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PHASE I STUDIES

Phase I trial of the oral smoothened inhibitor sonidegib in combination with paclitaxel in patients with advanced solid tumors

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Summary *Purpose* To establish a recommended phase II dose (RP2D) for the oral smoothened inhibitor sonidegib in combination with paclitaxel; secondary objectives include evaluation of safety, tolerability, markers of Hedgehog (Hh) signaling and preliminary antitumor activity. *Methods* Patients with advanced solid tumors were enrolled in cohorts of escalating sonidegib dose levels (400mg, 600mg and 800mg orally, once daily on days 1–28) in combination with paclitaxel 80 mg/m^2 on days 1, 8 and 15 in 4-weekly cycles. Dose-limiting toxicities (DLTs) were assessed using CTCAE v4. Once the RP2D was defined, patients with advanced ovarian carcinoma were treated at this dose level in an expansion phase. Biomarkers of Hh signaling were assessed by immunohistochemistry in archival tissue and antitumor activity evaluated using RECIST 1.1. *Results* 18 patients were treated: 3 at 400 mg, 3 at 600 mg and 12 at 800 mg sonidegib. Only one patient treated at 800 mg presented a DLT (prolonged neutropenia resulting in failure to receive 75% of the planned sonidegib dose). However, 4 of 12 patients treated at 800 mg had their sonidegib dose reduced for toxicity after cycle 1. Hh biomarker (SHH, Patched, SMO and GLI1) staining did not correlate with clinical activity. Best response was partial response in 3 patients (2 ovarian, 1 breast cancer) and stable disease >4 cycles in 3 patients (2 ovarian, 1 anal cancer). *Conclusions* The combination of sonidegib and paclitaxel is tolerable and evidence of antitumor activity was identified. The RP2D of sonidegib was 800 mg in combination with paclitaxel 80mg/m^2.

Keywords Phase I · Sonidegib · Hedgehog pathway inhibition · Paclitaxel

Introduction

The Hedgehog (Hh) signaling pathway plays a critical role in organ development and tissue homeostasis during embryogenesis and is also involved in tissue repair and regeneration of adult organs from stem cells [1, 2]. Aberrant Hh signaling via mutations in components of the pathway or inappropriate ligand expression has been observed across a number of different malignancies and this pathway has been identified as a potential target for the development of new anticancer agents [3]. Smoothened (SMO), a G protein-coupled receptor-like molecule that positively regulates signal transduction, represents a central component of the Hh pathway. In the absence of Hh ligands, SMO is inhibited by Patched (PTCH1), a 12-pass transmembrane protein present on the primary cilium of target cells. Following binding of Hh ligands to PTCH1, SMO repression is released, resulting in activation of the glioma-associated oncogene homolog (GLI) transcription factors

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and subsequently in the regulation of downstream target genes, including GLI1, PTCH1, MYC, BCL-2, and Cyclin D1 [4, 5].

Several SMO inhibitors have been developed and two of them, vismodegib and sonidegib, have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic or locally advanced basal cell carcinoma (BCC), a tumor type that commonly presents mutations leading to inactivation of PTCH1 or, less frequently, constitutive activation of SMO [6, 7].

Our phase I trial (NCT01954355) evaluated sonidegib in combination with weekly paclitaxel in advanced solid tumors. Paclitaxel is active as monotherapy in many malignancies, including ovarian, breast, endometrial and non-small cell lung cancer. A favorable toxicity profile renders paclitaxel suitable for evaluation in combination with targeted agents. In patients with advanced breast cancer, weekly administration results in superior efficacy versus every-3-weeks administration, in terms of response rate, time to progression and survival, as well as inducing less neutropenia [8, 9]. In relapsed ovarian cancer, response rates ranging from 25 to 56%, and up to 70% in terms of CA-125 response, have been reported with single-agent weekly paclitaxel, even in patients with prior 3-weekly paclitaxel treatment [10–12]. Weekly paclitaxel may also represent an appropriate partner for combination therapies in advanced ovarian carcinoma, in comparison to other chemotherapy agents [13].

