

Phase I Studies of CBP501, a G₂ Checkpoint Abrogator, as Monotherapy and in Combination with Cisplatin in Patients with Advanced Solid Tumors

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Abstract

Purpose: Two phase I dose-escalation studies were conducted to determine the maximum tolerated dose (MTD) and safety profile of the G₂ checkpoint abrogator CBP501, as a single agent and in combination with cisplatin.

Experimental Design: Patients with advanced solid tumors were treated with CBP501 alone (D1/D8/D15, q4w, from 0.9 mg/m²), or with cisplatin (both on D1, q3w, from 3.6 mg/m² CBP501, 50 mg/m² cisplatin). Dose escalation proceeded if dose-limiting toxicity (DLT) was observed in 1 or less of 3 to 6 patients; CBP501 dose increments were implemented according to the incidence of toxicity. MTD was determined from DLTs occurring during the first two cycles.

Results: In the combination study, the DLT was a histamine-release syndrome (HRS) occurring 10 to 60 minutes after initiating infusion that was attenuated by prophylaxis comprising dexamethasone, diphenhydramine, ranitidine, and loratadine. The MTD was 25 mg/m² CBP501 and 75 mg/m² cisplatin, with two patients at the highest dose (36.4 mg/m² CBP501, 75 mg/m² cisplatin) experiencing grade 3 HRS. The only DLT with monotherapy was transient G₃ rise of troponin in one patient. Grade 3 to 4 treatment-related events were rare. Promising activity was observed with CBP501/cisplatin, mainly in ovarian and mesothelioma patients who had previously progressed on platinum-containing regimens. Among ovarian cancer patients, low expression of DNA repair proteins was associated with partial response or stable disease.

Conclusions: CBP501 is well tolerated in patients as monotherapy and with cisplatin. At the recommended phase II dose (RP2D), the combination is feasible and HRS manageable with prophylaxis. Evidence of antitumor activity was observed in platinum-resistant patients. *Clin Cancer Res*; 17(10); 3431–42. ©2011 AACR.

Introduction

Most cancer cells exhibit genomic instability, often with mutations in genes encoding p53 and Rb pathway members, or oncoproteins such as KRAS and c-MYC, that compromise the G₁ checkpoint (1, 2). These cells are therefore dependent on the G₂ checkpoint for survival

following DNA damage (3). G₂ checkpoint abrogation is a therapeutic strategy designed to prevent cell cycle arrest in response to DNA damage, resulting in impaired DNA repair and increased tumor cell death (4). Because non-transformed cells retain both the G₁ checkpoint and backup p53-dependent pathways at the G₂ checkpoint, G₂ checkpoint abrogation in combination with DNA

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Translational Relevance

Abrogation of G₂ checkpoint control is a promising strategy to selectively augment DNA damage–induced cytotoxicity in tumor cells. CBP501 is a synthetic peptide that inhibits phosphorylation of CDC25C at Ser²¹⁶ by several kinases including checkpoint kinase 1. Preclinically, CBP501 enhances cisplatin-induced cytotoxicity *in vitro* and tumor growth delay *in vivo*. Two first-in-human phase I studies of CBP501 established an acceptable safety profile, with the principal toxicity of histamine-release syndrome (HRS), attenuated with a prophylactic regimen, and a recommended dose and schedule for CBP501 in combination with cisplatin. The combination produced partial responses, stable disease greater than 3 months, and CA125 reductions in platinum-resistant ovarian cancer patients, without worsening cisplatin-associated toxicity. In an exploratory biomarker study, compromised expression of DNA repair proteins tended to correlate with clinical benefit. These studies form the prerequisite for randomized trials to assess the contribution of CBP501-mediated G₂ checkpoint abrogation to DNA damage–induced antitumor activity.

damage is expected to selectively enhance the death of transformed cells (3).

