Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial


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Background: Platinum-based chemotherapy is standard second-line treatment of patients with advanced ovarian cancer (AOC) in late relapse. Pegylated liposomal doxorubicin (PLD) has significant single-agent activity in this setting. Therefore, we evaluated the use of PLD plus carboplatin in this patient population.

Patients and methods: PLD 30 mg/m2 followed by carboplatin at area under the curve (AUC) 5 mg·min/ml, repeated every 28 days for a maximum of nine cycles, was administered to 104 women with AOC relapsing >6 months after completion of first- or second-line therapy with platinum-taxane-based regimens.

Results: Overall response was 63%, with a 38% complete response, median progression-free survival of 9.4 months, and median overall survival (OS) of 32 months. Grade 3 or 4 neutropenia occurred in 51% of patients, but febrile neutropenia in only 3%. Nonhematologic toxic effects were primarily grades 1 and 2, with low rates of alopecia and neurotoxicity.

Conclusions: PLD plus carboplatin is highly effective, prolongs OS, and is well tolerated in women with AOC in late relapse previously treated with both platinum and taxanes. Evaluation of this regimen in phase III trials is warranted.

Key words: liposomal doxorubicin, ovarian cancer

introduction

Patients with advanced ovarian cancer (AOC) that relapses >6 months after completion of initial platinum-based chemotherapy are considered by many clinicians to be good candidates for re-treatment with a platinum-based regimen. Until recently, there has been no evidence of improved survival for combination versus single-agent platinum regimens in these women with AOC in late relapse. In the first large clinical trial to demonstrate a survival advantage when comparing platinum-containing regimens for AOC (ICON4-OVAR 2.2), there was an absolute difference in 2-year survival of 7% (57% versus 50%) and in median survival of 5 months (29 versus 24 months) favoring platinum plus paclitaxel (Taxol) over conventional platinum-based chemotherapy (primarily carboplatin alone) [1].

A potential barrier to using a platinum–taxane combination in women with AOC in late relapse is that many will have received first-line treatment with a platinum–taxane combination [2–11] and experienced adverse events including neurotoxicity and alopecia [1, 12]. They may, therefore, be at risk for more serious neurologic events if re-treated with a taxane. They also may be reluctant to experience hair loss again at the time of relapse. Therefore, efforts are underway to develop platinum combinations that are equally effective as platinum-taxane, but with less alopecia and neurotoxicity.

Pegylated liposomal doxorubicin (PLD; Caelyx, Schering-Plough International, Kenilworth, NJ) has a longer circulation time than conventional doxorubicin, allowing for lower peak plasma concentrations and increased tumor concentration of drug. Tumor concentrations of doxorubicin are 4- to 11-fold higher with PLD versus conventional doxorubicin [13, 14]. Main limiting toxic effects with PLD are skin and mucosal toxic effects, which are linked to the dose and dose interval. Alopecia, nausea, vomiting, and hematologic toxic effects are less common than with the conventional product, and cardiotoxicity is rare [15, 16].

Single-agent efficacy of PLD in ovarian cancer was demonstrated in two phase III studies comparing PLD with paclitaxel [17] or topotecan (Hycamtin) [18, 19] as second-line therapy. In the first
study, there were no significant efficacy differences between PLD and paclitaxel, regardless of platinum sensitivity. Toxicity profiles, however, differed, leading the authors to suggest that PLD may be advantageous for patients with musculoskeletal disorders or in whom alopecia was to be avoided [17]. In the comparison of PLD with topotecan, overall survival (OS) was superior with PLD (63 versus 60 weeks, \( P = 0.03 \), particularly in platinum-sensitive patients (112 versus 77 weeks, \( P = 0.002 \)) [18]. In addition, PLD had a more favorable safety profile and a less cumbersome administration schedule [17, 18].

