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SATRAPLATIN

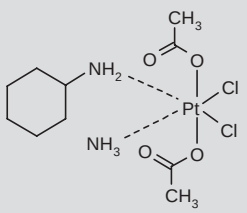
Rec INN; USAN

DNA-Alkylating Agent
Oncolytic Platinum Complex

BMS-182751
BMY-45594
JM-216
YHI-601

(*OC-6-43*)-Bis(acetato-*O*)amminedichloro(cyclohexylamine)platinum

InChI: 1S/C6H13N.2C2H4O2.2ClH.H3N.Pt/c7-6-4-2-1-3-5-6;2*1-2(3)4;;;;/h6H,1-5,7H2;2*1H3,(H,3,4);2*1H;1H3;/q;;;;;;+4/p-4



$C_{10}H_{22}Cl_2N_2O_4Pt$
Mol wt: 500.283
CAS: 129580-63-8
EN: 185356

ABSTRACT

Satraplatin is a third-generation, orally available platinum analogue which demonstrated a 33% reduction in the risk of progression in patients with metastatic castration-resistant prostate cancer (CRPC) following one prior chemotherapy regimen in the large phase III SPARC (Satraplatin and Prednisone Against Refractory Cancer) trial. Satraplatin also demonstrated beneficial effects on pain and displayed evidence of biological activity, with prostate-specific antigen (PSA) declines and objective responses. Satraplatin did not significantly extend survival, although this analysis may have been confounded by post-study therapy. Further development is ongoing with the evaluation of combination regimens containing satraplatin in other solid tumors. Efforts are ongoing to select patients more likely to benefit from satraplatin.

SYNTHESIS**

Satraplatin can be synthesized as follows.

Substitution of chlorine with iodine in potassium tetrachloroplatinate (I) by treatment with KI in water results in potassium tetraiodoplatinate (II), which by reaction with cyclohexylamine (III) yields *cis*-di(cyclohexylamine)diiodoplatinium (IV). Reaction of complex (IV) with $HClO_4$ in H_2O/EtOH furnishes dimer (V), which is then treated with NH_4OH in H_2O affording *cis*-ammine(cyclohexylamine)diiodoplatinium (VI). Nitration of complex (VI) with $AgNO_3$ in H_2O followed by chlorination with HCl gives *cis*-amminechloro(cyclohexylamine)platinium (VII) (1). Alternatively, treatment of cisplatin (VIII) with Et_4NCl in dimethylacetamide at 100 °C followed by ion exchange by DOWEX 50WX8 and HCl leads to amminetrichloroplatinum (IX), which is then treated with KCl, giving potassium *(SP-4-2)*-amminetrichloroplatinate (X). Subsequent reaction of compound (X) with cyclohexylamine (III) in the presence of NaI in water furnishes *(SP-4-3)*-amminechloro(cyclohexanamine)iodoplatinum (XI), which by subsequent nitration and chlorination with $AgNO_3$ in water and treatment with HCl affords complex (VII) (2). Then, compound (VII) is submitted to hydroxylation with H_2O_2 in water to give *(OC-6-43)*-amminedichloro(cyclohexylamine)dihydroxyplatinum (XII), which is finally acetylated with Ac_2O in CH_2Cl_2 (1, 3, 4). Scheme 1.

BACKGROUND

Docetaxel-based chemotherapy enhances survival in patients with metastatic castrate-refractory prostate cancer (CRPC) (5-7). However, the median progression-free survival (PFS) and overall survival (OS) are only approximately 6 months and 18-19 months, respectively, with docetaxel-based chemotherapy. Ongoing frontline randomized trials are evaluating the value of combining docetaxel with biological agents (e.g., bevacizumab, aflibercept, atrasentan, zibotentan, dasatinib). Effective salvage therapy following prior docetaxel is lacking, as only modest efficacy has been demonstrated with mitoxantrone or ixabepilone, with approximately 20% prostate-specific antigen (PSA) response rates and a median survival of less than 1 year (8, 9).

