Acta Oncologica, 2011; 50: 1105–1110

informa
healthcare

ORIGINAL ARTICLE

A phase I study of the oral platinum agent satraplatin in sequential combination with capecitabine in the treatment of patients with advanced solid malignancies

ELISA GALLERANI[1,2,3], JEAN BAUER[3,4], DAGMAR HESS[3,5], STEFFEN BOEHM[3,5], CORNELIA DROEGE[3,6], SANDRINE JECKELMANN[3,4], MONICA MIANI[7], RICHARD HERRMANN[3,6], SILVIA MARSONI[7], SABINE SPERKA[8] & CRISTIANA SESSA[1,3]

[1]*Istituto Oncologico della Svizzera Italiana (IOSI), Bellinzona, Switzerland,* [2]*PhD Programme in Experimental Medicine and Oncology, University of Insubria, Varese Italy,* [3]*Swiss Group for Clinical Cancer Research (SAKK), Bern, Switzerland,* [4]*Centre Pluridisciplinaire d'Oncologie (CPO), Lausanne, Switzerland,* [5]*Kantonsspital St. Gallen, St. Gallen, Switzerland,* [6]*Universitätsspital Basel, Basel, Switzerland,* [7]*Southern Europe New Drug Organization (SENDO), Milano, Italy and* [8]*Agennix AG, Planneg/Martinsried, Germany*

Abstract

Background. The broad spectrum of antitumor activity of both the oral platinum analogue satraplatin (S) and capecitabine (C), along with the advantage of their oral administration, prompted a clinical study aimed to define the maximum tolerated dose (MTD) of the combination. *Patients and methods.* Four dose levels of S (mg/m^2/day) and C (mg/m^2/day) were evaluated in adult patients with advanced solid tumors: 60/1650, 80/1650, 60/2000, 70/2000; a course consisted of 28 days with sequential administration of S (days 1–5) and C (days 8–21) followed by one week rest. *Results*. Thirty-seven patients were treated, 24 in the dose escalation and 13 in the expansion phase; at the MTD, defined at S 70/C 2000, two patients presented dose limiting toxicities: lack of recovery of neutropenia by day 42 and nausea with dose skip of C. Most frequent toxicities were nausea (57%), diarrhea (51%), neutropenia (46%), anorexia, fatigue, vomiting (38% each). Two partial responses were observed in platinum sensitive ovarian cancer and one in prostate cancer. *Conclusion*. At S 70/C 2000 the combination of sequential S and C is tolerated with manageable toxicities; its evaluation in platinum and fluorouracil sensitive tumor types is worthwhile because of the easier administration and lack of nephro- and neurotoxicity as compared to parent compounds.

Satraplatin (JM-216, bis (acetato) ammine dichloro (cyclohexylamine) platinum (IV)) is a third generation, orally administered platinum compound.

Future development of satraplatin (S) in combination with other standard cytotoxics is attractive because of oral dosing, observed manageable toxicities, and evidence of cytotoxicity in several platinum-resistant tumor cell lines [1].

In vitro, S has shown additive activity with some cytotoxics including fluorouracil and capecitabine [2]; S has shown *in vivo* antitumor activity against a variety of murine tumor models such as prostate, ovarian, colon cancer and plasmacytoma. Among the different schedules tested in phase I, the daily administration for five consecutive days every four weeks was selected for clinical development; the main DLTs were hematological and gastrointestinal, with lack of nephrotoxicity and neurotoxicity. The recommended dose (RD) was 100 and 120 mg/m^2/day for previously treated and untreated patients, respectively [3]. Phase II trials of single agent S were performed in a variety of tumor types, including small cell lung cancer (SCLC), non-small cell lung (NSCLC), prostate, breast, colon, gastric and ovarian cancer. Objective responses were observed in SCLC, relapsed ovarian and prostate cancer [4].

