A Phase Ib and Pharmacokinetic Trial of Patupilone Combined with Carboplatin in Patients with Advanced Cancer

Martin Forster,1 Stan Kaye,1 Amit Oza,2 Ivo Sklenar,3 Anandhi Johri,4 Wing Cheung,4 Sara Zaknoen,4 and Martin Gore1

Abstract Purpose: Patupilone is a microtubule-targeting chemotherapeutic agent with clinical activity in a broad range of taxane-sensitive/resistant tumor types. The present phase Ib study examined the safety/tolerability and pharmacokinetics of patupilone in combination with carboplatin in patients with advanced solid tumors.

Experimental Design: Patients with advanced cancer received patupilone via a 5- to 10-min i.v. infusion at doses of 3.6 to 6.0 mg/m² q3w, immediately followed by carboplatin area under the curve (AUC) 5 or 6 mg/mL/min.

Results: Of the 37 patients enrolled, the majority previously received taxanes (81%) and/or platinum-containing drugs (97.3%). The maximum tolerated dose (MTD) of patupilone with carboplatin AUC 6 was 4.8 mg/m²; additional patients were enrolled to consolidate experience at this dose. Of the 22 patients who received the MTD, the most common nonhematologic adverse events were fatigue in six (27.3%) and diarrhea, nausea, vomiting, abdominal pain, and neuropathy in one each (4.5%; all grade 3); hematologic toxicities included two patients (9.1%) with grade 3 neutropenia. The pharmacokinetics of patupilone were similar to those in a previous study of patupilone monotherapy. Of the 26 patients with recurrent platinum-sensitive ovarian cancer, tumor response was assessable by response evaluation criteria in solid tumors in 17; 1 patient (6%) achieved a complete response, and 10 (59%) achieved a partial response.

Conclusions: The combination of patupilone 4.8 mg/m²/carboplatin AUC 6 was well tolerated and showed antitumor activity similar to established regimens in patients with recurrent platinum-sensitive ovarian cancer. The optimal dose for this regimen is currently being further refined in phase II trials.

The taxanes paclitaxel and docetaxel inhibit cell proliferation by stabilizing microtubule dynamics, thereby inducing aberrant spindle formation during mitosis, mitotic cell-cycle arrest, and apoptotic cell death (1). They have shown potent activity and are widely employed in the treatment of several cancers, including carcinoma of the breast, bladder, esophagus, head and neck, ovary, and lung (2). However, they can cause significant side effects, including neutropenia, alopecia, major hypersensitivity, myalgia, and neurotoxicity, which limit their use in some patients (3). In addition, the majority of patients eventually develop resistance to these agents, and most metastatic solid tumors remain incurable. Resistance can occur through a variety of mechanisms, including the overexpression of P-glycoprotein or alterations in microtubule dynamics (4).

Early evidence of clinical activity with single-agent taxane therapy led to the rapid development of combination regimens with platinum compounds. These combinations have shown significant efficacy in a number of solid tumors, and despite significant toxicities, they are widely used (5, 6). The combination of paclitaxel with carboplatin has become the standard of care for the first-line treatment of ovarian cancer (7, 8). There is also evidence that this combination is superior to carboplatin alone in patients whose disease relapses after a platinum-free interval of >6 months (9). Nevertheless, toxicity and the emergence of resistance remain major problems for combination therapy. There is, therefore, a clear need for microtubule-stabilizing agents with improved antitumor activity, less toxicity, and a reduced propensity to elicit tumor resistance.

Patupilone (epothilone B; EPO906) is a macrocyclic polyketide that is a member of the epothilone class, a group of microtubule-stabilizing chemotherapeutic agents (10). This drug was originally discovered in a screening program for secondary metabolites from myxobacteria with antifungal activity and was subsequently shown to have potent cytotoxic activity in mammalian cells (11). It is structurally unrelated to the taxanes, and in vitro data show that it binds to similar but possibly not identical sites on the β-tubulin subunit of microtubules (12). Patupilone has a higher affinity for this target than other epothilones and taxanes (13). In addition,
patupilone, like paclitaxel, is able to induce the polymerization of tubulin to create microtubules. However, in vitro studies indicate that patupilone is a more potent inducer of tubulin dimerization than paclitaxel, and in one cell line, it was shown to be more effective than paclitaxel in stabilizing preformed microtubules (11, 13, 14). Preclinical pharmacokinetic analysis suggests that patupilone may also be retained in tumor tissue longer than paclitaxel. The patupilone half-life in tumor tissue after single dose administration was 89 h (18) (Pharmacokinetic Team, Novartis Pharmaceuticals) compared with 12 h for paclitaxel (15) and 22 h for docetaxel (16).