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**Synthesis prepared by R. Pandian, J. Bolós, R. Castañer.
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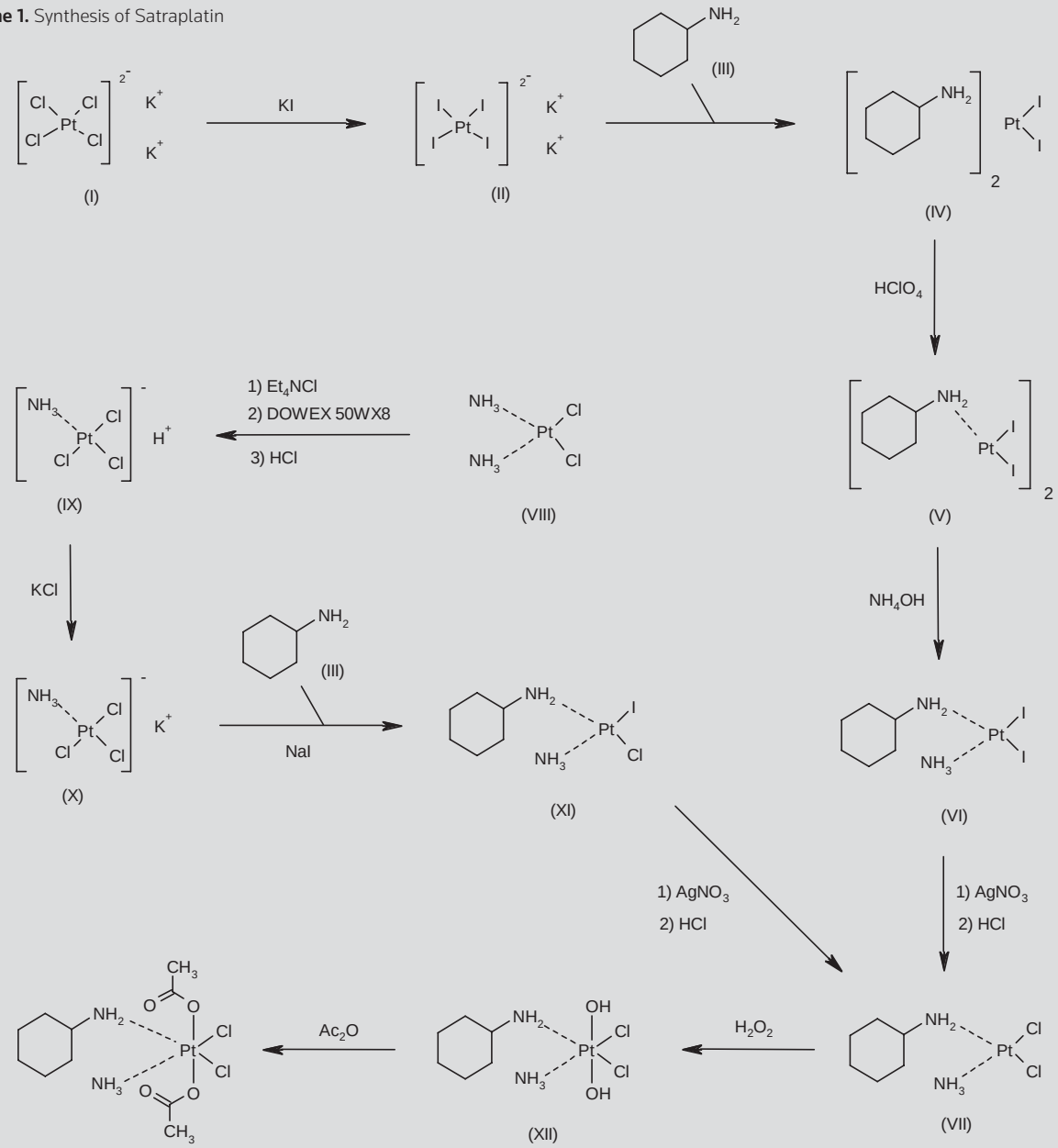
Scheme 1. Synthesis of Satraplatin



Carboplatin exhibits PSA response rates and measurable disease response rates of between 6% and 30% (10-14) in patients with metastatic CRPC. Several trials of carboplatin in combination with taxanes and estramustine phosphate as first-line treatment for CRPC have demonstrated both a high PSA response rate and a high objective measurable disease response rate (25-50%) (15-17). In a phase II trial, 34 men with metastatic CRPC that had progressed during or within 45 days after the completion of docetaxel-based chemotherapy were treated with docetaxel plus carboplatin (18). PSA declines of ≥ 50% were noted in 18% of patients, measurable responses were observed in 14% and the median OS was 12.4 months. Therefore, a rationale exists to further evaluate carboplatin and other highly active and tolerable platinum agents for advanced prostate cancer.