There is preclinical evidence that activated Hh pathway may induce chemoresistance in solid tumors [14]. Steg and colleagues evaluated the effect of SMO inhibition, alone and in combination with paclitaxel or carboplatin, in 3 pairs of parental and chemotherapy-resistant ovarian cancer cell lines. They observed significant sensitization to paclitaxel in the taxane-resistant cells, both in vitro and in vivo. This effect was mediated by downregulation of the multidrug resistance mediator P-glycoprotein (ABCB1/MDR1) [15].

We report the results of our phase I trial evaluating the SMO inhibitor sonidegib in combination with paclitaxel in patients with advanced solid tumors.

Patients and methods

Patient selection

The trial consisted of a dose-escalation and a dose-expansion phase. Patients were eligible for the dose-escalation phase if they had a histologically or cytologically documented advanced solid malignancy, refractory to standard therapy or for which no standard therapy existed, previously treated with ≤2 lines of chemotherapy for advanced disease. Patients were eligible for the dose-expansion phase if they had a histologically or cytologically confirmed diagnosis of advanced ovarian cancer previously treated with platinum and taxane chemotherapy (previous taxane could have been administered either on a 3-weekly, or on a weekly, schedule), were refractory (progressive disease during chemotherapy) or resistant (progressive disease within 6 months of completing chemotherapy) to their last platinum-containing chemotherapy regimen and had received ≤2 prior lines of chemotherapy for advanced disease.

Other key eligibility criteria for both phases included: Eastern Cooperative Oncology Group performance status 0 to 1; adequate hematologic, hepatic, and renal function (absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, AST/ALT ≤2.5 times upper limit of normal [ULN], or ≤5.0 x ULN if liver metastases were present, bilirubin ≤1.5 x ULN and creatinine clearance >50 mL/min, according to the formula of Cockcroft-Gault); a ≥ 4-week interval (6-week interval if prior nitrosoureas or mitomycin C) between trial treatment and any prior treatment with chemotherapy, radiotherapy or targeted agents; no concomitant treatment with strong CYP3A4/5 inhibitors or inducers, drugs metabolized by CYP2B6 or CYP2C9, or drugs with potential to cause rhabdomyolysis (such as 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitors, clofibrate, gemfibrozil); and no treatment with warfarin sodium. Patients with symptomatic brain metastases, prior therapy with Hh inhibitor, or known hypersensitivity to taxanes, and those positive for hepatitis B, C or HIV, were excluded.

The ethics committees of all participating centers approved the trial, which was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices. Written informed consent was obtained from all patients before registration in the trial.

Trial design and patient evaluation

This was a 4-center, open-label, phase I trial. During dose escalation, paclitaxel 80 mg/m^2 administered on days 1, 8 and 15 was combined with escalating doses of oral sonidegib given once daily (OD) continuously in 4-weekly cycles. The starting dose of sonidegib was 400 mg OD with two additional dose levels (DLs) of 600 mg and 800 mg OD. Dose escalation for sonidegib followed the standard 3 + 3 design and the RP2D defined as the highest dose level at which at a maximum of one of six patients developed a DLT. There was no dose escalation for paclitaxel. Premedication before paclitaxel administration consisted of intravenous dexamethasone 10 mg, clemastine 2 mg and ranitidine 50 mg.

Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. DLTs were defined as adverse events

occurring during the first cycle of treatment that were judged as possibly, probably or definitely related to trial treatment and fulfilled one of the following criteria: absolute neutrophil count $<0.5 \times 10^9$/L for $\geq 7 \pm 1$ days, febrile neutropenia, platelets $<25 \times 10^9$/L or $<50 \times 10^9$/L requiring transfusion, any grade ≥ 3 event that persisted despite adequate medical intervention; treatment-related toxicities that resulted in failure to receive ≥75% of the planned doses of sonidegib in the first cycle (i.e. ≥21 of 28 doses of sonidegib in one 28-day cycle), despite maximal (as judged by the investigator) supportive care measures; any adverse event at least possibly related to trial treatment that, regardless of grade, resulted in dose modification of sonidegib; inability to resume dosing for the subsequent cycle at the current dose level within 14 days due to treatment-related toxicity.

Tumor response was assessed in all patients every 2 cycles using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [16].

Once the RP2D was established, accrual began for the dose-expansion phase, with an initial plan of enrolling 12 patients with ovarian carcinoma (6 previously treated with taxane on a 3-weekly, and 6 on a weekly, schedule). However, after completion of the dose-escalation phase and enrolment of 6 ovarian carcinoma patients into the expansion phase, the trial was prematurely closed following a decision by the drug manufacturer to discontinue clinical development of sonidegib in solid tumors other than BCC.