Capecitabine (C) (XELODA®, Roche) is an orally administered systemic pro-drug of 5'-DFUR converted to 5-FU by the enzyme thymidine phosphorylase (TP). It has been shown that TP is overexpressed in some tumor tissues compared to normal

Correspondence: Cristiana Sessa, Istituto Oncologico della Svizzera Italiana (IOSI), Via Ospedale, 6500 Bellinzona, Switzerland. Tel. +41 91 811 8181. Fax: +41 91 811 9044. E-mail: cristiana.sessa@eoc.ch

(Received 20 September 2010; accepted 23 November 2010)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2010.543697

tissues, producing at least theoretically higher drug levels in tumors and less systemic toxicity. C is approved as single agent for the treatment of breast cancer failing both anthracycline- and paclitaxel-containing regimens, or in which further treatment with anthracycline is contraindicated, or in combination with docetaxel after progression on prior anthracycline-based chemotherapy, and for colorectal cancer in both the adjuvant and metastatic settings in combination with oxaliplatin.

The combination of 5-FU and a platinum compound has shown activity in a variety of cancers, such as head and neck, breast and gastrointestinal tumors. Due to the broad spectrum of antitumor activity of both C and S, it is likely that also their combination would show some clinical activity in a variety of advanced cancers with the advantage of the oral administration [5,6].

Patients and methods

Eligibility

Eligibility criteria included diagnosis of solid tumors for which treatment with C or platinum containing regimens could be of benefit, $\leq$ two previous lines of chemotherapy for advanced disease. ECOG PS $\leq$ two, adequate hematological (ANC $\geq$ 1500/µl, Platelet $\geq$ 100 000/µl) renal (serum creatinine $\leq$ 1.5 mg/dl) and liver function (total bilirubin $\leq$ ULN, AST, ALT and alkaline phosphatase (AP) $\leq 5 \times$ ULN). In case of AP value between 2.5 and $5 \times$ ULN, the hepatic isoenzyme of AP had to be $\leq 2.5 \times$ ULN.

Exclusion criteria were resistance to fluoropyrimidine or platinum defined as disease progression $<$ six months from the last treatment with each agent, prior radiotherapy involving $>$ 30% of active bone marrow, persisting $>$ G1 toxicity due to previous treatment, $>$ G1 neuropathy, $>$ G1 hearing loss and $>$ G2 tinnitus, impaired oral intake or abnormal absorption, symptomatic brain metastases, uncontrolled intercurrent illness, congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness. The concurrent use of cytochrome P450 3A4 inhibitors was not allowed. The protocol was approved by the local ethical committee of each participating center.

Treatment and study design

S was given daily from d1 to d5 and C twice a day (BID) from d8 to d21 of every four week cycle. Oral dexamethasone 4 mg and anti-HT3 serotoninergic anti-emetics were taken 30–60 minutes before S.

The starting doses of C and S were 1650 mg/m^2/day and 60 mg/m^2/day, respectively; a sequential scheme of administration was implemented to avoid any potential interaction and overlapping toxicities. An increment of 20 mg/m^2/day of S with a fixed dose of C was planned for the dose escalation. But, once the MTD was achieved, the protocol was amended to give an adequate dose of both drugs, and an increased dose of C (2000 mg/m^2/day) in combination with 60 mg/m^2/day of S was evaluated.

Three patients per cohort, six in case of toxicity, had to be treated at each dose level. Dose levels were to be escalated up to the MTD that was defined as one dose level below the dose at which two of three or two of six patients experienced a DLT. According to the protocol, the MTD corresponded to the RD at which additional patients had to be treated in the expansion phase, to define the safety profile and to evaluate hints of antitumor activity.

DLTs were defined as one of the following drug related toxicities occurring at cycle 1: $\geq$ 3/5 S or $\geq$ 4/14 C doses missed; $>$ two weeks delay in the start of second cycle; neutropenia $\geq$ G4 lasting $>$ five days or complicated by febrile neutropenia; G4 thrombocytopenia or G3 thrombocytopenia with signs of bleeding; persisting neuropathy G2 between cycles or $\geq$ G3 renal/gastrointestinal/other non-hematological toxicity. DLTs required a reduction of the dose at the second cycle.