Patupilone has been shown to inhibit the in vitro proliferative activity of a broad panel of human cancer cell lines, exhibiting 3- to 20-fold higher potency than paclitaxel. Importantly, it is as effective in paclitaxel-sensitive cells as it is in paclitaxel-resistant cells that overexpress the P-glycoprotein efflux pump, which confers multidrug resistance (11, 13, 17). In vitro experiments using median dose effect methodology (18) in A549 and HCT-116 cell lines have shown at least an additive effect when carboplatin has been dosed 24 h after patupilone treatment (Novartis). In animal models, patupilone is active against solid tumors such as epidermoid, prostate, lung, and colon cancers, including some that overexpress P-glycoprotein (14, 19, 20). Preclinical toxicology of the combination of carboplatin and patupilone showed increased but nonoverlapping toxicity compared with either drug alone (Novartis).

Single-agent patupilone has been investigated in several clinical trials. In the initial phase I study, patupilone was administered as one 5- to 10-min bolus infusion every 3 weeks (21). Forty-two patients were enrolled, and the maximum tolerated dose (MTD) in that study was 6 mg/m². The most common adverse events (AE) included diarrhea (starting at a dose of 8 mg/m²), fatigue, nausea, and mild peripheral neuropathies, particularly in patients who had undergone previous treatment with neurotoxic agents. No significant alopecia or myelosuppression was observed. A second trial reexamined the 3-weekly schedule given together with proactine antidiarrheal therapy (22). With this approach, the maximum dose given was 11 mg/m², and the dose of 10 mg/m², given as a 20-min infusion, was chosen as the dose for future comparative studies. A higher level of activity was observed in patients with platinum-resistant ovarian cancer, with eight objective responses observed from 33 patients treated at doses up to 11 mg/m².

In an earlier phase I study, an alternative schedule of patupilone, given as a 5-min i.v. bolus every week for 6 weeks followed by 3 weeks off treatment, modified later to a bolus every week for 3 weeks followed by 1 week off treatment, was studied (23). The MTD was 2.5 mg/m², and the most common AE was diarrhea, with minimal fatigue, nausea, and sensory neuropathy also occurring. This 2.5-mg/m² weekly schedule was used in a phase II trial of 53 patients with platinum- and paclitaxel-resistant/refractory ovarian cancer (24). The schedule was well tolerated and had a 6% and 17% response rate as defined by radiological and cancer antigen 125 (CA125) criteria, respectively.

The phase II study presented here was initiated because of the preclinical and clinical data described above. These data suggested that patupilone given with carboplatin on a 3-weekly schedule might have efficacy and/or safety advantages over the currently available carboplatin/taxane combinations. The study was designed to determine the MTD of carboplatin with patupilone administered every 3 weeks in patients with advanced cancer. Secondary objectives included an assessment of the safety and antitumor activity of this regimen.

**Materials and Methods**

**Patient selection.** Patients with advanced cancer who would normally be considered for carboplatin-based chemotherapy were eligible for this study. Patients were permitted to have received up to two prior chemotherapy regimens, including one with carboplatin.

Men and women aged ≥18 years were required to have evaluable disease that had been histologically or cytologically confirmed, WHO performance score ≤2, estimated life expectancy ≥3 months, and adequate bone marrow, liver, and renal function, defined as a neutrophil count >1.5 × 10⁹/L, platelet count ≥100 × 10⁹/L, serum alanine aminotransferase or aspartate aminotransferase <2.5× the upper limit of normal (ULN), serum total bilirubin <1.5 × ULN, serum creatinine <1.5 × ULN, and a glomerular filtration rate ≥60 mL/min. All patients were required to give written informed consent.

Patients were excluded if they had undergone major surgery ≤4 weeks before study entry, received any chemotherapy or investigational agent ≤30 days before study entry, received radiotherapy ≤4 weeks before the start of the study (except for palliative therapy of distant metastases), received radiotherapy to ≥25% of the bone marrow, or had clinical signs of symptomatic brain metastases or leptomeningeal disease. Additional exclusion criteria were previous malignancy ≤5 years from study entry, treatment with warfarin or other agents containing warfarin in doses ≥1 mg/day, and the presence of cardiac disease (New York Heart Association class III or IV), grade >1 unresolved diarrhea, grade ≥1 neuropathy, acute or chronic uncontrolled infection, hepatitis B or C, or HIV infection.