Delay of cell cycle progression after DNA damage is initiated by activation of the phosphatidylinositol-3-kinase-like protein kinases ATM (ataxia-telangiectasia mutated) and ATR (ATM and Rad3 related; ref. 5). These kinases phosphorylate substrates mediating checkpoint control and repair, including the checkpoint kinase Chk1 (6, 7). To establish the G₂ checkpoint, Chk1 phosphorylates the CDC25C phosphatase at Ser²¹⁶, resulting in its cytoplasmic sequestration (8–10). Consequently, inhibitory phosphates are not removed from cyclin-dependent kinase 1, so cells accumulate at the G₂ boundary, allowing time for DNA repair prior to mitotic entry. Of note, Ser²¹⁶ of CDC25C is also phosphorylated by other kinases, including MAPKAP-kinase 2 (MAPKAP-K2) and C-TAK1 (11, 12).

G₂ checkpoint abrogation has been previously studied with caffeine, an inhibitor of ATR and ATM (13, 14), 17-allylamino-17-demethoxygeldanamycin, an Hsp90 inhibitor that depletes cells of Chk1 and Wee1 kinases (15–17), and most extensively with the staurosporine analog UCN-01, an inhibitor of Chk1 (18–23). In initial clinical studies of combinations utilizing 72-hour infusion UCN-01, therapeutic dose levels of cisplatin were not achieved (24, 25). Nonetheless, evidence of target modulation has prompted alternative administration schedules and combinations (26, 27), as well as the development of novel agents.

CBP501 is a stable synthetic dodecapeptide obtained during G₂ abrogation phenotype-based optimization of the Chk1/2 inhibiting peptides TAT-216 and TAT-216A

(28). CBP501 inhibits the activities of multiple kinases that phosphorylate the Ser²¹⁶ residue of CDC25C, including Chk1, MAPKAP-K2, and C-Tak1, with no apparent activity on kinases upstream within the cascade. CBP501-mediated inhibition of these Ser²¹⁶ kinases causes reduced phosphorylation of CDC25C, and reduces cisplatin-mediated G₂ accumulation when applied in combination to cancer-derived cell lines, but not in nontransformed cells, including human umbilical vein endothelial cells, normal human diploid fibroblasts, and activated normal T lymphocytes (28). As a result, CBP501 enhanced the cytotoxicity of cisplatin and bleomycin in HCT116 colon cancer and MIAPaCa2 pancreatic cancer cells. In several instances, combining CBP501 with DNA damaging agents does not increase the proportion of cells in M phase, likely because cells are dying shortly after checkpoint abrogation (28, 29). These results were extended to xenograft models, with CBP501 augmenting tumor growth delay in combination with cisplatin or bleomycin, compared with either drug alone. This effect was observed without increased toxicity and also resulted in improved overall survival (28). Of note, compared with cells treated with cisplatin alone, coadministration of CBP501 was found to increase the intracellular cisplatin concentration, which may also contribute to the antitumor effects of this combination (29).

On the basis of the preclinical confirmation of mechanism and the efficacy showed both *in vitro* and *in vivo*, we conducted 2 phase I dose finding and pharmacokinetic studies with CBP501 in patients with advanced solid tumors, including a single-agent trial, and a trial of CBP501 combined with cisplatin.

Patients and Methods

Patient selection

These studies were conducted in compliance with the principles of CFR, ICH GCP, and the Declaration of Helsinki. Protocols were approved by institutional review boards. All patients were required to provide informed consent before undergoing study-specific procedures.

