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Veliparib and topotecan for patients with platinum-resistant or partially platinum-sensitive relapse of epithelial ovarian cancer with BRCA negative or unknown BRCA status

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Introduction

The majority of ovarian cancer patients experience relapse of their disease despite initial complete or partial response to treatment. Strategies for treating recurrent ovarian cancer depend on platinum sensitivity; however, regardless of primary platinum sensitivity, most tumors eventually become platinum resistant[1]. Non-platinum containing regimens in this setting include the topoisomerase I-inhibitor topotecan. Inhibition of the nuclear enzyme, topoisomerase I, which is involved in replication, transcription, and repair of DNA, induces temporary DNA single-strand breaks, which potentially induces cell apoptosis, predominantly in heavily replicating cells such as tumor cells[2]. Response rates of topotecan monotherapy in platinum resistant or partially platinum sensitive recurrent ovarian cancer vary from 0-18%, whereas the response in platinum sensitive ovarian cancers is somewhat better, 12-33%[2–5].

Pharmacological inhibition of another nuclear enzyme, poly-(adenosine-diphosphate-ribose) polymerase (PARP), was recently approved (olaparib) by The European Medicines Agency (EMA) as monotherapy of platinum sensitive relapse of BRCA1/2 (breast cancer early onset) mutated (germline and somatic) epithelial ovarian cancer based on randomized phase II trials[6–9]. Promptly after this, the United States Food and Drug Administration (U.S. FDA) approved olaparib as monotherapy of recurrent germline BRCA1/2 mutated epithelial ovarian cancer in patients previously treated with three or more prior lines of chemotherapy [10,11]. PARP is essential to repair of single-strand DNA breaks by the base-excision repair mechanism, whereas the BRCA1/2 proteins are essential to DNA double-strand break repair by homologous recombination (HR). A number of other genes are involved in the HR pathway, and the BRCA gene may be inactivated by hypermethylation in addition to germline or somatic mutation. The BRCAness phenomenon describes an HR deficient tumor without a germline BRCA mutation. PARP inhibition in an HR dysfunctional cell induces selective cell kill termed synthetic lethality. PARP inhibition generates non-repaired DNA single-strand breaks to accumulate as DNA double-strand breaks by subsequent replication. In an HR deficient cell, which relies on the error-prone mechanisms of non-homologous end joining (NHEJ) and single-strand-annealing, this accumulation results in cell death [12,13].

Originally, PARP inhibitors were proposed as chemotherapy sensitizers[14–16]. Inhibition of the PARP enzyme renders tumor cells especially sensitive to cytostatic agents by blocking the base excision repair of DNA single-strand breaks. This results, in part, in slower repair of DNA damage, a lower threshold for apoptosis and thus increased sensitivity to cytostatic drugs[17,18]. Previous studies have shown that PARPi is a potent chemotherapy sensitizer, regardless of BRCA function[19]. Studies combining PARPi with chemotherapy generally report enhanced hematological toxicity [20,21]; however successful combination regimens have led to further phase II [7] and ongoing phase III trials, e.g. ClinicalTrials.gov NCT02470585.

We hypothesized that co-administration of the PARP inhibitor veliparib with the topoisomerase-I inhibitor topotecan would enhance the anti-tumor effect in patients without BRCA1/2 germline mutations or unknown BRCA1/2 status.

Material and methods

Study design
This prospective, nonrandomized phase I/II study included women with advanced primary epithelial ovarian, fallopian tube or peritoneal cancer without germline BRCA1/2 mutations or with unknown BRCA mutation status. Patients were enrolled and treated at the Department of Oncology, Vejle Hospital, Denmark. Study subjects received an initial dose of oral veliparib, 30 mg twice a day, on days 1-3, 8-10 and 15-17, and intravenous topotecan (3 mg/m²) on days 2, 9, and 16. Treatment cycles of 28 days were repeated until progression, intolerable toxicity, patient wish for withdrawal, long term treatment delays (>4 weeks), or lack of study compliance. Dose escalation of veliparib took place in cohorts of 3 to 6 patients in a classic phase I, 3+3 design with an escalation to the next dose level if no dose limiting toxicities were seen; choice of dose, administration and dose escalation design was in continuation with 2 ongoing phase I/II studies (ClinicalTrials.gov, NCT00892736; NCT01012817). The study was commenced in January 2013 and the last patient included in October 2014. The last study treatment was administered in January 2015.