The single-agent efficacy of PLD [17–19] and carboplatin [1] and evidence from the ICON4-OVAR 2.2 study demonstrating that combination platinum-containing regimens are superior to single-agent platinum regimens [1] support an evaluation of combination therapy with PLD and carboplatin for ovarian cancer. On the basis of these favorable data, we investigated the efficacy and tolerability of combination therapy with PLD and carboplatin in women with AOC in late relapse who were pretreated with platinum and a taxane.

patients and methods

study design

This open-label, multicenter, phase II study evaluated the antitumor efficacy and safety of combination therapy with PLD plus carboplatin (Paraplatin, Bristol-Myers Squibb Company) in patients with late-relapsing (>6 months after last chemotherapy) ovarian cancer. Patients relapsed after completion of first- or second-line therapy with a platinum-taxane-based regimen. All patients provided signed informed consent. The study was approved by the ethics committee and conducted in accordance with the ethical principles that originated in the Declaration of Helsinki.

eligibility criteria

Eligible patients were ≥18 years old and had histologically confirmed primary ovarian adenocarcinoma with peritoneal or visceral metastatic disease and disease progression 26 months after the end of the last chemotherapy treatment. Prior treatment with two or less lines of chemotherapy, one of which included but was not limited to a platinum and a taxane, was required. While prior treatment with hormone therapy, immunotherapy, or radiotherapy was permitted, all such treatments were discontinued at least 4 weeks before study entry. Other eligibility criteria included measurable lesions and/or a CA 125 >75 U/ml and an Eastern Cooperative Oncology Group performance status ≤2.

Eligible patients were those 18 years of age and older who had pathologically confirmed primary adenocarcinoma of the ovary or uterus, with a CA 125 level of ≥75 U/ml. Patients had to have measurable disease, which was defined by the presence of lesions of >10 mm, either at the time of study entry or within 2 weeks of starting treatment. In addition, patients had to have a life expectancy of > 3 months and to have been free of any acute, serious, or unexplained illness. Patients were excluded from the study if they had prior bone marrow autograft or total abdominal irradiation. Other exclusion criteria were history of heart disease; cerebral or meningeal metastases or other malignant tumor, except curatively treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; and inadequate renal [serum creatinine clearance >1.25 × the upper limit of normal (ULN)], liver [serum bilirubin >1.25 × ULN and serum transaminase levels >2 × ULN in the absence of liver metastases or >5 × ULN with liver metastases], or hematologic function (white blood cell count <4.0 × 10⁹/l, granulocyte count <2.0 × 10⁹/l, and platelets <100 × 10⁹/l). Women who were pregnant, breast-feeding, or of reproductive age and not using adequate contraception were excluded.

treatment plan

PLD 30 mg/m² was infused over 1 h. After completion of the PLD infusion, carboplatin at area under the curve (AUC) 5 mg min/ml (Calvert formula [20]; maximum dose of 800 mg in patients with a creatinine clearance >135 ml/min) was infused over 30 min. Treatment was repeated every 28 days. Antiemetics, including corticosteroids, were permitted. A cooling cap was recommended during carboplatin administration in an attempt to reduce the risk and severity of alopecia. The use of hematopoietic growth factors was at the discretion of the investigator.

In the absence of unacceptable toxicity or disease progression, treatment was administered for at least two cycles. In patients with stable disease or response after cycle 2, treatment was continued at the discretion of the investigator for a maximum of nine cycles or until unacceptable toxicity.

Drug dosage was modified as a function of hematologic nadir, hematologic recovery, skin toxicity, or mucosal toxicity. In patients experiencing any other National Cancer Institute (NCI) common toxicity criteria (CTC) version 2.0 grade 3 or greater toxicity, with the exception of nausea and vomiting, dosage adjustment or treatment discontinuation was at the discretion of the investigator. Patients requiring more than one dose reduction for the same drug were discontinued from the study treatment. For a granulocyte count <0.5 × 10⁹/l (CTC grade 4) for ≥7 days, a granulocyte count <0.1 × 10⁹/l for 3 days, an episode of febrile neutropenia (defined as temperature ≥38.5°C at two independent measurements and granulocyte count <1 × 10⁹/l), an infection requiring intravenous antibiotics and/or hospitalization, platelet count <25 × 10⁹/l, or bleeding that required a platelet transfusion, the dose of PLD was reduced to 25 mg/m² and carboplatin to AUC 4 mg min/ml.