Here we present results from 18 patients treated in the trial: 12 patients in the dose- escalation, and 6 patients in the dose-expansion, phase.

Pretreatment evaluation and safety assessment

Pretreatment evaluation consisted of a complete medical history, physical examination, vital signs, ECG, blood sample for CBC (i.e., hemoglobin, WBC count with differential, platelet count), biochemistry analysis (AP, AST, ALT, bilirubin, serum creatinine, calculated creatinine clearance [according to the formula of Cockcroft-Gault], CPK, CPK-MB, myoglobin, total protein, albumin, calcium, magnesium, potassium, sodium, phosphorus), Quick, INR, aPTT, serum pregnancy test (women with child-bearing potential), HIV, Hepatitis B and C testing, CA-125 (patients with ovarian cancer), and baseline tumor measurements.

A clinical evaluation consisting of a brief history, physical examination and vital signs was performed on days 1, 8 and 15 in all cycles (and on day 22 of cycles 1 and 2). An ECG and urine pregnancy test (for women with child-bearing potential), were performed on day 1 of each cycle. Blood samples for CBC and biochemistry were obtained on days 1 and 15 in all cycles and on days 8 and 22 of cycles 1 and 2.

Duration of trial treatment

Patients with objective response or stable disease were allowed to remain on trial until disease progression, unacceptable adverse events, patient's decision to withdraw consent from the trial, or changes in the patient's condition including intercurrent illness rendering continuation of trial treatment unacceptable. Patients were allowed to continue on single-agent sonidegib if they needed to discontinue paclitaxel because of adverse events.

Hedgehog pathway signaling

Hh pathway signaling was evaluated using 4 biomarkers (SHH, Patched, SMO and GLI1) on archived paraffin-embedded specimens by immunohistochemistry (IHC). Briefly, 4 μm tissue section slides were dewaxed and rehydrated in alcohol scale, then unmasked in a microwave 15 min with pH 6 citrate buffer and cooled at room temperature (RT). Peroxidases were inhibited in 30% H_2O_2 for 10 min and nonspecific binding blocked with Protein Block Serum Free (DAKO, X0909) for 10 min at RT. The incubation with the primary antibodies was performed for 1 h at RT. The primary antibodies used were: GLI1 (LSBio, LS-C180157, dilution 1:800), PTCH1 (Abcam, ab129341, dilution 1:200), SMO (Abcam, ab113438, dilution 1:200) and SHH (Merck Millipore, 06–1106, dilution 1:250). Signal amplification was achieved with LSAB2 System HRP (DAKO, K0675), applying each reagent (Biotinylated link; streptavidin-HRP) for 30 min at RT. Reactions were developed with ImmPACT DAB Peroxidase (HRP) Substrate (Vector Lab SK-4105) for 4 min at RT. Slides were then stained with hematoxylin for 1 min, dehydrated and mounted using anhydrous mounting medium.

Staining was evaluated independently by two operators. The percentage of positive tumor cells and the intensity of staining, as well as the cellular localization (membranous, cytoplasmic and/or nucleus staining), were recorded. The H-score index was calculated using the following formula: H-Score = ((percentage of 1+ positive cells*1) + (percentage of 2+ positive cells*2) + (percentage of 3+ positive cells*3)). Association with response to trial treatment was explored. Fischer's exact test and Wilcoxon–Mann–Whitney test were used to compare Hedgehog pathway protein expression in patients responding to treatment versus those with no response and in patients with either response or prolonged (>4 cycles) stable disease versus those with either progressive or stable disease up to 4 cycles.

Results

Trial population

Between October 2013 and March 2015 a total of 19 patients were enrolled at the participating centers. One patient (with ovarian carcinoma) withdrew consent before starting treatment. Of the 18 patients who received study treatment, three received 400 mg, three 600 mg, and twelve 800 mg, of sonidegib (6 during dose escalation and 6 in the expansion phase). All patients received paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 28 days in combination with sonidegib. Median age was 59 years (range 46–77). A median of 3.5 cycles (range 1–17) of treatment were delivered. Baseline characteristics of the trial population are summarized in Table 1.