**Treatment.** The first two cohorts (nine patients) were treated with i.v. patupilone at doses of 3.6 and 4.8 mg/m² as a 5-min i.v. bolus infusion followed by a fixed dose of carboplatin (dose levels 1 and 2, respectively). The dose of carboplatin was the area under the curve (AUC) 5 mg/mL × min given as a 60-min continuous i.v. infusion administered once every 3 weeks, with the glomerular filtration rate (GFR) estimated by the EDTA clearance method. To be consistent with the more widely used practice of calculating GFR by the Cockcroft and Gault formula, a protocol modification was made. This required carboplatin to be subsequently given at an AUC of 6 as calculated by the GFR according to the Cockcroft and Gault formula, which is broadly equivalent to AUC 5 using EDTA measurement of GFR. These cohorts received patupilone 4.8 and 6.0 mg/m² (dose levels 3 and 4, respectively).

Treatment was continued until the development of dose-limiting toxicity, disease progression, or the decision by the investigator or patient to discontinue treatment. Patients experiencing unacceptable toxicity attributable to patupilone temporarily halted treatment, which could be resumed if the toxicity resolved before the start of the next cycle. Patients could continue on carboplatin alone if patupilone-induced toxicity did not resolve. Patients who experienced toxicity attributable to carboplatin could continue treatment with patupilone alone after resolution of the toxicity.

In the expansion phase of the study, patients who were unable to complete the first cycle of treatment for any reason other than toxicity attributable to patupilone were discontinued and replaced. Patients who experienced grade 3 or 4 neuropathy or hematologic, hepatic, or renal toxicity attributed to carboplatin during the first cycle that led to substantial delay (>7 days) in initiating the second cycle were discontinued and replaced.

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patient were documented and

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5 Unpublished data.
maintained throughout the study period. Other anticancer agents were prohibited during the study. Hematopoietic growth factors were prohibited for prophylactic use unless approved by the sponsor and used in accordance with the American Society of Clinical Oncology guidelines. Prophylactic antiemetics were allowed according to institutional guidelines. The use of analgesics was maintained during the trial. Herbal and nontraditional medications were prohibited.

In earlier phase I studies, diarrhea was determined to be the dose-limiting toxicity for patupilone. Therefore, antidiarrheal medication was recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea. Patients were provided loperamide on day 1 of cycle 1 and were called twice weekly during the first 8 weeks of treatment to ensure early detection and management of diarrhea; thereafter, patients were contacted weekly and instructed to call if a problem occurred. Diarrhea first reported at grade 1 or 2 was treated with standard loperamide (initial dose of 4 mg, followed by 2 mg q4h or after each unformed stool), which was discontinued after 12 diarrhea-free hours. If diarrhea progressed to (or was initially reported at) grade 3 or 4, the patient was hospitalized and treated with high-dose loperamide, opium tincture, or dihydromorphine; i.v. fluids and antibiotics were initiated as needed.

Study design. A standard phase I study design was used in which three patients were initially accrued at each dose level. Evaluable patients were defined as those who completed the first treatment cycle or discontinued due to dose-limiting toxicity. The sample size of a cohort was expanded to six patients if one dose-limiting toxicity occurred. Dose escalation was continued if no further dose-limiting toxicities were observed after all evaluable patients completed the first cycle of treatment. Dose escalation was terminated if more than one patient experienced a dose-limiting toxicity, and the immediate lower dose level was considered the MTD.

The study was conducted in accordance with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice, the US 21 Code of Federal Regulations, and the Declaration of Helsinki.