**Patients**

Eligibility criteria were histologically confirmed diagnosis of epithelial primary ovarian, fallopian tube or peritoneal cancer, stage I-IV, minimum age of 18 years, written informed consent, ECOG performance status 0-2, platinum resistant or partially platinum sensitive disease, adequate liver, bone marrow and renal function and coagulation parameters (7 days prior to inclusion), tumor tissue available for BRCAness analysis (somatic BRCA1/2 and other HR-gene mutations), a washout period of 28 days of prior anticancer treatment, verified disease progression by RECIST criteria and/or by GCIG CA-125 criteria after previous first line chemotherapy or progression after further regimens of chemotherapy, and measurable disease by RECIST 1.1 or evaluable by GCIG CA-125 criteria[22,23].

Key exclusion criteria were prior treatment with a PARP inhibitor, known BRCA1/2 germline mutations, previous topotecan treatment terminated or dose reduced due to toxicity, other previous or present malignancy, CNS metastasis, and uncontrolled chronic, medical or psychiatric conditions.

The study was conducted in accordance with the Helsinki II Declaration and the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the applicable official legislation and approved by The Regional Committee on Health Research Ethics for Southern Denmark (S-20120078), The Danish Health and Medicines Authority and the Data Protection Agency. ClinicalTrials.gov, NCT01690598.

**Study end points**

The primary endpoints of the phase I study were maximum tolerated dose (MTD) of veliparib, dose limiting toxicities (DLT), and identification of recommended dose for phase II. In the phase II study the primary endpoint was rate of response to combination treatment veliparib and topotecan in patients with relapsed advanced ovarian cancer without germline BRCA1/2 mutations or unknown BRCA1/2 status. Secondary endpoints were progression free survival (PFS), overall survival (OS), safety and toxicity.

**Evaluation and safety**

Assessment of tumor size and activity was performed at baseline and every three cycles (or prematurely if investigator suspected progression) by the RECIST 1.1 and GCIG CA-125 criteria. CT scans of 22 out of 27 included subjects were available for evaluation by RECIST 1.1 criteria, however CT scans of six of those subjects were evaluated by RECIST 1.0 criteria. Baseline evaluation comprised a full clinical exam including...
gynecological examination and laboratory tests of liver, renal, bone marrow function and coagulation parameters. Laboratory tests were additionally run before every administration of topotecan. Toxicity was registered at baseline and before every treatment cycle. All adverse events were evaluated on the basis of the criteria for adverse events established by the NCI (National Cancer Institute) CT-CAE (Common terminology Criteria for Adverse Events) version 4.0 and if necessary reported to the relevant authorities according to the applicable rules.

Results

Twenty nine patients were screened and 27 found eligible and enrolled in the study. They all received at least one cycle of veliparib and topotecan treatment. Baseline characteristics are presented in Table 1. The majority of the patients had serous adenocarcinoma (88.9%) and approximately half of them (51.9%) were heavily pretreated with four or more previous lines of treatment (median 4; range [2–8]). CA-125 was generally highly elevated with a median of 504 [range 16-21.575]. The superiority of patients were platinum resistant (92.6%); two (7.4 %) were partially platinum sensitive.

At inclusion, 26 of 27 patients were tested negative of a BRCA1/2 germline mutation; one patient was enrolled as “unknown BRCA1/2 status” and received one treatment cycle while BRCA1/2 testing was ongoing. The test result showed a pathogenic germline mutation in the BRCA1 gene, and the patient was subsequently excluded from further treatment according to the protocol. This subject was included in our intention-to-treat analysis.

Of the 27 patients, 22 had primary ovarian cancer (81.5%), three had primary fallopian tube cancer (11.1 %), and two had primary peritoneal cancer (7.4%). We enrolled 12 patients in the phase I part and another 15 patients in the phase II part of the study. All of them initially received the starting dose of veliparib of 30 mg twice daily; one patient (06) was dose reduced from cycle 2 onwards due to febrile neutropenia (veliparib 20 mg twice daily; topotecan 2 mg/m²). Consequently, topotecan was reduced to 2 mg/m² from included individual number 07 due to dose limiting toxicity, and according to the protocol this was incompatible with dose escalation of veliparib. Therefore, moving into phase II, the initial starting dose of veliparib 30 mg twice daily continued as the starting dose for all patients.

Treatment delay for more than seven days occurred in four of 27 patients; of those, 1 patient (01) was excluded from the study, since treatment was delayed for more than 28 days (due to ileus/volvolus). The other three patients had treatment delayed due to hematologic toxicity, none of those received G-CSF, and only one patient had a subsequent dose reduction of veliparib and topotecan.