Dose escalation and recommended phase II dose

Six patients (three per DL) were treated at DL 1 and 2 (400 mg and 600 mg OD sonidegib respectively) with no DLTs being reported. At DL 3 (800 mg OD sonidegib) one out of 6 treated patients presented a DLT consisting of inability to receive at least 75% of sonidegib doses during cycle 1, due to prolonged grade 3 neutropenia. Therefore, the RP2D of sonidegib is 800 mg OD continuously in combination with intravenous paclitaxel dosed at 80 mg/m^2 on days 1, 8 and 15 every 4 weeks (Table 2).

Safety and compliance

Toxicities that were judged to be at least possibly attributable to trial treatment and occurred in ≥10% of patients are summarized in Table 3. Anemia (72%; 6% grade ≥ 3), diarrhea (50%; 11% grade ≥ 3) and dysgeusia (50%; 6% grade ≥ 3) were the most common adverse events. Other grade ≥ 3 toxicities observed were neutropenia (11%), CPK increase (6%),

Table 1 Baseline characteristics of treated patients

	No. of patients
Total no. Patients treated	18
Female: Male	15:3
Median age (Range) years	59 (46–77)
ECOG performance status 0:1	10:8
Tumor type	
Ovarian	9
Breast	2
Pancreas	2
NSCLC	1
Anal canal	1
Cervix uteri	1
Myxofibrosarcoma	1
Klatskin cancer	1
Prior systemic therapies	
0:1:2:3:4	0:4:7:6:1
Prior taxanes	12

Table 2 Dose-limiting toxicities in patients receiving sonidegib (administered as a continuous once-daily dose) in combination with paclitaxel (80 mg/m^2 on days 1,8,15 q28)

Dose level (DL)	Sonidegib dose	No. pts. with DLT/ No. pts. treated	Nature of DLT
1	400 mg OD	0/3	-
2	600 mg OD	0/3	-
3	800 mg OD	1/6	<75% of planned sonidegib dose received due to prolonged G3 neutropenia

Table 3 Common observed toxicities (≥10% of patients) judged to be at least possibly related to treatment

AE Term	Any grade N (%)	Grade ≥ 3 N (%)
Anemia	13 (72%)	1 (6%)
Diarrhea	9 (50%)	2 (11%)
Dysgeusia	9 (50%)	1 (6%)
CPK increased	8 (44%)	1 (6%)
Alopecia	7 (39%)	-
Fatigue	7 (39%)	-
Myalgia	7 (39%)	1 (6%)
Nausea	7 (39%)	-
Neutrophil count decreased	7 (39%)	2 (11%)
Weight loss	5 (28%)	-
Aspartate aminotransferase increased	4 (22%)	-
Constipation	4 (22%)	-
Peripheral sensory neuropathy	4 (22%)	-
Alanine aminotransferase increased	3 (17%)	-
Alkaline phosphatase increased	3 (17%)	-
Anorexia	3 (17%)	-
Blood bilirubin increased	3 (17%)	-
Pain	3 (17%)	-
Vomiting	3 (17%)	1 (6%)
Abdominal pain	2 (11%)	-
Arthralgia	2 (11%)	-
Bladder infection	2 (11%)	-
Creatinine increased	2 (11%)	-
Dry skin	2 (11%)	-
Edema limbs	2 (11%)	-
Mucositis oral	2 (11%)	-
Paresthesia	2 (11%)	-
Urinary tract infection	2 (11%)	-

myalgia (6%) and vomiting (6%). All toxicities were reversible with supportive measures, and interruption of trial treatment. Four patients, all treated at the RP2D (4/12: 33%) had their sonidegib dose reduced to 600 mg (two of them with concomitant reduction of paclitaxel to 60 mg/m^2) for treatment-related adverse events. In particular, 2 patients had their sonidegib dose reduced during cycle 3 (one due to nausea and one due to myalgia), 1 patient had both sonidegib and paclitaxel doses reduced during cycle 1 (due to prolonged neutropenia) and 1 patient had both sonidegib and paclitaxel doses reduced during cycle 5 (due to myalgia and neuropathy). Reasons for treatment discontinuation included: documented progressive disease (13 patients), investigator decision due to lack of response (3 patients) and treatment-related adverse events (2 patients, both treated at the RP2D), consisting of vomiting and myalgia in 1 patient (discontinued after 3 cycles, despite dose reduction) and lower limb muscle weakness in 1 patient (discontinued after 2 cycles, without dose reduction).