Treatment was held for a granulocyte count <1.5 × 10⁹/l and a platelet count <100 × 10⁹/l. If hematologic recovery was achieved between days 35 and 42, PLD and carboplatin doses were reduced as above. If hematologic recovery was inadequate by day 42, the patient was removed from the study. In patients experiencing skin or mucosal toxicity (any grade), treatment was withheld until the toxicity resolved. Treatment was subsequently restarted or discontinued based on preestablished guidelines (Table 2).

clinical, laboratory, and radiologic assessments

Before study entry, clinical, laboratory, and radiologic assessments were carried out. Clinical assessment included complete medical history, physical examination, weight, height, performance status, and electrocardiogram. Laboratory measurements included complete blood cell count with differential, creatinine clearance, serum bilirubin level, transaminase levels, alkaline phosphatase levels, and CA 125 levels. Radiologic assessment included chest X-ray, abdominal–pelvic scan (magnetic resonance imaging or ultrasound), and ventricular ejection fraction by echocardiogram or scan. Differential blood count was done at least weekly thereafter and clinical and other laboratory assessments, including CA 125 levels, were repeated before each treatment. Chest X-ray and abdominal–pelvic scan were repeated at least every two cycles.

efficacy assessment

The primary efficacy variable was overall or objective response (OR), which was assessed every two cycles. In patients achieving an OR, confirmation was recommended at a second analysis at least 4 weeks after OR was initially identified. Patients with at least one measurable lesion were evaluated for response according to standard World Health Organization (WHO) efficacy criteria. Nonmeasurable lesions were categorized as evaluable or not evaluable. Each OR was reviewed by an independent panel.

In patients with measurable disease, a clinical complete response (CR) was defined as the complete disappearance of all signs of measurable or evaluable disease with CA 125 level normalization for at least 4 weeks. Partial response (PR) was defined as per WHO efficacy criteria. Patients who showed neither a CR nor a PR were considered nonresponders.

Patients with nonmeasurable disease and CA 125 levels ≥40 IU/ml were evaluated according to Rustin’s criteria [21]. Evaluation required at least four CA 125 samples, with the first taken between 9 and 35 days after the
first cycle of chemotherapy. This first level must have been ≥40 IU/ml for inclusion in the analysis. A serologic response was achieved if the CA 125 level from samples 2 and 3 was ≥50% lower than in the first sample. This response must have been confirmed by a fourth sample taken at least 28 days after the preceding one. The serologic response was considered complete (i.e. serologic CR) when the CA 125 level was normalized for at least 28 days.

Patients not assessable if they had no measurable disease and a CA 125 level <40 IU/ml (ineligible) or a CA 125 level ≥40 IU/ml and less than four samples available for evaluation. When insufficient samples were related to early disease progression, patients were classified as having progressive disease (PD).

Secondary efficacy variables included progression-free survival (PFS) and OS. PFS was calculated from the first day of treatment to the date of progression or death from any cause. PD was defined as an increase of 25% or more in existing lesions, and/or the appearance of new lesions, and/or serologic progression or death from any cause. PD was defined as an increase of 25% or more in existing lesions, and/or the appearance of new lesions, and/or serologic progression according to Gynecologic Cancer Intergroup (GCIG) criteria [22]. OS was calculated from the first day of treatment to the date of death.

safety assessment

Safety was evaluated during each cycle. Using NCI CTC version 2.0, the highest grade of toxicity encountered during treatment was recorded before each cycle and during follow-up. Follow-up visits were planned every 3 months for 2 years, then every 6 months for 5 years or until death. All patients receiving at least one cycle of treatment were assessable for toxicity.

statistical analysis

The sample size was determined for analysis of the primary end point, OR, using a stepwise approach according to O’Brien and Fleming [23]. Because there is contradictory experience regarding the impact of the number of lines of treatment on response, patients were divided into two groups, those receiving treatment as second-line therapy and those receiving treatment as third-line therapy. In patients receiving treatment as second-line therapy, accepting alpha and beta risks on the order of 5% and assuming that the treatment must be considered ineffective below an OR of 30%, an OR of 50% was established as the cut-off. Interim analysis of OR was carried out after 15 and 30 patients were enrolled. If an OR ≥80% was observed at the time of either interim analysis, the study was stopped and the combination considered ineffective. Using this approach, a sample size of 45 patients was required.

