequent platinum do not appear to be influenced by patient baseline characteristics (Table 5).

discussion

OVA-301 was a large randomized trial that evaluated trabectedin/PLD versus PLD alone in patients with relapsed ovarian cancer. The trial met its primary end point, demonstrating significantly superior PFS with the combination, and also showed a positive trend in OS in a protocol-specified interim analysis [9, 10]. An analysis of updated OS data, conducted at the request of regulatory authorities with one additional year of follow-up, confirmed and strengthened the survival outcomes previously reported. Compared with PLD alone, the trabectedin/PLD combination resulted in a 15% decrease (HR = 0.85, $P = 0.092$) and a 41% decrease (HR = 0.59, $P = 0.0015$) in the risk of death in all randomized patients and in the partially platinum-sensitive subset of patients, respectively [8, 12].

The present exploratory analyses indicate that the favorable survival outcomes obtained with trabectedin/PLD combination over single-agent PLD in OVA-301 cannot be explained by differences in the extent or nature of subsequent therapies received by the patients after discontinuing study medication in this trial. Similar proportions of patients received subsequent treatments in each arm (77% versus 76%), and indeed platinum-based regimens were slightly less commonly administered (49% versus 55%) and prescribed at a later stage to patients randomly allocated to the arm with the longest survival (trabectedin/PLD). Although this was a *post hoc* analysis, the data (Table 5) demonstrate no major imbalance between the two treatment arms; any differences in baseline characteristics in fact favor the PLD alone arm.

The efficacy of platinum rechallenge in relapsed ovarian cancer has been described as strongly correlated with PFI. Patients with PFI < 6 months are considered to have platinum-resistant disease, while patients with PFI ≥ 6 months are regarded as having platinum-sensitive disease. PFI ≥ 6 months predicts sensitivity to platinum, although a PFI of 6–12 months is considered to indicate a partially platinum-sensitive disease. In this subset of patients, the response rates to further platinum are lower (25%–30%) compared with those in patients with PFI > 12 months (up to 60%) [18]. Whether this is a specific indication of platinum sensitivity or illustrates a more general chemosensitivity effect is being a matter of debate [20]. In OVA-301, subsequent platinum-based chemotherapy was administered to 52% patients. It is noteworthy that most of subsequent platinum was administered as a combination regimen, with a similar proportion between arms: 80% (PLD arm) and 82% (trabectedin/PLD arm). As expected, the administration of subsequent platinum to OVA-301 patients was increasingly more common as their baseline PFI was longer.

One striking finding in the OVA-301 trial is the unexpectedly high proportion of patients with platinum-resistant disease at baseline in whom a platinum rechallenge was adopted (86 of 242; 36%). Treatment options for platinum-resistant patients are limited, and the main goals of therapy are disease/symptom control and maintenance or