S was supplied by GPC Biotech AG in gelatine capsules of 10 mg and 50 mg for oral use, with doses taken approximately 24 hours apart and to be swallowed with at least 200 ml of water.

C was supplied as 500 mg and 150 mg strength tablets to be administered in a dose of 825 or 1000 mg/m^2 orally BID for a total daily dose of 1650 or 2000 mg/m^2. C was to be taken with water within 30 minutes after a meal.

Treatment assessment

Full chemistry was performed weekly at the first cycle, then before each subsequent cycle. Complete blood count was performed weekly at the first cycle and then, in case of no toxicity, twice a cycle. Tumor assessment by radiological imaging was carried out at baseline, then every two cycles. ECG was performed at screening and then only when clinically indicated. Patients could continue the treatment until progression, appearance of toxicity, or refusal.

NCI-CTCAE version 3 and modified RECIST criteria for the definition of response was applied [7].

Efficacy was evaluated every two cycles. The evaluation of measurable disease was based on modified RECIST; in case of non-measurable disease in ovarian cancer and prostate cancer, tumor markers and specific guidelines were implemented to validate the response [8,9].

Results

Patient characteristics

Thirty-seven patients were treated and were evaluable for safety, 34 were evaluable for efficacy and 33 for DLT. One patient was not evaluable for DLT assessment because only 5/28 C doses were taken due to a streptococcus pneumonia infection. The infection was judged to be not related to the study medication. One patient started treatment with borderline number of platelets and experienced early thrombocytopenia but always > 75 G/l. According to protocol the patient could have continued treatment but the investigator decided not to start C on precaution. One patient showed a significant lack of compliance after the first intake of S because of nausea and vomiting G2 reported related to extreme anxiety of the patient. The fourth patient not evaluable for DLT skipped 2/28 C doses because of drug-related G2 epigastric pain lasting one day and after recovery refused to resume treatment. Thus 20/28 doses of C were skipped on patient's request. Beside epigastric pain the only other drug-related AE in this patient was nausea G1.

Table I reports the characteristics of the 37 treated patients. Seventeen were entered in the dose escalation at doses other than the MTD/RD and overall 20 were treated at the MTD/RD (seven in the dose escalation and 13 in the RD expansion phase). Prostate and ovarian were the most represented tumor types (51% and 19% respectively); all patients but one had received at least one prior chemotherapy with 36% having a platinum compound included in their prior treatment.

Table I. Patient characteristics.

	Dose escalation*	Recommended dose**
No. of treated patients	17	20
Median age (range)	68 (35–78)	67 (56–77)
Male/Female	12/5	13/7
ECOG PS 0/1/2	9/7/1	11/9/0
Tumor type		
Prostate	8	11
Ovarian	2	5
Others	7	4
Prior cancer treatments		
Radiotherapy	13	10
Chemotherapy	17	20
No. of chemotherapy lines for advanced disease		
0	1[a]	1[b]
1	11	13
2	5	6
Prior platinum	7	6
Prior fluoropyrimidine	4	0

Legend: RD, recommended dose; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

*Patients enrolled in the Dose Escalation Phase of the study, excluding seven patients treated at the Recommended Dose of S 70/C 2000.

**All patients treated at the Recommended Dose, including seven patients enrolled in the Dose Escalation Phase and 13 patients enrolled in the RD Expansion Phase.

[a]One patient with metastatic pancreatic cancer received the study treatment as first line.

[b]One patient received only adjuvant chemotherapy.

Dose escalation, DLT, MTD

No DLTs were observed at the first dose level; at the second dose level (S 80/C 1650) two of six patients presented DLTs; the MTD was thus initially defined as one dose level below, corresponding to a RD of S 60/C 1650 (Table II). Based on the acceptable tolerability of S 60/C 1650 and as the occurrence of DLTs seemed to be mainly related to S, two new dose cohorts were planned, the first one combining S 60 with an increased C dose of 2000 mg/m^2/day and the second one escalating the S dose to 70 mg/m^2/day with C 2000.