Satraplatin is a third-generation, orally available platinum analogue that shares some structural similarities with cisplatin. Satraplatin is more lipophilic than cisplatin and is orally bioavailable. Satraplatin appears to act by binding to DNA and forming intra- and interstrand crosslinks, resulting in cell cycle arrest in the G_2 phase and eventual apoptosis. Evidence suggests that while satraplatin DNA adducts

are efficiently repaired by the nucleotide excision repair pathway, they are not recognized by the DNA mismatch repair system that acts on cisplatin and carboplatin adducts (19).

PRECLINICAL PHARMACOLOGY

Satraplatin has demonstrated potent preclinical antitumor activity in several animal models, including small cell lung cancer and ovarian cancer (19-21). Satraplatin inhibited the growth of cancer cells resistant to cisplatin and exhibited additive or synergistic preclinical activity when combined with other chemotherapeutic agents (with etoposide in leukemia) and radiation (in lung cancer) (21-23). Micromolar concentrations of satraplatin were also cytotoxic against androgen-sensitive and -insensitive human prostate carcinoma cell lines, including several cell lines displaying resistance to cisplatin, docetaxel and mitoxantrone (24). Satraplatin and JM-118, an active metabolite, inhibited the growth of prostate cancer cells in vitro and in vivo in a concentration/dose-dependent fashion. The IC_{50} for satraplatin ranged from 1 to 3 μM for androgen-insensitive cells and was 11 μM for the androgen-sensitive cell lines. JM-118 was up to 16-fold more potent than satraplatin. Satraplatin had no effect on PSA transcription, independent of a decrease in cell number. Expression of MDR1, BCRP, MRP1 and altered tubulin or topoisomerase I were not found to mediate resistance, although these resistance mechanisms contribute to drug resistance to many other chemotherapeutics.

In small-animal tumor models a daily x 5 schedule was associated with optimal pharmacokinetics, antitumor activity and tolerability (25).

PHARMACOKINETICS AND METABOLISM

Phase I trials have determined that satraplatin is rapidly absorbed following oral administration, attaining peak plasma levels within 2 h. Satraplatin undergoes rapid biotransformation, with the most active metabolite being JM-118 (26). At a dose of 100 mg/m^2, the half-life of satraplatin on day 5 was relatively prolonged at approximately 12 h (26, 27). Satraplatin and its metabolites are largely bound to blood components and plasma proteins. Pharmacokinetic studies demonstrated a linear correlation between plasma AUC and dose at a dose of 150 mg/m^2/day x 5 days. At higher doses (> 200 mg/m^2/day), pharmacokinetics were nonlinear due to saturable absorption of satraplatin from the gut. There was also a correlation between systemic satraplatin exposure, as measured by ultrafiltrate AUC on days 1 and 5, and the level of thrombocytopenia (26).

SAFETY

Phase I trials of single-agent satraplatin have explored a number of different dosing schedules, including once- and twice-daily dosing to dosing every 3 weeks (25-30). The recommended dose and schedule in chemonaïve patients was 80-120 mg/m^2/day for 5 consecutive days, repeated every 4-5 weeks. The toxicity profile resembles that of carboplatin. The dose-limiting toxicity was myelosuppression (primarily neutropenia and thrombocytopenia), which is dose-dependent, reversible and noncumulative. While satraplatin can cause emesis (grade 3/4 in 13% of courses), this was generally manageable by premedication with 5-HT_3 antagonists. Nephrotoxicity, ototoxicity and neurotoxicity were uncommon.