Hedgehog signaling biomarkers

Samples from 18 patients were received and processed for IHC. All 4 markers were evaluated in 17 patients; tissue samples were insufficient for evaluation in the remaining patient. For each marker the H-score index was determined including the staining intensity and the percentage of positive cells in the tumor. No significant association was found between staining for Hh biomarkers (SHH, Patched, SMO and GLI1) and clinical activity (objective response and/or prolonged stable disease), whether H-score was examined using different cut-offs to classify patients as low or high expression ((100 (low: ≤100 vs. high: >100), 200 (low: <200 vs. high: ≥200), 100 & 200 (low: <100 vs. high: ≥200)) or as a continuous variable (data not shown).

Antitumor activity

Preliminary evidence of antitumor activity was observed. Partial response was achieved in 3 patients (17%): two with ovarian carcinoma (one with platinum-sensitive disease treated at DL 1 and one with platinum-resistant disease treated at DL 3) and 1 patient with breast carcinoma treated at DL 3. Three patients (17%) had stable disease for >4 cycles of treatment: two with ovarian carcinoma (both treated at DL 3) and one with anal carcinoma (treated at DL 1) (Fig. 1). Among 8 patients with tumors considered resistant or refractory to previous taxane-based chemotherapy (5 ovarian, 1 breast, 1 sarcoma, 1 cervix uteri carcinoma), best response was prolonged stable disease for 6 and 17 cycles, respectively, in 2 patients (both with ovarian carcinoma treated at DL 3).

Discussion

The results of this phase I trial indicate that the RP2D of sonidegib given in combination with paclitaxel at 80 mg/m^2 on days 1, 8 and 15 every 28 days is 800 mg daily on days 1–28. The combination of sonidegib and paclitaxel was well tolerated. Common toxicities included anemia, diarrhea, dysgeusia and musculoskeletal disorders (including myalgia and CPK increase). No new toxicities were identified. The toxicity profile was comparable to previous experience with single-agent sonidegib in a phase I trial [17] and a randomized phase II trial in patients with advanced or metastatic BCC [7], although we found a higher frequency and severity of some adverse events such as anemia and diarrhea, probably reflecting concomitant administration of paclitaxel. While the RP2D of sonidegib in our trial based on the toxicities

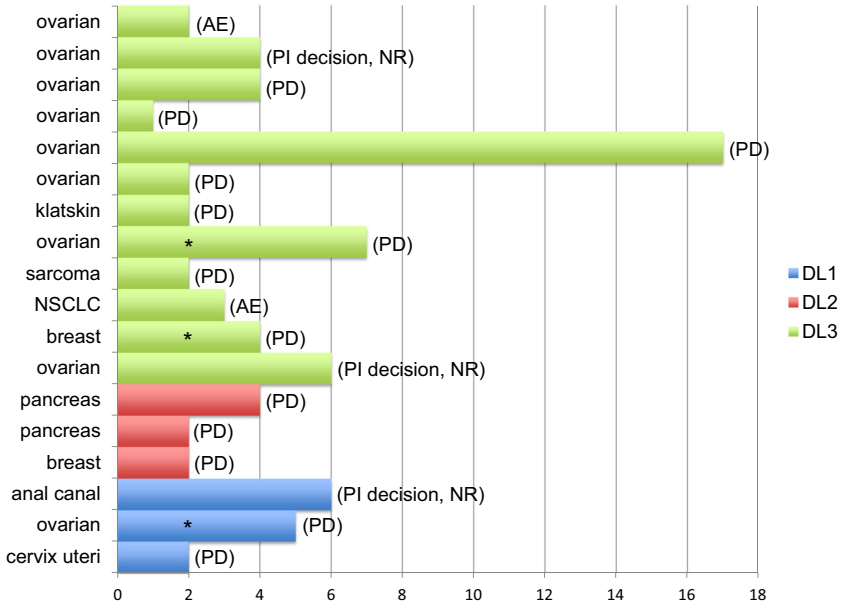

Fig. 1 Antitumor activity of sonidegib in combination with paclitaxel. Cycles on treatment are shown along the x axis and reason for treatment discontinuation in parenthesis at the end of each bar (n = 18 patients). * denotes patients with partial response (n = 3); DL: dose level; AE: adverse event; NR: no response; PD: progressive disease

observed during cycle 1 was 800 mg, 33% of the patients treated at this dose level required dose reduction due to toxicities. The earlier randomized trial also found a significantly higher frequency of adverse events and dosage reductions at the 800 mg, than the 200 mg, dose level [7]. However, response rates did not differ between these two doses. Thus, a lower dose results in less toxicities while retaining antitumor activity in a disease type driven by ligand-independent Hh pathway activation. Results of the randomized trial were not available at the time our study was designed.