The median number of treatment cycles was three, range [1-12]. Four patients were excluded from the study before radiologic or serologic progression was established. Of those, two patients received one treatment cycle (exclusion due to a pathogenic BRCA1 mutation and long term treatment delay, respectively). One patient died of the cancer disease after four treatment cycles, and one patient withdrew her consent after two treatment cycles.

Response rates: Clinical benefit (all stable disease) was seen in 10 patients (37%) in terms of disease control (Table 2). Two patients showed response according to the GCIG CA-125 criteria, one of which, however, at
the same time had progressive disease according to the RECIST criteria and therefore discontinued
treatment. Fifteen patients had stable disease according to GCIG CA-125, eight of which showed
progressive disease according to the RECIST criteria. One of these patients continued treatment until
progressive disease was confirmed according to both GCIG CA-125 and the RECIST criteria, whereas the
remaining seven discontinued study treatment. None of the patients showed complete or partial
radiological response and thus the best response according to RECIST was no change. Out of eight patients
with stable disease by radiology, one had GCIG CA-125 progression at the same time. This patient
continued study treatment until progression by both the RECIST and GCIG CA-125 criteria i.e. continued
study treatment beyond progression. As the vast majority (92.6 %) of patients was platinum resistant,
stratification by platinum sensitivity was not considered statistically meaningful. One out of the two
patients, that were partially platinum sensitive, was the subject included as “BRCA negative/unknown” and
subsequently identified as a BRCA1 germline mutation carrier, showed clinical benefit (no change by RECIST
and not evaluable by CA-125 criteria). The other partially platinum sensitive subject showed PD clinically
and according to GCIG CA-125 criteria after one series of study treatment, and was hence withdrawn from
protocol treatment without further CT scans.

Survival: Median progression free survival (time from first dose of veliparib/topotecan until progression)
was 2.8 months (95% CI [2.6-3.6]), Figure 1. Median overall survival (time from first
dose of veliparib/topotecan until death) was 7.1 months (95% CI [4.8-10.8]), Figure 2.

Safety: Adverse events reported, regardless of relation to study treatment, were mainly grade 1 or 2 and
are listed in Table 3. The most commonly reported ones were fatigue (48.1%) and abdominal pain (55.5%).
Features of myelosuppression were anemia (81.5%), neutropenia (22.2%), (neutropenia grade 3-4: 11.1%)
and thrombocytopenia (29.6%). Grade 3-4 infection occurred in 22.2% of the patients. Serious adverse
events occurred in 12 of 27 patients (44.4%) (Table 3). One SAE (grade 3 thromboembolic event with
pulmonary embolism and an arterial aortic embolism) may have been related to the study treatment, but
was considered most likely due to the disseminated cancer.

Discussion

Few studies have evaluated the effect of PARP inhibitor treatment in sporadic ovarian cancer [6–8], as the
concept of synthetic lethality exploiting the deficiency in DNA repair inherently existing in BRCA1/2
mutation carriers, rapidly occurred as a main mechanism of action of this group of agents rather than a
simple sensitizer to chemotherapy.

The present phase I/II clinical trial of PARP inhibitor veliparib in combination with topoisomerase I inhibitor
topotecan in recurrent epithelial ovarian cancer without germline BRCA1/2 mutations or with unknown
BRCA1/2 status verifies the clinical safety of the combination treatment. None of the patients showed
radiological response to the treatment. However, determining the fraction of patients with disease control
by either CA-125 response or stable disease (RECIST or GCIG CA-125 criteria), 10 in 27 patients (37%)
showed response/disease control of any kind, regardless of the duration of response. This is lower than in
other studies on PARP inhibition in ovarian cancer, presumably due, in part, to difference in study
population and the exclusion of BRCA1/2 positive as well as platinum sensitive patients rendering this cohort in a poor prognostic setting.