At S 60/C 2000 no DLTs were observed while at the subsequent level of S 70/C 2000 one of six patients presented DLTs with G3 nausea and prolonged G2 neutropenia with > two weeks delay of cycle 2. This dose level was defined as the new MTD/RD and 13 additional patients were treated; only one experienced a DLT, consisting of four dosing days of C skipped due to uncontrolled G2 nausea and vomiting.

Safety

Myelotoxicity, in particular thrombocytopenia, and gastrointestinal toxicity with nausea and vomiting, were dose limiting. Overall myelotoxicity consisted of thrombocytopenia in 84% of patients and neutropenia in 46% (Table III) while the most frequent non-hematological toxicities were nausea (57%), diarrhea (51%), vomiting, fatigue, anorexia (38% each) (Table IV).

At the RD S 70/C 2000 the median time to thrombocytopenia nadir was 26 days and the median time to recovery 7.5 days. Overall, neutropenia was neither dose dependent nor cumulative; it was severe (G3 and G4) at first cycle in 11% of patients and in 16% of patients over all cycles.

Three patients (8%) had a treatment-related adverse event that led to discontinuation; these patients were not treated at the RD.

S dose reduction was due to hematological toxicity which primarily occurred at the higher dose levels of S 70/C 2000 (RD) and S 80/C 1650. Thus, five of 20 (25%) and five of six (83%) patients had at least one dose reduction and 15% and 40% of cycles administered at a reduced S dose, respectively (Figure 1). Overall,

Table II. Number of patients and DLTs per dose level.

	Dose level S (mg/m^2/day)/ C (mg/m^2/day)	Number of evaluable/ treated patients	Number of patients with DLT	DLT description
Dose Escalation Phase	S 60/C 1650	6/7*	0	None
	S 80/C 1650	6/6	2	• Thrombocytopenia maximum G3 with $>$ 4 dosing days of C skipped • Thrombocytopenia G4 with hemorrhage
	S 60/C 2000	3/4**	0	None
	S 70/C 2000 MTD/RD	6/7[a]	1	• Nausea G3 and lack of recovery by day 42 of neutropenia G2
RD Expansion Phase	S 70/C 2000	12/13[b]	1	• $>$ 4 doising days of C skipped for G2 nausea and vomiting

Legend: S, satraplatin; C, capecitabine; DLT, dose limiting toxicity; G, severity grade by NCI-CTCAE criteria; MTD, maximum tolerated dose; RD, recommended dose.
*Non drug-related Serious Adverse Event.
**Early occurrence of thrombocytopenia.
[a]No patient's compliance.
[b]Patient's decision to withdraw the study.

20 cycles of 130 (15%) were delayed for toxicity – hematological in all cases but one – and further 18 cycle delays were due to reasons unrelated to safety.

In 17 cycles (13%) at least one dose of C was skipped due to treatment-related AEs; the proportion was higher at dose level S 80/C 1650 (5/15 cycles, 33%), while at S 70/C 2000 the number of cycles with $<$ 14 C dosing days due to toxicity was six of 67 (9%).

Anti-tumor activity

Among 34 evaluable patients, three achieved a partial response (9%), 15 stable disease (44%), 16 progressive disease (47%). The three partial responses were observed in two ovarian cancer patients with platinum sensitive disease and in one patient with prostate cancer, treated respectively with S/C doses of 60/1650, 60/2000, 70/2000.

All patients had measurable disease and were evaluated radiologically according to the RECIST criteria. The patients affected by ovarian cancer had abdominal measurable disease, while the patient with prostate cancer had liver metastases.

Five patients had a tumor stabilization lasting $\geq$ six months and two over one year. Among 19 patients with prostate cancer, one patient refractory to castration

Table III. Hematological toxicity by patient.