Efficacy results in our trial demonstrated objective responses in 3 patients and prolonged (>4 cycles) stable disease in 3 patients. Among 9 patients with advanced ovarian carcinoma, 2 patients achieved a partial remission and two had stable disease for 6 and 17 cycles, respectively. Of 5 ovarian cancer patients considered resistant to previous taxane-containing chemotherapy, best response was stable disease in 2 patients previously treated with a 3-weekly taxane regimen, lasting 6 and 17 cycles as noted previously. As mentioned previously, there is preclinical evidence that treatment with SMO inhibitors may reverse tumor resistance to paclitaxel. Steg et al. showed that treatment with sonidegib was able to sensitize ovarian cancer cells to paclitaxel, but not to carboplatin [15]. This was attributed to downregulation of P-glycoprotein (ABCB1/MDR1), resulting in increased uptake of paclitaxel, but not carboplatin, in the cancer cells. Our trial was not designed to establish whether treatment with sonidegib can increase taxane sensitivity in ovarian or other solid tumors. The trial was closed before completion of the expansion phase, due to discontinuation of clinical development of sonidegib in solid tumors other than BCC. Currently sonidegib is approved by the FDA for the treatment of locally advanced or metastatic BCC at the dose of 200 mg once daily.

Several other SMO inhibitors have been developed and tested in clinical trials [18–20]. As with vismodegib and sonidegib, single-agent activity was limited to BCC and medulloblastoma, two tumor types with known mutations (mainly PATCH1 and SMO) leading to ligand-independent Hh pathway activation. The limited single-agent activity observed in other solid tumors prompted combination studies with chemotherapy. However, results of these studies failed to demonstrate any benefit of adding an Hh inhibitor to standard chemotherapy regimens in advanced small cell-lung cancer (SCLC), pancreatic and colon cancer [21–24]. In a recently reported phase I trial sonidegib was combined with etoposide and cisplatin in 15 patients with newly diagnosed extensive SCLC. Next generation sequencing (NGS) analysis performed in a patient with an exceptionally durable response (that continued on sonidegib for >27 months after completing combination treatment), revealed tumor-specific amplification of SOX2 and PIK3CA, both on chromosome 3q26.3–27 [25]. However, currently it is unknown whether specific molecular subsets may benefit from Hh inhibition in tumors without PATCH1 or SMO mutations.

In summary, the data from this phase I trial demonstrate that the SMO inhibitor sonidegib can safely be combined with weekly paclitaxel in patients with advanced solid tumors. Antitumor activity was seen in ovarian, anal and breast cancers. We identified an RP2D for sonidegib of 800 mg daily on days 1–28 with paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 28 days, although 33% of patients (4/12) treated at this dose level required dose reduction (with concomitant paclitaxel dose reductions in two cases). Markers of Hh signaling assessed by IHC in archival tumor tissue did not correlate with clinical outcome.

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Compliance with ethical standards

Conflict of interest Author A. Stathis declares that has no conflict of interest. Author D. Hess declares that is shareholder of Novartis. Author R. von Moos declares that is advisory board participant of Novartis and BMS. Author K. Homicsko declares that has no conflict of interest. Author G. Griguolo declares that has no conflict of interest. Author M. Joerger declares that has no conflict of interest. Author M. Mark declares that has no conflict of interest. Author C.J. Ackermann declares that has no conflict of interest. Author S. Allegrini declares that has no conflict of interest. Author C.V. Catapano declares that has no conflict of interest. Author A. Xyrafas declares that has no conflict of interest. Author M. Enoiu declares that has no conflict of interest. Author S. Berardi declares that has no conflict of interest. Author P. Gargiulo declares that has no conflict of interest. Author C. Sessa declares that has no conflict of interest.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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