CLINICAL STUDIES

Early phase II and III trials of satraplatin for metastatic CRPC

Satraplatin has been evaluated in phase II trials as frontline therapy in patients with metastatic CRPC (31). A multicenter phase II trial of satraplatin in 39 chemonaïve patients with progressive CRPC, 22 of whom were evaluable for response, has been reported (32). Patients were treated with satraplatin 120 mg/m^2/day x 5 every 28 days, with prophylactic ondansetron. Preliminary evidence of efficacy was observed, with manageable toxicities. Of the 9 patients with measurable disease, 1 patient with measurable liver lesions had a partial response and 6 had stable disease. PSA declines of > 50% were noted in 7 patients (32%) for more than 4 weeks and 6 (27%) had PSA decreases of > 80%. Toxicities consisted of myelosuppression, gastrointestinal and biochemical liver enzyme elevations.

These encouraging results led the European Organization for Cancer Research (EORTC) to initiate a phase III trial of satraplatin plus prednisone versus prednisone alone for the first-line treatment of patients with metastatic CRPC (33). The target accrual was 380 patients, but only 50 were enrolled when the study was terminated early by the sponsor. The combination of satraplatin and prednisone resulted in a statistically significant increase in PSA response rates compared to the prednisone alone arm (33% vs. 9%; $P = 0.046$). Median PFS was also significantly greater for the satraplatin/prednisone combination (5.2 months vs. 2.5 months; $P = 0.023$; hazard ratio [HR]: 0.50). The median survival in the satraplatin arm was nearly 15 months compared with approximately 12 months for the prednisone arm (14.9 months vs. 11.9 months; $P = 0.579$). Toxicities were generally manageable with the satraplatin/prednisone combination. Serious grade 3 hematological toxicities on the satraplatin arm included neutropenia (25.9%) and thrombocytopenia (29.6%). Serious nonhematological toxicities (all grade 3) were minimal (all 7.4%) and consisted of diarrhea, vomiting, infection, cardiovascular morbidity and hyperglycemia. Grade 3/4 alkaline phosphatase elevation (11.1%) was also noted. Six patients (22%) required a reduction in the dose of satraplatin due to hematological toxicities and 9 patients (33%) had a dose delay related to toxicity; 4 patients (15%) discontinued therapy with satraplatin due to toxicity or refusal. These encouraging results supported the further investigation of this regimen in a large phase III trial in the second-line setting.

Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial for progressive CRPC following prior chemotherapy

The Satraplatin and Prednisone Against Refractory Cancer (SPARC) randomized phase III trial was conducted to determine the efficacy and tolerability of satraplatin in men with metastatic CRPC progressing after one prior chemotherapy regimen (34, 35). Eligibility criteria included metastatic adenocarcinoma of the prostate and progression following at least two cycles of one prior chemotherapy regimen. Other inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; life expectancy > 3 months; surgical or ongoing medical castration; and adequate bone marrow, hepatic and renal function. Prior bisphosphonate therapy was acceptable if bone symptoms were stabilized and therapy continued during the trial. Key exclusion criteria included more than one prior chemotherapy regimen, prior platinum therapy and brain metastases. Patients were stratified for baseline ECOG PS (0-1 vs. 2),

mean baseline Present Pain Intensity (PPI) score (0-1 vs. 2-5) and type of disease progression (objective progression or PSA increase only). Patients were randomized 2:1 to receive satraplatin plus prednisone or placebo plus prednisone. Satraplatin 80 mg/m^2 was administered orally once daily in the fasting state on days 1-5 every 35 days. Prednisone 5 mg orally was administered twice daily. Antiemetic prophylaxis (granisetron 1 mg orally twice daily) was administered daily, 1 h before and 8 h after each satraplatin dose. Treatment continued until disease progression, unacceptable toxicities or death, and crossover was not permitted. Dose escalation to 100 mg/m^2 was allowed for patients without progression and without substantial toxicity after two cycles of study drug. The composite endpoint of PFS was based on first occurrence of radiographic progression (two new lesions), skeletal-related events, symptomatic progression or death (35, 36). Increase in serum PSA was not a component of PFS. A blinded Independent Review Committee retrospectively evaluated disease progression. However, treating investigators independently assessed progression and, in the absence of progression or unacceptable toxicity, patients continued to receive therapy. The trial was powered with 912 patients and 700 events to detect a 30% increase in time to progression relative to an expected median value of 4.0 months in the placebo arm at the 0.05 level of significance.