Gelmon et al. [8] reported data on olaparib monotherapy in patients with recurrent high grade serous or poorly differentiated ovarian carcinoma, BRCA1/2 mutated and wildtype. They found partial responders among BRCA1/2 mutated as well as wildtype cancers (41% and 24%, respectively) and total disease control fractions of 62% (BRCA1/2 mutated) and 76% (BRCA1/2 wildtype). Important features of their findings were higher response rates among BRCA1/2 mutated cancers and platinum-sensitive cancers (regardless of mutational status), and that all of the BRCA1/2 wildtype responders had high grade serous carcinoma. Ledermann et al. [6] reported similar findings on olaparib maintenance monotherapy versus placebo in platinum-sensitive serous ovarian cancer with a statistically significant increase in PFS in favor of olaparib. This was observed in both BRCA1/2 mutated and wildtype cancers, but to a higher degree in the first group. Likewise they detected a tendency towards better overall survival in the olaparib group, especially among the BRCA1/2 mutated cancers, but the overall survival benefit was statistically insignificant[24]. Oza et al. [7] conducted a study of 156 patients with recurrent platinum-sensitive, high grade ovarian cancer with up to three previous platinum-based chemotherapy regimens, who had been progression free for at least 6 months before inclusion. They compared carboplatin and paclitaxel chemotherapy alone with the same chemotherapy regimen in combination with olaparib and subsequent olaparib maintenance therapy and found a significant increase in PFS with the combination therapy. They also looked at subgroup analyses by BRCA1/2 mutation status and found the highest gain among BRCA1/2 mutated patients. However, they did not, either, find an increase in overall survival for the total group or the BRCA1/2 mutated subgroup.

As outlined above, BRCA1/2 wildtype ovarian cancer patients exhibited response to PARPi, albeit at a lower magnitude in comparison with germline BRCA1/2 mutation carriers. Mirza et al. [25] demonstrated efficacy of PARPi niraparib as maintenance therapy in platinum-sensitive, recurrent ovarian cancer compared to placebo. In addition to stratifying patients by germline BRCA1/2 status they did HR deficiency testing on DNA from archival tumor tissue, including somatic BRCA1/2 mutation test. They found a statistically significant better response to niraparib compared to placebo in all subgroups; germline BRCA1/2 carriers, HR-deficient cases, and the overall non-germline BRCA1/2 group, but to a greater extend among BRCA1/2 mutation carriers – germline and somatic alike. Kummar et al. [21] also did HR deficiency testing as part of a large gene expression profile of multiple (211) genes involved in DNA damage response, on tumor derived DNA from ovarian cancer patients receiving either oral cyclophosphamide alone or in combination with veliparib. However, they did not report a statistically significant correlation between any of the DNA repair defects identified, including BRCA1/2 mutations, and response to PARPi veliparib and/or chemotherapy treatment. All together encouraging why there may be a rationale for PARPi treatment in a BRCA1/2 negative population as in the current study.

PARPi have several biologic mechanisms of action; firstly inhibition of the catalytic activity of PARP culminating in accumulation of unrepaired DNA single strand breaks, secondly PARP trapping, by which PARP enzyme is trapped on DNA complexes thus interfering with DNA replication[26,27]. The contribution of each mechanism to the clinical activity of PARPi is not fully understood, and the PARP trapping efficiency of veliparib has been argued less potent compared to other PARPi[27]. Despite variation in PARP trapping efficiency among different PARPi, veliparib has demonstrated equal anti-tumor activity in pre-clinical in-vivo models[28], supporting that veliparib is not less efficient than other PARPi.
In summary there seems to be a subgroup of patients gaining the highest benefit from PARPi, i.e. ovarian cancers harboring BRCA1/2 mutations, high grade serous histology, and platinum sensitive disease. The studies described are different in terms of design and combination of drugs, and comparison with our response rate directly is therefore dubious. However, all but one study [21] identified response to PARPi, also among BRCA1/2 wildtype patients. Our finding of a smaller clinical benefit compared to other studies is consistent with these trends, as we analyzed a group of heavily pretreated ovarian cancers whose likelihood of response to any kind of treatment was low. Also, with the studies referred above in mind, our inclusion criteria per se identified the group of patients that would benefit the least from PARP inhibition, as we included only platinum resistant or partially sensitive cancers, and on top of this the key inclusion criterion was negative or unknown BRCA1/2 status. Additionally, the dosing regimen of topotecan and the MTD of veliparib (30 mg. twice daily) were lower than in most other studies, possibly explaining, in part, lack of response to therapy. Unfortunately toxicity, presumably due to topotecan, prevented further dosing escalation of veliparib according to study protocol.

We suspected that a subgroup of responders could be identified as HR deficient due to other mechanisms than germline BRCA1/2 mutations, i.e. somatic BRCA1/2 mutations, mutations in other genes related to the HR pathway or by epigenetic mechanisms such as hypermethylation of BRCA1 promoter region. However, we refrained from performing BRCAness analyses on tumor tissue as best clinical response was disease control and translational research of good and poor responders, respectively, would be obsolete. Our hypothesis of PARPi acting as a chemosensitizer regardless of BRCA status was not verified in this small subset of ovarian cancer patients with limited clinical benefit.