Pharmacokinetic sampling. Serial blood samples were collected from 14 patients at the MTD for patupilone pharmacokinetic determination before and after dosing (predose, at the end of the infusion, and at 30 min, 1, 2, 4, 8, 24, 72, 168, 336, and 504 h). Samples were analyzed using a high-performance liquid chromatography tandem mass spectrometry (HPLC/MS/MS) analytic method validated according to Food and Drug Administration guidance for industry. Liquid/liquid extraction of the blood samples was done using methyl tert-butyl ether. The organic layer was separated, evaporated to dryness under a nitrogen stream, and reconstituted in ammonium acetate (0.05 mol/L)-methanol (35:65, v/v). The reconstituted extracts were injected into a Nucleosil 50-C18 5-μm 125 × 4-mm HPLC column using gradient conditions [mobile phase A = ammonium acetate (0.05 mol/L)-methanol (35:65, v/v), mobile phase B = methanol] and analyzed by HPLC/MS/MS using atmospheric pressure chemical ionization interface (m/z = 508 to >320). 

Baseline WHOPerformance status

<table>
<thead>
<tr>
<th>Number of prior lines of therapy</th>
<th>Patients (N = 37), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 1. Patient demographics and baseline disease in all dose levels

be expected if carboplatin alone were administered at the dose used. Toxicity grading was in accordance with NIH–National Cancer Institute Common Toxicity Criteria, version 2.0.

Dose-limiting toxicities (DLT) were defined as at least one of the following occurring during the first cycle: grade 4 neutropenia with an absolute neutrophil count <500/μL for ≥5 days; febrile neutropenia requiring i.v. antibiotics and hospitalization; thrombocytopenia (platelet count <25,000/μL or need for platelet transfusion); any toxicity of grade ≥3 (except alopecia, myalgia, or arthralgia that responded to symptomatic therapy); or a two-grade increase in serum creatinine. Treatment delays of ≥2 weeks for any reason were also defined as dose-limiting toxicities.

Tumor assessments. Tumor response was not a primary end point of this study; however, response data, as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, were recorded whenever possible (25). Tumor response was assessed by the appropriate radiographic or physical examination at baseline, following every two cycles thereafter and when the patient went off the study (e.g., due to toxicity or disease progression). Plasma CA125 levels were measured at baseline and after every cycle, and although Rustin criteria were not strictly followed, CA125 response was recorded (26). Patients who missed tumor assessments, who died, or who discontinued the study before their first assessment (day 1 of cycle 3) were considered nonresponders.

Results

Patients. A total of 37 patients were enrolled in the trial and were treated until disease progression or unacceptable toxicity occurred. Patient demographics and baseline disease characteristics are shown in Table 1. All but one patient had received therapy with a platinum-containing compound, and 30 had received prior taxane therapy. The majority of patients (31; 83.8%) had ovarian/peritoneal cancer. Five of these patients had platinum-resistant disease, defined as a relapse within 6 months of platinum treatment, but treatment with a carboplatin...
combination was still considered appropriate; the majority of these patients had received another (non–platinum-based) treatment after initial relapse, i.e., before entry into this study.

**Toxicity and tolerability.** All 37 patients were evaluable for safety; 40.5% discontinued therapy due to an AE (33.3%, 33.3%, 36.4%, and 66.7% at levels 1, 2, 3, and 4, respectively). Adverse events leading to discontinuation were colitis, abdominal pain, back pain, bowel obstruction, vaginal bleeding, fatigue, palmar erythema, allergic reaction, stomatitis, and neuropathy. Additional findings leading to discontinuation were related to laboratory abnormalities such as thrombocytopenia, abnormal γ-glutamyl transferase, hypercalcemia, and neutropenia. All patients were alive at follow-up, with the exception of one patient at level 3 who died during the study because of disease progression. The mean numbers of cycles initiated at levels 1, 2, 3, and 4 were 6.7 ± 2.08, 4.5 ± 1.76, 5.2 ± 2.70, and 3.8 ± 2.04, respectively. Mean durations of treatment at each dose level were 135.0 ± 43.6, 82.2 ± 41.9, 99.4 ± 63.0, and 76.7 ± 58.1 days, respectively.

Nonhematologic toxicities of grade ≥3 independent of the relationship to study drug were experienced by 21 patients (56.7%). All of these toxicities were grade 3, other than one case of grade 4 hypokalemia associated with subacute bowel obstruction and vomiting. There was also one patient who developed a severe pericardial effusion unrelated to the study drug. Treatment-related grade 3/4 nonhematologic AEs occurring in ≥5% of patients during any cycle of treatment are summarized in Table 2. Patients could have multiple events, as listed in the table. The most frequently reported treatment-related grade 3/4 nonhematologic AEs across all treatment groups were fatigue (9 patients, 24.3%), vomiting (3 patients, 8.1%), abdominal pain (3 patients, 8.1%), diarrhea (2 patients, 5.4%), and nausea (2 patients, 5.4%).