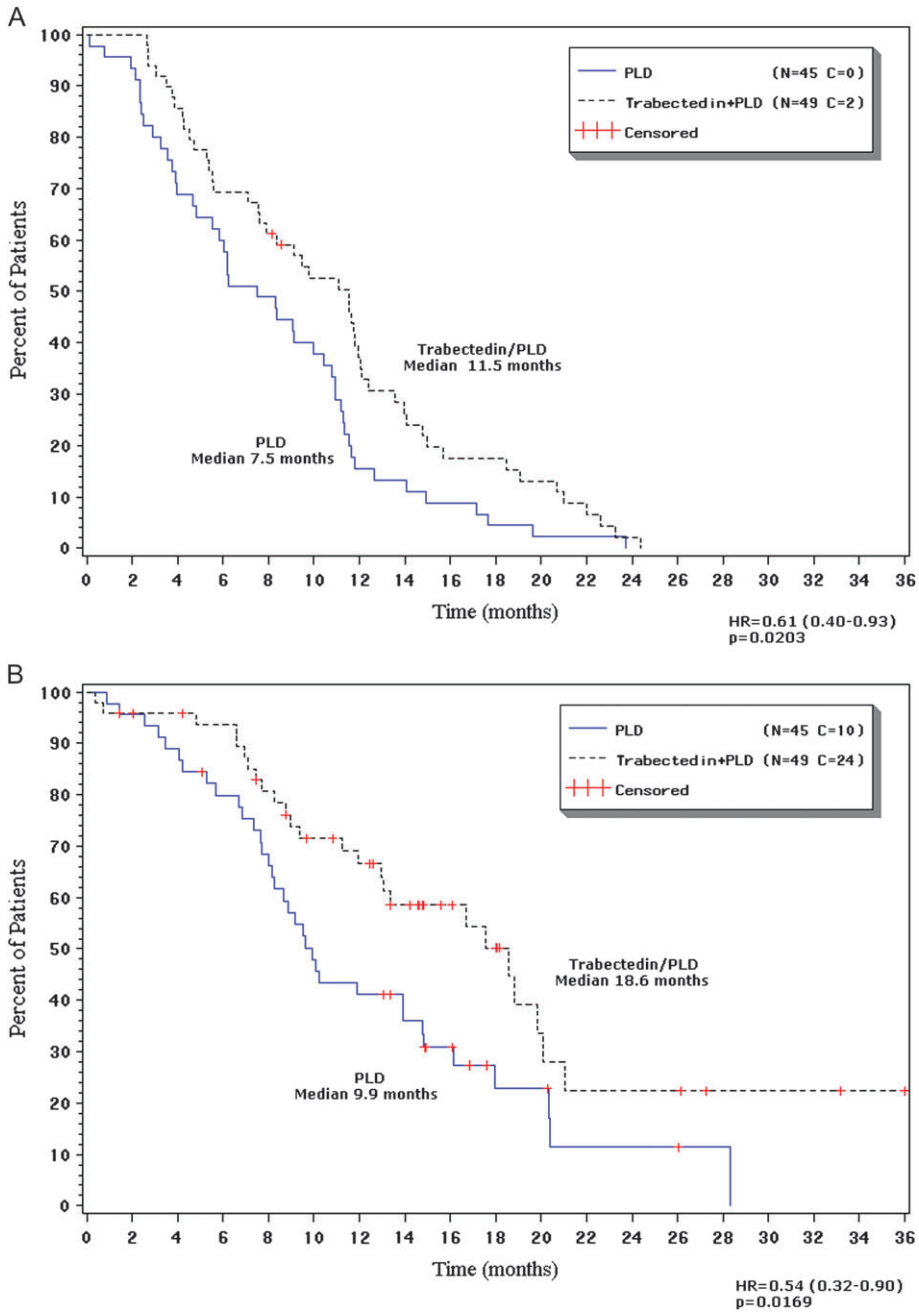

Figure 6. Time to subsequent chemotherapy and median OS from the administration of platinum-based therapy as subsequent line in the platinum-free interval 6–12 subset. (A) Time to subsequent chemotherapy; (B) Overall survival. C, number of censored patients; HR, hazard ratio; *P*, log-rank test *P* value; PLD, pegylated liposomal doxorubicin; OS, overall survival.

improvement of quality of life. For these reasons, quite often a nonplatinum single agent is recommended as the preferred palliative option [21, 22]. The data in OVA-301 presented here suggest that, given the poor response induced by the available cytotoxic agents, patients with platinum-resistant ovarian cancer are rechallenged with subsequent platinum-based therapy more often than recommended in the guidelines. Platinum plus gemcitabine, previously described as modestly active in platinum-resistant ovarian cancer [23–25], was administered to 38 of 73 patients (52%) who received further platinum-based combinations.

Another interesting finding in the current dataset was that the proportion of platinum rechallenge in patients with partially platinum-sensitive disease (57%) was remarkably similar to that of patients with fully platinum-sensitive disease (64%). Platinum-based regimens are recommended as standard second-line therapy in patients with PFI > 12 months, but benefits of platinum rechallenge in the partially platinum-sensitive subgroup, with response rates to further platinum of 25%–30%, are less obvious; thus, the recommendation of platinum rechallenge in this subset is less universal [17]. In addition, the common occurrence of hypersensitivity reactions

Table 5. Key patient baseline characteristics by platinum-sensitivity subsets in patients with subsequent therapy