The adverse events in our study were similar to the ones reported in previous studies of combined PARP inhibitor and cytostatic treatment in ovarian cancers, and in other solid tumor types as well[21,29–32]. In general, toxicity was acceptable and manageable. The rates of adverse events were somewhat differing, probably due to divergent dosing regimens and distinct tumor types.

Conclusion

In conclusion, the safety of this combination regimen of veliparib and topotecan for recurrent epithelial ovarian cancer in non-BRCA1/2 germline mutation carriers was satisfying and comparable to findings in other studies. However, the best clinical response was stable disease. There seems to be a subgroup of patients beyond the BRCA1/2 germline mutated cancers, which will benefit from treatment with PARPi. This group is yet to be specifically identified and future studies of PARP inhibitors with or without accompanying chemotherapy in sporadic ovarian cancer should have priority.

Clinical Practice Points

- Veliparib and topotecan is a safe combination treatment for recurrent epithelial ovarian cancer in non-BRCA1/2 germline mutation carriers.
- In this study, best clinical response to the regimen was stable disease.
Acknowledgements

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Disclosure

The authors have no conflicts of interest regarding this study.

References


Table 1) Patient clinicopathologic characteristics (ECOG: Eastern Cooperative Oncology Group).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td>56.0</td>
</tr>
<tr>
<td>Median</td>
<td>35.8-73.5</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Histological tumour type – no. (%)</td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>HGSOC</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>LGSOC</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>Not graded/unknown</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Non-serous</td>
<td></td>
</tr>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>ECOG performance status – no. (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (63.0)</td>
</tr>
<tr>
<td>1</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Number of previous treatment regimens – no. (%)</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>3</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>≥4</td>
<td>14 (51.9)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Baseline CA-125 (kU/L)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Median</td>
<td>504</td>
</tr>
<tr>
<td>Range</td>
<td>16-21575</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Platinum sensitivity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Partially sensitive</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Resistant</td>
<td>25 (92.6)</td>
</tr>
</tbody>
</table>

Table 2) Clinical responses in study patients for whom the response could be evaluated.

<table>
<thead>
<tr>
<th>RECIST N = 27</th>
<th>GCIG CA-125</th>
<th>PR (RE)</th>
<th>SD</th>
<th>PD</th>
<th>NE</th>
<th>Total</th>
<th>Disease Control n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 27</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n (%)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR (RE)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SD</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>PD</td>
<td>13</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>13 (80.0)</td>
</tr>
<tr>
<td>NE</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2 (11.1)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>15</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>27 (100.0)</td>
</tr>
<tr>
<td>Disease control n (%)</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>10</td>
<td>10 (37.0)</td>
</tr>
</tbody>
</table>

Table 3) Adverse events of grade 1-2 reported in > 5 % of patients; adverse events grade 3-4 reported in any number of patients; total number of patients = 27.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1-2 – no. (%)</th>
<th>Grade 3-4 – no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>13 (48.1)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (25.9)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7 (25.9)</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>9 (33.3)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (29.6)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (25.9)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8 (29.6)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>5 (18.5)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Neuropathy – sensory</td>
<td>6 (22.2)</td>
<td>0</td>
</tr>
<tr>
<td>Condition</td>
<td>Count (Percentage)</td>
<td>Grade 2</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Seizure</td>
<td>4 (14.8)</td>
<td>0</td>
</tr>
<tr>
<td>Skin toxicity</td>
<td>2 (7.4)</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>8 (29.6)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (3.7)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Fever without neutropenia</td>
<td>5 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>3 (11.1)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>22 (81.5)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (22.2)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (29.6)</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>11 (40.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>3 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15 (55.5)</td>
<td></td>
</tr>
<tr>
<td>Pain unspecified</td>
<td>7 (25.9)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (7.4)</td>
<td></td>
</tr>
</tbody>
</table>

* Both were grade 3 adverse events; one patient experienced worsening from grade 2 to 3, the other from grade 0 to 3.

§ Worsening from grade 1 to 3.

# Both patients registered with grade 3 abdominal pain after treatment and grade 1 at baseline.

^ The patient registered a worsening of leg pain from 1 at baseline to 3 after treatment.