Parameter and dose level S (mg/m^2/day)/ C (mg/m^2/day)	Patients n	Cycle 1 G1 n	G2 n	G3 n	G4 n	All grades (%) n (%)	All cycles 1 n	2 n	3 n	4 n	All grades (%) n (%)
Thrombocytopenia											
Any dose level	37	15	5	2	1	23 (62.2%)	17	10	3	1	31 (83.8%)
S 60/C 1650	7	4	0	0	0	4 (57.1%)	5	0	0	0	5 (71.4%)
S 80/C 1650	6	1	1	2	1	5 (83.3%)	0	2	3	1	6 (100.0%)
S 60/C 2000	4	1	1	0	0	2 (50.0%)	2	1	0	0	3 (75.0%)
S 70/C 2000	20	9	3	0	0	12 (60.0%)	10	7	0	0	17 (85.0%)
Neutropenia											
Any dose level	37	4	6	4	0	14 (37.8%)	3	8	5	1	17 (45.9%)
S 60/C 1650	7	2	1	1	0	4 (57.1%)	2	1	1	0	4 (57.1%)
S 80/C 1650	6	0	1	2	0	3 (50.0%)	0	2	2	0	4 (66.7%)
S 60/C 2000	4	2	1	0	0	3 (75.0%)	1	2	0	0	3 (75.0%)
S 70/C 2000	20	0	3	1	0	4 (20.0%)	0	3	2	1	6 (30.0%)

Legend: S, satraplatin; C, capecitabine; n (%), number of patients (percentages based on the number of treated patients); G, severity grade by NCI-CTCAE criteria.

Table IV. Common (incidence ≥10%) and severe non-hematological toxicities.

	Dose escalation* All grades		Recommended dose** G3		Recommended dose** All grades	
Adverse event	n	%	n	%	n	%
Nausea	10	58.8	2	10.0	11	55.0
Fatigue	7	41.2	1	5.0	7	35.0
Anorexia	7	41.2			7	35.0
Diarrhea	6	35.3			13	65.0
Vomiting	6	35.3	1	5.0	8	40.0
Asthenia	2	11.8			4	20.0
Peripheral sensory neuropathy	2	11.8			1	5.0

Legend: RD, recommended dose; n (%), number of patients (percentages based on the number of treated patients); G, severity grade by NCI-CTCAE criteria.

*Patients enrolled in the Dose Escalation Phase of the study, excluding seven patients treated at the Recommended Dose of S 70/C 2000.

**All patients treated at the Recommended Dose, including seven patients enrolled in the Dose Escalation Phase and 13 patients enrolled in the RD Expansion Phase.

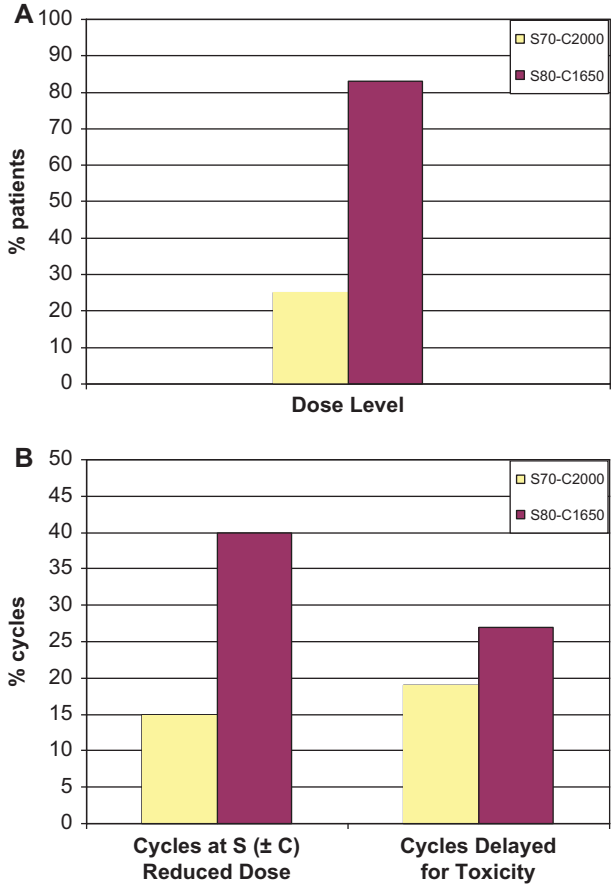

Figure 1. Treatment modifications at S 70/C 2000 (RD) and S 80/C 1650. A) Patients with at least one S (± C) Dose Reduction. B) Cycles administered at Reduced S (± C) Dose and Delayed for Toxicity.