All randomized patients with subsequent platinum therapy	PLD (n = 183)	Trabectedin/PLD (n = 164)	Total (N = 347)
Median age (range), years	58 (34–87)	55 (26–82)	56 (26–87)
Performance status (0 versus >0)	62/38	75/25	68/32
Histology (papillary/serous carcinoma)[a]	69	67	69
Histology (grade 3)	48	48	48
Previous taxanes	80	75	77
Visceral metastases	41	38	39
Bulky disease	40	41	41
Platinum-resistant subset (PFI < 6 months)	**PLD (n = 47)**	**Trabectedin/PLD (n = 39)**	**Total (N = 86)**
Median age (range), years	56 (34–79)	56 (26–79)	56 (26–79)
Performance status (0 versus >0)	64/36	82/18	72/28
Histology (papillary/serous carcinoma)[a]	70	64	67
Histology (grade 3)	47	41	44
Previous taxanes	85	80	83
Visceral metastases	36	31	34
Bulky disease	28	31	29
Partially platinum-sensitive subset (PFI 6–12 months)	**PLD (n = 52)**	**Trabectedin/PLD (n = 69)**	**Total (N = 121)**
Median age (range), years	54 (37–79)	57 (40–76)	56 (37–79)
Performance status (0 versus >0)	64/36	72/28	69/31
Histology (papillary/serous carcinoma)[a]	67	72	70
Histology (grade 3)	53	49	50
Previous taxanes	81	71	75
Visceral metastases	42	44	43
Bulky disease	48	39	43
Platinum-sensitive subset (PFI >12 months)	**PLD (n = 84)**	**Trabectedin/PLD (n = 55)**	**Total (N = 139)**
Median age (range), years	59 (34–87)	52 (37–82)	57 (34–87)
Performance status (0 versus >0)	60/40	74/26	66/34
Histology (papillary/serous carcinoma)[a]	70	66	68
Histology (grade 3)	45	53	48
Previous taxanes	76	76	76
Visceral metastases	44	36	41
Bulky disease	44	51	47

Data shown are percentages of patients except for age (median and range).

[a]Most common histological type.

PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin.

and residual neurotoxicity may hinder platinum rechallenge, underlining the need for effective nonplatinum regimens [20, 26], particularly in the partially platinum-sensitive population [18, 19]. The current data, obtained from a large randomized clinical trial conducted in an extensive geographical area (21 countries from four continents, America, Asia, Australia and Europe) suggest that platinum rechallenge is an extended practice in relapsed ovarian cancer patients at all PFI levels, despite the widespread knowledge of longer PFI effect on treatment effectiveness [20].

The current hypothesis-generating analyses indicate that the enhanced survival benefits with trabectedin/PLD over single-agent PLD in OVA-301, particularly in patients with partially platinum-sensitive disease, may be due to an extension of the PFI. It is postulated that treatment of these patients with trabectedin/PLD, a nonplatinum combination, has contributed to positive outcomes because of their longer survival after the start of subsequent platinum-based chemotherapy. Patients randomly allocated to trabectedin/PLD received subsequent chemotherapy, including platinum-based regimens, at a later time than patients in the PLD arm: 6 months for all patients who received subsequent platinum at any time following OVA-301 trial and 2.7 months for those patients who received subsequent platinum (3.3 for those in whom platinum was the first option; data not shown). A provocative finding in this trial is that OS counted from the administration of subsequent platinum therapy was significantly prolonged in the partially platinum-sensitive subset (PFI 6–12 months), possibly by a reversal effect of the partial resistance pattern in this patient subset [16]. Preclinical data indicate that the mechanisms underlying resistance to carboplatin and trabectedin differ in respect of the DNA repair pathways involved, and this may also partially explain the superior outcome with platinum-based treatment in therapy [27]. Delay of platinum re-treatment might theoretically reduce the effectiveness of such therapy, particularly if a nonplatinum second-line agent is used between platinum regimens. However, the majority of previous reports [13–16, 18, 22, 28] as well as the data in the current study rather support an increased effectiveness of such

intervention. This needs to be confirmed in prospective randomized trials.

In the platinum-resistant stratum, the lower effect in sPFI prolongation in the trabectedin/PLD arm (HR = 0.86; P = 0.4854) may be due to the well-established lack of chemosensitivity in this clinical situation. Results are difficult to interpret in the platinum-sensitive subset, where a HR of 0.83 (P = 0.3017) was obtained, possibly due, at least in part, to the immature nature of the data, with a very high proportion of censoring in this more chemosensitive cohort. A third of these patients were still alive and they did not yet require subsequent platinum.

In conclusion, the superior results obtained with trabectedin/PLD over single-agent PLD in OVA-301 trial cannot be explained by differences in the extent or nature of subsequent therapies administered to the patients after completion of on-study therapy. The current analyses indicate that enhanced survival with trabectedin/PLD over single-agent PLD in this trial, particularly in patients with partially platinum-sensitive disease, may be due to an extension of the PFI coupled with longer survival after the start of subsequent platinum-based chemotherapy. A large, randomized prospective clinical trial to test this hypothesis is in preparation.

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disclosure

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