Inclusion criteria included: pathologically confirmed, locally advanced, or metastatic solid tumors, refractory to standard therapy or for which conventional therapy is not reliably effective; age 18 or more years; Eastern Cooperative Oncology Group Performance Score (ECOG PS) 0 to 2 (0–1 for the combination study); life expectancy more than 3 months; adequate organ function [hematological (absolute neutrophil count $\geq 1.5 \times 10^9$ cells/L, platelets $\geq 100 \times 10^9$ /L, hemoglobin ≥ 9 g/dL, INR $\leq 1.5 \times$ ULN); hepatic (bilirubin $\leq 1.5 \times$ ULN, ALT-AST $\leq 2.5 \times$ ULN); renal (serum creatinine < 1.5 mg/dL, creatinine clearance ≥ 60 mL/min); metabolic (serum potassium, calcium, and magnesium \geq LLN); and cardiac (CPK-MB, CPK-MM \leq ULN, and troponin I within normal values)]; signed informed consent. Exclusion criteria included: previous anticancer treatment less than 4 weeks prior to first dose of study treatment (6 weeks for mitomycin C and anti-androgen therapy, 8 weeks for bicalutamide); patients with

active central nervous system metastasis, patients with evidence of peripheral neuropathy of greater than grade 1 severity (combination study only).

Treatment plan

Single-agent CBP501 was administered by 1-hour intravenous infusions for 3 consecutive weeks (days 1, 8, 15), repeated every 28 days (starting dose 0.9 mg/m²); in the combination study, CBP501 (i.v., starting dose 3.6 mg/m²) was administered 1 hour before cisplatin (i.v., starting dose 50 mg/m²) on day 1 of a 3-week cycle. A cohort of patients treated at the maximum tolerated dose (MTD) in the combination study received a single dose of CBP501 alone on day -7, so that CBP501 pharmacokinetics could be compared in the absence and presence of cisplatin.

Initially, diphenhydramine was used in the single-agent study as prophylaxis for a histamine-release syndrome (HRS) observed with CBP501 in animals (30, 31). With successive modifications, the final prophylactic treatment in both studies consisted of dexamethasone (8 mg orally the night before, and 8 mg i.v. immediately before CBP501 administration), diphenhydramine, and ranitidine (both at 50 mg i.v. immediately before CBP501 infusion) and loratadine (10 mg orally the day before, the day of CBP501 administration, and the day after) at each infusion. In the event of anaphylactoid reactions, standard treatment was administered. Prophylactic antiemetics were administered according to standard treatment center regimens.

A standard 3 + 3 dose-escalation scheme was employed: in the absence of dose-limiting toxicity (DLT), the dose was escalated to the next dose level (DL); if DLT was reported in 1 patient, 3 additional patients were to be included at that DL; if no further patients experienced DLT, the dose was escalated. If 2 or more of 3 to 6 patients experienced DLT, escalation would be halted. The MTD was defined as the DL below that in which DLT was observed during the first 2 cycles in at least 2 of 3 to 6 assessable patients. In each study, 6 to 12 additional patients were to be treated at the MTD to achieve a total of at least 10 evaluable patients to verify the MTD. On the basis of preliminary activity during dose escalation, 14 additional patients with ovarian or endometrial cancer were treated at the MTD in the combination study under a protocol amendment.

During dose escalation, increments were determined according to the severity of treatment-related adverse events (AE) observed during the observation period in the previous DL. In the single-agent study, in the absence of toxicity, dose escalation was by 100% increments; with grade 1 toxicity, 50% increments were used; with grade 2 to 4 toxicity, 33% increments were used.

In the combination study, dose escalation was conducted in 2 steps: first, cisplatin was evaluated at 2 dose levels (50 and 75 mg/m²) with a fixed dose of CBP501 (3.6 mg/m²); second, CBP501 was escalated, combined with the highest tolerated dose of cisplatin (75 mg/m²). CBP501 dose increments were as follows: with grade 0 to 1 toxicity,

100% increments; with grade 2 to 4 events (non-DLT), 50% increments; in the case of DLTs, 33% increments were used.

DLT in both studies was defined as any of the following: grade 4 neutropenia lasting 7 or more days (≥ 5 days for the combination study) or grade 3 to 4 neutropenia with fever and/or infection; grade 4 thrombocytopenia (or grade 3 with bleeding); grade 3 or 4 treatment-related nonhematological toxicity (excluding grade 3 vomiting with suboptimal treatment); dosing delay greater than 2 weeks following treatment-related adverse events or laboratory abnormalities.