and pre-treated with docetaxel achieved a PR with a TTP of 188 days. One prostate cancer patient previously treated with chemotherapy continued treatment for one year with stable disease.

Discussion

S is a new generation oral platinum (IV) compound whose structural difference from the platinum (II) compounds cisplatin and carboplatin results in oral bioavailability with antitumor activity comparable to carboplatin. Many phase I trials were performed with S single agent; the RD and schedule were 100–120 mg/m^2/day for five consecutive days every four weeks; DLTs were hematological and gastrointestinal. Differently from similar platinum compounds neither nephro-, neuro-, nor ototoxicity was observed [3,10–13].

Phase I trials of S in combination with different cytotoxics were performed with acceptable toxicity and hints of antitumor activity [14,15].

The promising activity of S in patients with hormone resistant prostate cancer (HRPC) in a phase III EORTC study of S and prednisone (P) versus P alone in the first-line setting brought about further clinical evaluations of the compound [16]. In addition, the results of the SPARC study, comparing S and P versus placebo and P in chemotherapy pretreated HRPC, showed a significant clinical benefit, defined as a composite endpoint of radiological and symptomatic progression, skeletal events, death, in patients receiving S, but the overall survival were similar in the two groups [17].

The combination of S and C looked particularly promising because of the *in vitro* additive activity and the attractiveness of oral administration [2]. In the present study S and C were given sequentially in an attempt to avoid overlapping toxicities, in particular gastrointestinal.

The RD was S 70/C 2000 with hematological and gastrointestinal DLT, in particular nausea and/or vomiting despite anti-emetic prophylaxis, in one case associated with prolonged moderate neutropenia.

The combination was associated with an acceptable safety profile. The main toxicities at the RD were myelotoxicity (thrombocytopenia G1-2 85%, neutropenia 30% overall, 15% G3-4), diarrhea G1-2 (65%), nausea G1-3 (55%), fatigue G1-3 (35%). Most likely these side effects can be reduced with more intensive supportive treatment.

Three confirmed PRs, two in patients with platinum sensitive ovarian cancer and one in hormone refractory prostate cancer patient were reported; 15 patients among 34 evaluable had a stable disease.

Responses were observed at all dose levels, including the lowest tested of 60 mg/m^2/day of S. The antitumor

activity observed in prostate cancer, even though preliminary, looks promising because of the lower dose of S 60 mg/m^2/day than the one of 100–120 mg/m^2/day estimated to be active in prostate cancer [16] and because of the poor patient selection with prior treatment with docetaxel in all but three patients.

The treatment was well tolerated and its evaluation with an adequate anti-emetic prophylaxis in fluorouracil or platinum sensitive tumors is worthwhile because of the confirmed lack of nephrotoxicity and neurotoxicity and ease of administration.

Acknowledgements

The authors thank Irene Corradino and Annamalia Bartosek from SENDO along with all the data managers and study nurses, for their cooperation in this study. The study was sponsored by GPC Biotech AG. Ethical Committees approval dates and study registration numbers are reported below:

Site	EC registration number for the study	EC approval date
Istituto Oncologico della Svizzera Italiana, Bellinzona	1745	Jan 24, 2006
Centre Pluridisciplinaire d'Oncologie, Lausanne	58/06	Mar 13, 2006
Kantonsspital St. Gallen, St. Gallen	EKSG 06/028 SG 266/06	Jun 2, 2006
Universitätsspital Basel, Basel	114/06	Jun 2, 2006

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Wosikowski K, Lamphere L, Unteregger G, Jung V, Kaplan F, Xu JP, et al. Preclinical antitumor activity of the oral platinum analog satraplatin. Cancer Chemother Pharmacol 2007; 60:589–600.