Three patients from cohort 4 developed grade 3 nonhematologic toxicities during the first cycle of treatment. In one patient, this dose-limiting toxicity comprised severe fatigue associated with grade 2 diarrhea but no other specific toxicities. The other two patients developed severe abdominal cramping pains that seemed to be drug related. In both patients, the pains were associated with significant fatigue, nausea, and vomiting, and one patient required in-patient hospital management. The MTD was defined as one dose level below that where these DLTs occurred and, therefore, was determined to be patupilone 4.8 mg/m² plus carboplatin AUC 6 (level 3).

This dose level was expanded, and a total of 22 patients were treated. The most common grade 3/4 AEs reported during all courses of treatment at this dose level were fatigue in six patients (27.3%) and abdominal pain, diarrhea, nausea, vomiting, and a peripheral neuropathy that occurred in one patient each (4.5%). These included four DLTs, which were grade 3 fatigue in two patients, vomiting in one patient and diarrhea in another, giving a DLT rate of 18% at this MTD dose level.

Across all courses of all treatment groups, nonspecific abdominal pains of grade 2 or 3 were described more frequently than expected (three patients at both grades). In general, they developed within 24 to 48 h of treatment and were clinically severe. There were no specific features, and although these AEs seemed to be drug related, the causative mechanism is unclear. Abdominal pain generally responded to an increase in analgesia, although one patient also had features of an acute allergic reaction and required hospitalization. It is noteworthy that two of the three patients with grade 3 abdominal pain (one at 6.0 mg/m² and one at 4.8 mg/m²) had widespread diffuse peritoneal disease when treated, although neither had any preexisting pain or bowel dysfunction.

Overall, 32 patients (86.5%) experienced diarrhea of any cause, and diarrhea-control medication was required in 58.3% of these patients. No cases of treatment-related grade 4 diarrhea were observed.

Treatment-related peripheral neuropathy was reported in 10 patients, with 8 describing grade 1 severity and 1 each experiencing grades 2 and 3 neuropathy. The patient with grade 3 neuropathy developed symptoms after six cycles of treatment, and it resolved totally within 2 months of completing treatment. She had previously been treated with carboplatin, gemcitabine, and 12 weeks of paclitaxel.

Alopecia was observed in ~32% of patients, but in all but one, it was reported as mild. Hypersensitivity to either drug was

### Table 2. Incidence of grade 3/4 treatment-related nonhematologic toxicities by dosage group

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>3.6 mg/m² + AUC 5* (n = 3)</th>
<th>4.8 mg/m² + AUC 5* (n = 6)</th>
<th>4.8 mg/m² + AUC 6* (n = 22)</th>
<th>6.0 mg/m² + AUC 6* (n = 6)</th>
<th>Total (N = 37)</th>
<th>Total (N = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Nausea</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Constipation</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Dermatologic alopecia</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>(peripheral)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>DLTs (first cycle)</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
<td>0/3</td>
</tr>
</tbody>
</table>

NOTE: Patients may be entered with multiple events during all cycles of treatment.

* Dose of patupilone + carboplatin.

† Dose-limiting toxicity.

‡ Alopecia grade 2.
uncommon, occurring in seven patients in total (19%), including two with a grade 1 reaction.

Hematologic AEs were uncommon, with no grade 4 AEs reported and four patients experiencing grade 3 AEs. One patient in the lowest dose cohort developed a transient grade 3 thrombocytopenia after six cycles of therapy, and treatment was stopped at this point. There were two cases of grade 3 neutropenia in all cycles of patients treated at the MTD, which resolved spontaneously after 28 and 36 days. One patient had previously received combination chemotherapy with carboplatin, paclitaxel, and gemcitabine, and the other had received five cycles of cisplatin. There was one further case of transient grade 3 neutropenia in a patient in the highest cohort after six cycles of treatment.

Clinically relevant changes in laboratory values were infrequent. The following were observed: hypomagnesemia (grade 3, one patient), hypokalemia (grade 4, one patient), elevated total bilirubin levels (grade 3, two patients), and elevated γ-glutamyl transferase levels (grade 3, one patient). The raised γ-glutamyl transferase was a dose-limiting toxicity and suspected to be possibly treatment related, increasing transiently after a number of treatment cycles, although it did not require any action to be taken nor dose modification for future cycles. An increase in bilirubin levels was observed in two patients, but was considered to be unrelated to treatment.