Cardiac monitoring

Cardiac monitoring was conducted in both studies to address mild myocardial fibrosis associated with histamine release observed in preclinical toxicology studies (31), and included left ventricular ejection fraction (LVEF) by echocardiogram or MUGA (multiple-gated acquisition) scan (at baseline and every 2 cycles), assessment of cardiac enzymes (CPK-MB, CPK-MM, and troponin I, at baseline and prior to each administration), and electrocardiogram (ECG) assessment (before CBP501 infusion, at the end of infusion, and 1 hour after the end of infusion). In both studies, an interim central review of ECGs was implemented to ensure reliability of these parameters, primarily QTc.

Pharmacokinetics

In the single-agent study, samples for CBP501 pharmacokinetic (PK) analysis were taken before the infusion start (time 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours after the infusion start on days 1 and 15 of cycle 1. In the combination study, samples for CBP501 PK analysis were collected at time 0 (before CBP501 infusion), 30 minutes after the start of the infusion, at the end of the infusion, and at 0.5, 1, 2, 3, 5, 7, and 23 hours after the infusion on day 1 of cycle 1, and in some cases on day -7. Blood samples for cisplatin analysis were collected on day 1 of cycle 1 immediately before the start of the cisplatin infusion, at the end of the infusion, and 1, 3, and 21 hours after the end of the infusion.

Plasma CBP501 was determined using a validated LC/MS/MS method; total plasma and ultrafiltrate platinum concentrations were determined using ICP-MS; all assays had a limit of quantification of 10 ng/mL. Noncompartmental analysis was carried out to determine maximal concentration (C_{max}); area under the concentration time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$); terminal half-life ($T_{1/2}$); and plasma clearance (Cl). Pharmacokinetic parameters are summarized by geometric mean and geometric coefficient of variation.

DNA damage pathway and repair biomarker study

Archival formalin-fixed paraffin-embedded tumor blocks were collected from 10 of the 14 ovarian cancer patients enrolled in the study. These were analyzed immunohistochemically with commercially available antibodies using standard procedures for several markers of DNA

Table 1. Baseline and disease characteristics of treated patients

	CBP501 single agent	CBP501/cisplatin combination
<i>N</i> patients	30	48
Median age, yr (range)	64 (25–82)	62 (31–81)
Sex: male/female	17/13	18/30
ECOG PS		
0	9	15
1	20	33
2	1	–
Primary tumor		
Ovarian	6 (20%)	14 (29%)
Pancreas/biliary	6 (20%)	3 (6%)
Mesothelioma	–	8 (17%)
NSCLC	2 (7%)	5 (10%)
Colorectal	5 (17%)	1 (2%)
Prostate	2 (7%)	4 (8%)
Endometrial	–	4 (8%)
Gastric	–	3 (6%)
Breast	1 (3%)	2 (4%)
Sarcoma	1 (3%)	2 (4%)
Kidney	2 (7%)	–
Melanoma	2 (7%)	–
Neuroendocrine	1 (3%)	1 (2%)
Esophageal	1 (3%)	–
Salivary gland	–	1 (2%)
Cervix	1 (3%)	–
Median number of metastatic sites (range)	2 (1–6)	3 (1–6)
Median number of prior systemic treatments (range)	4 (1–11)	4 (1–13)

repair and DNA damage response pathways, including Rad51, BRCA1, FANCD2, Mus81, polη, XPF, ATM, and phospho-MAPKAP-K2. Positive and negative control slides, and a commercial tumor microarray (TMA) containing approximately 75 ovarian cancers, were stained simultaneously. Stained slides were imaged on the Aperio ScanScope Digital Pathology platform. Tumor regions were annotated by a certified pathologist. Biomarker-specific automated scoring algorithms were employed, in which 50 to 100 nuclei per tumor field were rated from 0 to 3 for intensity of staining and samples were assigned a score [designated quality index method (QIM)], calculated as $3 \times (\%3+ \text{ cells}) + 2 \times (\%2+ \text{ cells}) + 1 \times (\%1+ \text{ cells})$. A composite score for each sample was obtained by averaging the sum of the QIM scores for the various biomarkers. Individual QIM scores and composite scores were correlated with best response to CBP501/cisplatin treatment.