A similar approach was used in patients receiving third-line treatment. Accepting alpha and beta risks of 5% and assuming that below a response rate of 20% the treatment would be considered ineffective, a response rate of 40% was established as the cut-off. Assuming 45 assessable patients and seven ineligible patients per group, a sample size of 104 was considered adequate for analysis of the primary end point. All eligible patients receiving at least one cycle of study treatment were assessable for response. Efficacy was analyzed as a function of the number of prior lines of chemotherapy and treatment-free interval (TFI; i.e. 6–12 months or ≥12 months).

results

A total of 105 patients were enrolled in the study, of which 104 received treatment (Table 1). Measurable lesions were reported in 57% of patients and 42% had more than one metastatic site. Baseline CA 125 levels ≥40 IU/ml were reported in 86% of patients; 39% had no measurable lesion at baseline but had elevated CA 125 levels. All patients had been pretreated with platinum and taxane, and 64% achieved a CR to prior treatment. Second-line therapy included a platinum in 59% of patients and a taxane in 56%.

Patients received a median of six cycles of PLD–carboplatin chemotherapy (range, 1–10). The median doses of PLD and carboplatin were 97% and 95%, respectively, of the planned doses. Granulocyte colony-stimulating factor, red blood cells, or platelets were required in 16%, 12%, and 3% of patients, respectively. Dose reduction and course delay, due mainly to delays in hematologic recovery, were observed in 33% and 54% of patients and 7% and 20% of cycles, respectively.

efficacy

This intention-to-treat efficacy analysis was based on 104 patients, including four patients not assessable for response as

Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Assessable patients, N</th>
<th>104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61</td>
</tr>
<tr>
<td>Median</td>
<td>23–79</td>
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<tr>
<td>Range</td>
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</tr>
<tr>
<td>Histologic subtype, %</td>
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</tr>
<tr>
<td>Serous papillary</td>
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<tr>
<td>Endometrioid</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
</tr>
<tr>
<td>Histologic grade, %</td>
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</tr>
<tr>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
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<td>3</td>
<td>26</td>
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<td>43</td>
</tr>
<tr>
<td>Number of previous chemotherapy regimens, %</td>
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</tr>
<tr>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>≥2</td>
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<tr>
<td>Treatment-free interval, %</td>
<td></td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>4</td>
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<tr>
<td>&lt;12 months</td>
<td>43</td>
</tr>
<tr>
<td>≥12 months</td>
<td>53</td>
</tr>
<tr>
<td>Response to previous platinum–taxane regimen, %</td>
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</tr>
<tr>
<td>Pathologic complete</td>
<td>10</td>
</tr>
<tr>
<td>Clinical complete</td>
<td>64</td>
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<tr>
<td>Clinical partial</td>
<td>18</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>ECOG performance status, %</td>
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</tr>
<tr>
<td>0</td>
<td>53</td>
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<tr>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
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<tr>
<td>Ascites, %</td>
<td>29</td>
</tr>
<tr>
<td>Measurable lesion, %</td>
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</tr>
<tr>
<td>&lt;5 cm</td>
<td>35</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>22</td>
</tr>
<tr>
<td>None (CA 125 ≥ 40 IU/ml)</td>
<td>39</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4</td>
</tr>
<tr>
<td>Number of disease sites, %*</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>58</td>
</tr>
<tr>
<td>&gt;1</td>
<td>42</td>
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</table>

*Site = peritoneal, retroperitoneal, or single visceral disease.

ECOG, Eastern Cooperative Oncology Group.
they had no measurable lesion or CA 125 levels ≥40 IU/ml at baseline and five patients with major eligibility criteria violations. Four of these patients had a TFI <6 months (actual, 5 months) and one received three lines of prior chemotherapy. OR was similar in the overall population and in women with and without measurable disease (60%–65%) (Table 3), as well as in patients receiving second-line treatment (66%) and third-line treatment (65%).

Median PFS for the total patient population was 9.4 months and was independent of the presence or absence of measurable disease. Median PFS was 9.5 months for patients treated with second-line and 9.2 months for patients treated with third-line therapy. Patients with a TFI <12 months, however, had a significantly lower median PFS (11.4 months, \( P = 0.001 \)) (Figure 1).

A longer TFI also was associated with significantly longer OS (Figure 2). Median OS was 32 months for the entire group. In women with a TFI ≥12 months, median OS was 36 months compared with 21 months in women with a TFI of 6–12 months (\( P = 0.006 \), log-rank).

safety
Thirteen of the 104 patients assessable for safety discontinued treatment prematurely due to toxicity, including hematologic toxicity (\( n = 4 \)), hematologic toxicity and PD (resulting in death, \( n = 2 \)), hand food syndrome (HFS, \( n = 2 \)), hypersensitivity (\( n = 2 \)), and patient convenience (\( n = 3 \)).