A total of 950 patients (n = 635 satraplatin; n = 315 placebo) were enrolled in 16 countries. Patient demographics and baseline characteristics were balanced between the two groups. Prior docetaxel had been administered in 51.5% and 51.1% of patients, respectively, in the satraplatin and placebo arms. The median PFS was 11.1 weeks (95% confidence interval [CI]: 10.3-12.3) in the satraplatin arm and 9.7 weeks (95% CI: 9.3-10.0) in the placebo arm (log-rank $P < 0.001$). Estimated PFS at 6 months for the satraplatin and placebo groups was 30% and 16%, respectively; corresponding 1-year data were 17% and 7%, respectively. The Cox proportional hazards model revealed a significant (log-rank $P < 0.001$) 33% reduction in the risk of progression for satraplatin versus placebo (HR: 0.67; 95% CI: 0.57-0.77). The median OS for the stratified intent-to-treat (ITT) population was 61.3 weeks for satraplatin and 61.4 weeks for placebo (HR: 0.98; 95% CI: 0.84-1.15; $P = 0.80$) (37). The median time to pain progression favored satraplatin over placebo (66.1 weeks vs. 22.3 weeks), with a significant 36% reduction in the risk of pain progression with satraplatin (HR: 0.64; 95% CI: 0.51-0.79; $P < 0.001$). The number of patients with measurable soft tissue lesions who achieved an objective response by RECIST was significantly greater in the satraplatin arm versus placebo (8.0% vs. 0.7%; $P = 0.002$). A significantly higher percentage of satraplatin recipients achieved a pain response compared with placebo recipients (24.2% vs. 13.8%; $P = 0.005$). A PSA response was observed in 25.4% and 12.4% of patients, respectively ($P < 0.001$). Drug exposure was greater in the satraplatin group, with a median of 4 cycles and duration of 20.0 weeks compared with 2 cycles and duration of 10.1 weeks in the placebo group. Dose reductions and delays of ≥ 7 days were 20.8% and 41.7%, respectively, for satraplatin and 0.3% and 10.5%, respectively, for placebo. Most discontinuations were due to investigator-determined progressive disease (75.7%). Post-study anticancer treatment (radiation, immunotherapy and/or chemotherapy) was received by 61.7% of satraplatin patients and 68.6% of placebo patients. Post-study chemotherapy was received by 44.9% of satraplatin patients and 52.4% of placebo patients. Retrospective data collection revealed that 18.3% and 24.4% of the satraplatin and placebo arms, respectively, received post-study docetaxel.

Hematological toxicities were the major dose-limiting toxicity in the satraplatin group and gastrointestinal disorders were the most frequent nonhematological complications. Drug discontinuations due to toxicities were more common with satraplatin (14.9% vs. 10.2%). No significant differences were observed between the satraplatin and placebo arms for overall (all grades) hepatic toxicity (5.9% vs. 4.2%), renal toxicity (3.3% vs. 2.9%) or neuropathy (9.4% vs. 8.3%).

Satraplatin for other malignancies

In a phase II study, single-agent satraplatin (120-140 mg/m^2/day for 5 days repeated every 3 weeks) was given to 27 chemotherapy-naïve patients with limited or extensive-stage small cell lung cancer who were unfit for intensive combination chemotherapy (38). Of 26 patients available for tumor response assessment, 10 (38%) achieved a partial response. The median overall time to progression was 110 days and the median OS was 210 days. Myelosuppression was manageable and no nephrotoxicity or neurotoxicity was seen.

When satraplatin monotherapy was compared with cisplatin monotherapy for advanced non-small cell lung cancer (NSCLC), a partial response was seen in 4% of patients on satraplatin and in 13% of the patients receiving cisplatin (39). When satraplatin was combined with radiotherapy for NSCLC, 1 complete response and 6 partial responses were observed in 15 NSCLC patients, and 7 of 8 patients with squamous cell carcinoma of the head and neck treated concurrently with radiotherapy (70 G) achieved a complete response (40).

Satraplatin demonstrated similar efficacy when compared to cisplatin or carboplatin in a phase II randomized trial in patients with recurrent ovarian cancer. The objective response rates were 35% in both arms (41). In a phase II trial in 18 patients with advanced or recurrent squamous cell carcinoma of the uterine cervix, there was 1 partial response and 12 patients had stable disease (42). Satraplatin demonstrated little activity in an unselected population with advanced breast cancer that had received up to one prior regimen (43).