Statistical methods

These studies were designed to establish the MTD of each regimen: sample size was not based on statistical considerations. Descriptive statistics are used: continuous variables are summarized using *N*, mean, SD, median, minimum, and maximum. Categorical variables are presented using frequencies and percentages. Adverse events,

classified according to MedDRA and NCI-CTCAE (Version 3.0), were summarized by incidence and classified by the worst observed grade. On the basis of the small sample size in the biomarker study, trends correlating immunohistochemical scores and best response were described, but no formal statistical analysis was carried out.

Results

Patient demographics and treatment

Seventy-eight patients were treated with CBP501 in 4 US centers between June 2005 and January 2009. In both studies, patients were in good physical condition, with just 1 patient having an ECOG PS of 2 at baseline (Table 1). Patients in both studies were heavily pretreated, with a median of 4 (range 1–13) prior lines of systemic treatment.

CBP501 single agent. Thirty patients were treated in 8 dose levels, with the highest dose being 22.5 mg/m² CBP501 (Table 2); a total of 68 cycles were administered, with a median 2 cycles per patient (range 1–8). The majority of patients (26 patients, 87%) discontinued due to progressive disease; 2 patients discontinued at investigator discretion, 1 patient withdrew consent, and 1 patient died due to an adverse event (sepsis, unrelated to treatment).

Table 2. Dose levels and DLTs

CBP501 single agent				CBP501/cisplatin combination					
CBP501 dose, mg/m ²	N patients	N cycles		N DLTs	CBP501/cisplatin dose, mg/m ²	N patients	N cycles		N DLTs
		Median (range)	Total				Median (range)	Total	
0.9	4	2 (1-2)	7	–	3.6/50	3	2 (2-2)	6	–
1.8	3	2 (1-2)	5	–	3.6/75	3	2 (2-3)	8	–
3.6	4	2.5 (1-8)	14	–	7.2/75	3	9 (2-13)	24	–
7.2	3	2 (2-2)	6	–	10.8/75	5	3 (2-4)	14	–
9.6	3	2 (2-3)	7	–	16.2/75	4	2 (1-5)	10	–
12.7	3	2 (2-7)	11	–	25 ^a /75	24	2 (1-12)	94	–
16.9	3	2 (1-4)	7	–	36.4/75	6	4 (2-9)	26	2 ^b
22.5	7	2 (1-2)	11	1 ^c					

^a24.3 mg/m² during the initial dose escalation, and rounded to 25 mg/m² during MTD confirmation and cohort expansion.

^bGrade 3 allergic reaction (2 patients) without respiratory or hemodynamic events.

^cGrade 3 troponin I increase.

CBP501/cisplatin. Forty-eight patients were treated in 7 dose levels, with the highest dose level being 36.4 mg/m² CBP501 and 75 mg/m² cisplatin (Table 2). The most frequent tumor types were ovarian cancer and malignant pleural mesothelioma. A total of 182 cycles were administered, with a median 2 cycles per patient (range 1–13). At the recommended dose, 25 mg/m² CBP501 and 75 mg/m² cisplatin, 24 patients were treated, receiving 94 cycles. Fourteen of these patients were enrolled following a protocol amendment to evaluate additional ovarian or endometrial cancer patients.

Dose-limiting toxicity and definition of MTDs

CBP501 single agent. Twenty-seven patients were assessable for determination of MTD. The 3 nonassessable patients (1 in each of DL 0.9, DL 3.6, and DL 22.5) experienced disease progression less than 21 days after treatment initiation. Only 1 DLT was reported (Table 2); at the highest dose level, 1 patient experienced transient grade 3 troponin increase during the first cycle. Three additional patients were included at this DL, with no further DLTs reported. No further dose escalation occurred, however, as escalation was halted at 22.5 mg/m², when the dose was overtaken by that in the rapidly accruing combination study that had in the meantime been initiated. Thus, no formal MTD was reached with single-agent CBP501.