Pharmacokinetics. Pharmacokinetic data were available from 14 patients enrolled at the MTD. Mean pharmacokinetic parameters of clearance (91.9 ± 36.3 mL/min/m²; n = 9) and apparent volume of distribution at steady state (707 ± 297 L/m²; n = 9) observed in this study were comparable to mean pharmacokinetic parameters of the 3.6- and 5.4-mg/m² doses (mean dose 4.4 mg/m²; n = 11) given in the single-agent 3-weekly patupilone study (clearance 88.0 ± 31.7 mL/min/m² and volume of distribution 583 ± 167 L/m²; Table 3). The concentration-time profiles of patupilone in patients receiving patupilone concomitantly with carboplatin or as monotherapy were also similar5 (Novartis).

Response evaluation. All 37 patients enrolled in the trial were assessable for response, and the response data are presented in Table 4. Thirty-one patients had ovarian or peritoneal cancer, and response was fully assessable by RECIST in 21. The remaining 10 patients included 3 with nonmeasurable peritoneal disease at baseline, which remained stable or subjectively improved with treatment. Of the other seven patients, one had an unconfirmed partial response, one unconfirmed stable disease, and three suspected progressive disease. Response assessment in the other two patients was considered inconclusive because patupilone was stopped after one cycle due to toxicity. Both patients continued with single-agent carboplatin or cisplatin, respectively, and had a partial response on evaluation after further treatment. Of the fully assessable 21 patients, one patient (5%) achieved a complete response, and 12 (57%) achieved a partial response, for an overall best response rate of 62%. Three patients (14%) had stable disease, and five (24%) had progressive disease. Of the fully assessable 17 patients with platinum-sensitive disease, 11 (65%) had an objective response. Of the five patients with platinum-resistant disease, two had a partial response (40%), and one had stable disease. Three patients with ovarian cancer were CA125 nonsecretors, and the remaining 28 patients were assessed by CA125 criteria; 20 (71%) of these experienced a ≥50% response, and 18 (64%) experienced a ≥75% response.

Conclusion

This study was primarily intended to assess the safety of the novel chemotherapeutic agent patupilone in combination with carboplatin in patients with advanced solid tumors and to establish a recommended dose of this regimen. The study shows that patupilone plus carboplatin is a safe and well-tolerated therapy, and the MTD was determined to be patupilone 4.8 mg/m² plus carboplatin AUC 6. This is a lower dose than was expected after the single-agent studies, where

### Table 3. Mean patupilone pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Patupilone + carboplatin (current study), mean ± SD (n)</th>
<th>Patupilone alone (single agent), mean ± SD (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (mg/m²)</td>
<td>4.68 ± 0.13 (14)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>93.4 ± 81.8 (14)</td>
</tr>
<tr>
<td>AUC0-inf (ng·h/mL)</td>
<td>919 ± 296 (10)</td>
</tr>
<tr>
<td>CL (mL/min/m²)</td>
<td>96.3 ± 36.0 (8)</td>
</tr>
<tr>
<td>Vss (L/m²)</td>
<td>697 ± 316 (8)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>132 ± 34 (10)</td>
</tr>
</tbody>
</table>

NOTE: In patients who received 4.8 mg/m² patupilone concomitantly with carboplatin (current study) and mean patupilone pharmacokinetic parameters in patients who received either 3.6 or 5.4 mg/m² patupilone alone every 3 wks in a previous phase I single-agent study.

### Table 4. Best overall response at study completion based on RECIST

<table>
<thead>
<tr>
<th>Best overall response, n</th>
<th>3.6 mg/m² + AUC 5* (n = 3)</th>
<th>4.8 mg/m² + AUC 5* (n = 6)</th>
<th>4.8 mg/m² + AUC 6* (n = 22)</th>
<th>6.0 mg/m² + AUC 6* (n = 6)</th>
<th>Total (N = 37)</th>
<th>Ovarian/peritoneal patients (n = 31)</th>
<th>Platinum-sensitive patients (n = 26)</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Partial response</td>
<td>2</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>12</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Stable disease</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>4</td>
<td>3</td>
<td>2</td>
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<tr>
<td>Progressive disease</td>
<td>0</td>
<td>3</td>
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<td>2</td>
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<td>10</td>
<td>9</td>
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</table>