Hematologic toxicity was more common than nonhematologic toxicity. During 527 evaluable cycles, grade 3 or 4 neutropenia was reported in 51%, leukopenia in 27%, thrombocytopenia in 26%, and anemia in 12% of patients. Febrile neutropenia was reported in 3% of patients.

Nonhematologic adverse reactions were primarily grade 1 or 2; there were no grade 4 nonhematologic adverse reactions (Table 4). More than 50% of patients experienced nausea and vomiting or asthenia. Palmar/plantar erythrodysesthesia was reported in one-third of patients, but was grades 1 and 2 only. Most alopecia was grade 1. No clinical evidence of cardiotoxicity was observed during the study.

discussion
The potential for platinum sensitivity is one of the most important factors in making treatment decisions in relapsed AOC. Tumor response to most agents is related to platinum-free interval. Since the median progression-free interval after initial therapy with platinum–paclitaxel is 16–22 months, most patients are categorized as having late relapse and considered platinum sensitive. These patients are generally re-treated with platinum–paclitaxel at first relapse but, because most toxic effects are cumulative, are at increased risk of neurotoxicity and myelosuppression [24].
While prolonging survival is an important consideration in treatment selection, other factors should also be considered. Since the treatment of relapsed AOC is rarely curative, tolerability, convenience of administration, and quality of life should be considered as well. We demonstrate here that combination therapy with PLD (30 mg/m²) and carboplatin (AUC 5 mg · min/ml) yields a high OR (63%) and is well tolerated in patients with AOC in late relapse. Moreover, OR based on WHO criteria (60%) was similar to OR based on changes in CA 125 (65%). As would be expected, PFS and OS increased in patients with a longer TFI. Hematologic toxicity was moderate. There was a low incidence of both alopecia and neurotoxicity, with HFS limited to grades 1 and 2. Treatment is conveniently administered at 4-week intervals. Others schedules of the combination using higher doses of carboplatin and/or PLD have been reported in small series of ovarian cancer patients [25, 26]. A direct comparison between these different schedules of PLD–carboplatin would be necessary to determine whether the expected augmentation of toxicity induced by higher drug dosages within the combination might translate into better efficacy.

While we acknowledge the difficulties associated with comparing results across studies, our data are similar to those reported for the carboplatin–paclitaxel arm of the ICON4-OVAR 2.2 study [1]. Despite poorer performance status, a greater number of previous chemotherapy treatments (including paclitaxel), and more patients relapsing within 12 months in our study, the 32-month median survival reported here compares with the median survival of 29 months for platinum–taxane in ICON4-OVAR 2.2. Although PFS was 12 months in the ICON4-OVAR 2.2 study versus 9.4 months in our study, the criteria for PFS differed. In our study, progression criteria included an isolated elevation of CA 125 levels. In the ICON4-OVAR 2.2 study, a raised CA 125 level in the absence of clinical or radiologic evidence of PD was not considered PD.

Toxic effects were also notably different with platinum–taxane and PLD–carboplatin. Grade 2 or greater neurotoxicity (7% with PLD–carboplatin versus 20% with platinum–taxane) and alopecia (12% versus 86%, respectively) were more common with platinum–taxane, while mucositis (12% versus 8%, respectively) and HFS (11% versus 0%, respectively) were more common with PLD–carboplatin.

These data support the clinical efficacy and tolerability of PLD in combination with carboplatin for second-line therapy of AOC in late relapse. A phase III intergroup study is being conducted to confirm our findings. It will compare PLD plus carboplatin with paclitaxel plus carboplatin for recurrent epithelial ovarian or peritoneal carcinoma in women in late relapse after failure of initial platinum-based chemotherapy and with limited neurotoxicity from prior treatment. Ongoing trials are also evaluating platinum–taxane–PLD triplets as a strategy to improve survival after first-line therapy.

**contributors**

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**Table 4.** Nonhematologic toxicity, % of patients (N = 104)

<table>
<thead>
<tr>
<th>NCI grade</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>21</td>
<td>12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>28</td>
<td>25</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Mucositis</td>
<td>10</td>
<td>8</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>11</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>PPE</td>
<td>21</td>
<td>11</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>21</td>
<td>6</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Asthenia</td>
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<td>33</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

PPE, palmar/plantar erythrodysesthesia; NCI, National Cancer Institute.
On 21 August 2018

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