CBP501/cisplatin. No DLT was reported for cisplatin 50 or 75 mg/m² combined with up to 25 mg/m² of CBP501. At the highest dose level (CBP501 36.4 mg/m², cisplatin 75 mg/m²), 2 DLTs were reported in 6 evaluable patients; both patients experienced grade 3 HRS. In both cases, hospitalization was unnecessary and no respiratory or hemodynamic consequences were observed. The severity was determined as grade 3 based on the degree of erythema of the skin rash induced. The MTD was thus defined as the dose level immediately below: 25 mg/m² CBP501 and 75

mg/m² cisplatin. Of note, the occurrence of grade 1 to 2 HRS determined that CBP501 dose escalations represented only 33% or 50% increases in the highest dose levels in each study.

Safety

CBP501 single agent. No grade 4 treatment-related adverse events were reported, and just 1 patient experienced a grade 3-related adverse event (troponin increase, Table 3). The principal toxicities reported were mild or moderate HRS and gastrointestinal disorders. None of the patients in the single-agent study discontinued treatment or required dose reductions due to related adverse events.

CBP501/cisplatin. The most frequently reported treatment-related adverse events were HRS (34 patients, 71%), asthenia (27 patients, 56%), and gastrointestinal events. No grade 4 treatment-related events were observed. Eleven patients (23%) had grade 3 treatment-related events, including asthenia (4 patients), nausea (3 patients), HRS (allergic reaction; 2 patients), vomiting- and renal failure (1 patient each).

Three patients were discontinued due to treatment-related adverse events: grade 2 ototoxicity (DL I), grade 1 sensory neuropathy and nausea (DL III), grade 3 neutropenia, and grade 2 thrombocytopenia (DL VI). Twelve patients (25%) underwent dose reductions. CBP501 alone was reduced in 1 patient due to fatigue; cisplatin alone was reduced in 10 patients, due to persistent nausea (2), severe peripheral neuropathy (2), fatigue (1), and decrease of the glomerular filtration rate (5); both agents were reduced in 1 patient due to HRS and nausea.

Histamine-mediated adverse events

The principal adverse event was HRS, variably reported as "allergic reaction," "acute infusion reaction," "rash," "urticaria," "erythema," or "pruritus." The reaction was

Table 3. Treatment-related adverse events occurring in 5% or more of treated patients and/or occurring at grade 3 to 4

Adverse event	CBP501 single agent (N = 30) NCI-CTC grade		CBP501/cisplatin combination (N = 48) NCI-CTC grade	
	1-2	3	1-2	3
Nausea	5 (17%)	–	28 (58%)	3 (6%)
Asthenia	6 (20%)	–	23 (48%)	4 (8%)
HRS (allergic reaction)	18 (60%)	–	32 (67%)	2 (4%)
Vomiting	2 (7%)	–	9 (19%)	1 (2%)
Dehydration	1 (3%)	–	6 (13%)	–
Anorexia	1 (3%)	–	6 (13%)	–
Diarrhea	3 (10%)	–	2 (4%)	–
Dysgeusia	1 (3%)	–	4 (8%)	–
Peripheral sensory neuropathy	–	–	7 (15%)	–
Constipation	2 (7%)	–	2 (4%)	–
Headache	2 (7%)	–	2 (4%)	–
Muscular weakness	–	–	4 (8%)	–
Tinnitus	–	–	4 (8%)	–
Renal failure	–	–	6 (13%)	1 (2%)
Troponin I increased	1 (3%)	1 (3%)	–	–
Hematological abnormalities				
Anemia	26 (87%)	–	31 (65%)	2 (4%)
Thrombocytopenia	6 (20%)	–	6 (13%)	–
Neutropenia	–	–	12 (25%)	2 (4%)
Increased INR	9 (30%)	5 (20%)	8 (17%)	–
Hepatic abnormalities				
Increased ALT	12 (40%)	–	10 (21%)	–
Increased AST	9 (30%)	–	13 (27%)	–
Increased AP	11 (37%)	1 (3%)	12 (25%)	–
Increased GGT	12 (40%)	2 (7%)	15 (31%)	3 (6%)
Increased bilirubin	4 (13%)	–	4 (8%)	–
Other laboratory abnormalities				
Hypokalemia	9 (30%)	–	11 (23%)	2 (4%)
Hyponatremia	13 (43%)	–	14 (29%)	5 (10%)
Increased serum creatinine	6 (20%)	–	12 (25%)	1 (2%)