*Dose of patupilone + carboplatin.
10 mg/m² every 3 weeks was the proposed single-agent dose. It is interesting to note that neither of the dose-liming toxicities were of the nature that would have been predicted from previous experiences with carboplatin or patupilone. The patients who developed dose-limiting abdominal pain had extensive intra-abdominal disease that may have contributed to these symptoms. It is conceivable that a higher dose would have been achievable in a different patient population, and further experience will be necessary to ascertain whether these symptoms relate to specific subgroups of patients (e.g., those with large-volume intra-abdominal disease). The extent to which carboplatin may have contributed to the patupilone toxicity is unclear and will be further investigated in secondary studies.

Currently, the combination of carboplatin with paclitaxel is considered to be the standard first-line therapy for the treatment of ovarian cancer (7, 8). The optimum combination to treat patients with potentially platinum-sensitive relapsed disease remains to be determined. Paclitaxel in combination with carboplatin is associated with significant clinical toxicity, e.g., total alopecia, neurotoxicity, and bone marrow suppression (8). The data from this study suggest that the substitution of paclitaxel by patupilone in a carboplatin combination is feasible and should be considered for further evaluation, particularly in patients with platinum-sensitive relapsed ovarian cancer who have already been treated with carboplatin and paclitaxel.

Treatment-related diarrhea occurred in 86.5% of patients, but except for two patients (5.4%), it was grade ≤2 and easily manageable with standard antidiarrheal treatments. The incidence of diarrhea was slightly lower than might be predicted from the single-agent patupilone studies, and it did not result in the discontinuation of any patient from the trial. Alopecia was observed in ~32% of patients, with only one case of severe alopecia requiring a wig, which occurred at the highest carboplatin/patupilone dose level. This is certainly a lower incidence than that seen with carboplatin/paclitaxel, reported as ~80% to 90% (27). This difference may be confirmed in future randomized trials. The relatively low rate of alopecia with carboplatin/patupilone is an important advantage to this combination, particularly in the treatment of women. Alopecia has been cited as the most disturbing side effect anticipated by almost 60% of women preparing for chemotherapy and is a risk factor for the discontinuation of therapy (28). Treatment-related neuropathy, a significant side effect of the taxanes, was uncommon. It occurred in 10 patients (27.0%), the majority of whom experienced grade 1 severity. Further experience will determine whether neurotoxicity, when it does develop, relates to cumulative (total) dose. The low rate of hematologic toxicity is also noteworthy.

Hypersensitivity was infrequent, despite the absence of premedication, occurring in only seven patients during all treatment cycles (grade 3, four patients; grade 2, one patient; grade 1, two patients). It is also likely that most of the hypersensitivity reactions may have been due to the carboplatin, a phenomenon that is well recognized in a pretreated population (29). Of the four patients who developed a grade 3 hypersensitivity reaction, treatment was stopped in two patients and was successfully continued for several further cycles in the other two patients, with the administration of appropriate premedication. These data suggest that in this combination, premedication would not be routinely required but may be useful in patients that develop significant allergic reactions.

The pharmacokinetics of patupilone observed in this study when the drug was administered concomitantly with carboplatin seemed to be similar to those noted in single-agent patupilone trials (Table 3, previously unpublished data; Novartis). This trial was not designed to assess the efficacy of carboplatin/patupilone. However, the results provide preliminary evidence that the efficacy of this regimen (65% best response in fully assessable patients with carboplatin-sensitive relapsed ovarian and peritoneal cancer) is comparable to that obtained with other treatment regimens used in this patient population. In addition, 40% of carboplatin-resistant patients showed RECIST tumor partial responses. Furthermore, CA125 reductions from baseline were observed in 94% of patients with ovarian or peritoneum cancer; more than two thirds of patients had ≥50% reductions, and 64% of patients had ≥75% reductions.

This study shows that carboplatin/patupilone therapy is feasible and well tolerated in patients with advanced solid tumors. It is noteworthy that as a single agent, the dose of patupilone recommended for further study on a 3-weekly regimen is higher (10 mg/m²) than that identified in this combination trial (4.8 mg/m²). Further studies are, therefore, planned to confirm the optimal dose for this combination, and in addition, phase II studies are currently under consideration to investigate the safety and efficacy of this combination in a broad range of solid tumors.

References

14. Altman KH, Wartmann M, O'Reilly T. Epothilones

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