Satraplatin as a component of combination regimens

Combinations of satraplatin and other chemotherapeutic or biological agents are being studied for synergistic or additive effects (Table I). Satraplatin appears feasible in combination with oral uracil–tegafur or paclitaxel for solid tumors (44, 45). Satraplatin also appears to have activity that is similar to other platinum agents when combined with paclitaxel as frontline therapy for NSCLC (46). Phase I trials employing a combination of satraplatin with docetaxel or capecitabine demonstrate preliminary feasibility, with expected toxicities (47, 48). In a recently reported phase I trial of advanced solid tumors the combination of satraplatin and gemcitabine showed an acceptable toxicity profile and promising antitumor activity (49). The combination of satraplatin and bevacizumab was evaluated in a phase II trial accruing docetaxel-treated patients with metastatic CRPC and demonstrated tolerability and significant activity (50). A phase II study evaluating a combination of satraplatin

Table I. *Ongoing clinical trials of satraplatin.*

Institution	Phase	Therapy	Eligibility	Objective
NCI	II	Satraplatin plus prednisone	Metastatic CRPC, one prior chemotherapy	Correlation of ERCC-1 with PFS
University of Wisconsin	I	Satraplatin plus docetaxel	Advanced solid tumors	Safety and feasibility
Sarah Cannon	I	Satraplatin plus docetaxel	Advanced solid tumors, two previous chemotherapy regimens	Safety and feasibility
Northwestern University	I	Satraplatin plus capecitabine	Advanced solid tumors	Safety and feasibility
Yale	I	Satraplatin plus nab-paclitaxel	Advanced solid tumors	Safety and feasibility
Rome	I	Satraplatin plus gemcitabine	Advanced solid tumors	Safety and feasibility
Wayne State University	I/II	Satraplatin plus bevacizumab	Metastatic CRPC, prior docetaxel	Safety and activity
Fox Chase	II	Satraplatin→erlotinib versus erlotinib	Advanced NSCLC, ≥ 70 years, untreated, not candidates for combination chemotherapy	Comparison of PFS

NCI, National Cancer Institute; CRPC, castration-resistant prostate cancer; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

and erlotinib is currently recruiting elderly patients with unresectable stage III/IV NSCLC (Table I).

CONCLUSIONS

Satraplatin is a novel, orally administered third-generation platinum agent that has demonstrated evidence of biological activity and enhanced PFS in patients with metastatic CRPC following prior chemotherapy. Unfortunately, given the lack of an OS benefit (which may have been confounded by post-study therapy, especially docetaxel) and the composite PFS endpoint being an unvalidated, albeit clinically relevant, endpoint, satraplatin has not received approval by the regulatory authority in the U.S. Satraplatin possesses several advantages compared to other available platinum agents in terms of toxicities and convenience and may warrant development in other settings where activity has been demonstrated. Ongoing trials are attempting to demonstrate the activity and feasibility of satraplatin in combination with chemotherapeutic and biological agents for advanced malignancies (Table I) (51). Another direction is to develop satraplatin for well-defined subsets known to be more sensitive to platinum therapy, e.g., triple-negative breast cancer and ERCC-1 (a DNA nucleotide excision repair enzyme)-negative tumors (Table I). Additionally, satraplatin may be a reasonable agent to develop as adjuvant therapy in settings where other platinum agents are efficacious or as a sensitizing agent in combination with radiation therapy. The development of satraplatin guided by knowledge of biology and proper patient selection may enable its addition to the therapeutic armamentarium.

SOURCES

GPC Biotech (licensed from Spectrum Pharmaceuticals; discovered by Johnson Matthey); licensed to Yakult Honsha for Japan.

DISCLOSURE

Guru Sonpavde, MD, receives research support from Eli Lilly, Bristol-Myers Squibb, Pfizer, Celgene, Novartis and AstraZeneca and is on the speakers' bureau for Pfizer, Novartis, Wyeth and sanofi-aventis. Cora N. Sternberg, MD, FACP, receives research support from Eli Lilly, sanofi-aventis, Pharmion, GPC Biotech and Bayer/Onyx and Pfizer.

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