[2] Obermayr F. Synergistic in vitro anticancer activity with sequential schedules of JM-118, a metabolite of satraplatin, in combination with erlotinib, paclitaxel, or 5-FU. In AACR-NCI-EORTC Conference; 2005 Poster no. A216.

[3] McKeage MJ, Raynaud F, Ward J, Berry C, O'Dell D, Kelland LR, et al. Phase I and pharmacokinetic study of an oral platinum complex given daily for 5 days in patients with cancer. J Clin Oncol 1997;15:2691–700.

[4] Fokkema E, Groen HJ, Bauer J, Uges DR, Weil C, Smith IE. Phase II study of oral platinum drug JM216 as first-line treatment in patients with small-cell lung cancer. J Clin Oncol 1999;17:3822–7.

[5] Kucuk O, Pandya KJ, Skeel RT, Hochster H, Abeloff MD. Phase II study of cisplatin and 5-fluorouracil in previously treated metastatic breast cancer: An Eastern Cooperative Oncology Group study (PA 185). Breast Cancer Res Treat 1999;57:201–6.

[6] Pivot X, Chamorey E, Guardiola E, Magné N, Thyss A, Otto J, et al. Phase I and pharmacokinetic study of the association of capecitabine-cisplatin in head and neck cancer patients. Ann Oncol 2003;14:1578–86.

[7] Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.

[8] Guppy AE, Rustin GJ. CA125 response: Can it replace the traditional response criteria in ovarian cancer? Oncologist 2002;7:437–43.

[9] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26: 1148–59.

[10] McKeage MJ, Mistry P, Ward J, Boxall FE, Loh S, O'Neill C, et al. A phase I and pharmacology study of an oral platinum complex, JM216: Dose-dependent pharmacokinetics with single-dose administration. Cancer Chemother Pharmacol 1995;36: 451–8.

[11] Vouillamoz-Lorenz S, Buclin T, Lejeune F, Bauer J, Leyvraz S, Decosterd LA. Pharmacokinetics of satraplatin (JM216), an oral platinum (IV) complex under daily oral administration for 5 or 14 days. Anticancer Res 2003;23:2757–65.

[12] Beale P, Raynaud F, Hanwell J, Berry C, Moore S, Odell D, et al. Phase I study of oral JM216 given twice daily. Cancer Chemother Pharmacol 1998;42:142–8.

[13] Sessa C, Minoia C, Ronchi A, Zucchetti M, Bauer J, Borner M, et al. Phase I clinical and pharmacokinetic study of the oral platinum analogue JM216 given daily for 14 days. Ann Oncol 1998;9:1315–22.

[14] DeMario MD, Ratain MJ, Vogelzang NJ, Mani S, Vokes EE, Fleming GF, et al. A phase I study of oral uracil/ftorafur (UFT) plus leucovorin and bis-acetato-ammine-dichloro-cyclohexylamine-platinum IV (JM-216) each given over 14 days every 28 days. Cancer Chemother Pharmacol 1999;43:385–8.

[15] Jones S, Hainsworth J, Burris HA 3rd, Thompson D, Raefsky E, Johnson V, et al. Phase I study of JM-216 (an oral platinum analogue) in combination with paclitaxel in patients with advanced malignancies. Invest New Drugs 2002;20: 55–61.

[16] Sternberg CN, Whelan P, Hetherington J, Paluchowska B, Slee PH, Vekemans K, et al. Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. Oncology 2005;68: 2–9. Epub 2005 Feb 28.

[17] Sternberg CN, Petrylak DP, Sartor O, Witjes JA, Demkow T, Ferrero JM, et al. Multinational, double-blind, phase III study of prednisone and either satraplatin or placebo in patients with castrate-refractory prostate cancer progressing after prior chemotherapy: The SPARC trial. J Clin Oncol 2009;27:5431–8. Epub 2009 Oct 5.