characterized by rash, hot flushes, and urticaria, starting in the head, neck, and upper chest 10 to 60 minutes after initiation of the infusion. The reaction lasted from minutes to a few hours, and was controllable with additional doses of steroids and diphenhydramine. The protocol-specified prophylactic regimen attenuated but did not completely prevent the reaction. Reactions were usually reported after the first dose in cycle 1, and typically recurred in subsequent cycles without change in severity. The reaction showed some CBP501 dose-dependency, as the 2 grade 3 events qualifying as DLTs in the combination study both occurred at the highest dose level explored. No respiratory or hemodynamic changes were reported, and no patients were hospitalized due to HRS. One patient discontinued from the study due to this reaction. Histamine-mediated adverse events were reported in 18 patients (60%) treated with CBP501 alone, and 34 patients (71%) receiving

CBP501 in combination with cisplatin, including 2 patients (4%) with grade 3 events.

In multiple patients the reaction caused temporary interruption in the treatment administration. A protocol amendment allowed prolongation of the infusion of CBP501 to 2 hours. In the combination study, 9 patients (19%) received a prolonged infusion, but the incidence of HRS was not reduced and the duration of the infusion returned to the original 1 hour.

Cardiac monitoring

CBP501 single agent. Among patients with normal QTc (≤ 450 milliseconds) at baseline, 2 patients showed QTc more than 450 milliseconds within 1 hour after the end of the first infusion of study drug, and showed increased prolongation of the QTc interval in subsequent cycles of treatment; however, none of these patients had

QTc prolongation more than 60 milliseconds by either Bazett's or Fridericia's corrections, and there were no clinical sequelae.

No clinically significant LVEF abnormalities or CPK-MB elevations were detected. Abnormal troponin I was observed in 2 patients. The first of these patients, with mesothelioma and pericardial infiltration, was treated with CBP501 at 22.5 mg/m²; grade 3 troponin increase was reported during cycle 1 prior to administration of the third dose of CBP501, and was considered dose limiting. This increase was an isolated occurrence, with no creatinine phosphokinase (CPK) elevations and no changes in ECG compared with baseline. This event could have been due to the patient's pericardial infiltration, but was also considered as possibly related to the study drug. Another patient, treated with single-agent CBP501 at 12.7 mg/m², experienced increased troponin I 30 days after receiving the last dose; ECG and echocardiogram were carried out, with no clinically significant findings, and the troponin I increase was not considered clinically relevant.

CBP501/cisplatin. Centralized ECG review was conducted for the 48 patients enrolled. QTcF (Fridericia formula) prolongation to more than 470 milliseconds was observed in 2 patients, 1 with hypertension, hypomagnesemia, and hypothyroidism, and the other with significant cardiac history. Two patients had QTcF prolongation more than 60 milliseconds above baseline, one of them also with a prolongation to more than 470 milliseconds. None of the patients had a QT interval more than 500 milliseconds according to the Fridericia formula, but using Bazett's formula, a QT interval more than 500 milliseconds was observed in 1 patient during cycle 9. The patient, who received 13 cycles without dose reduction, had a history of coronary artery bypass, aortic and carotid repair, hypertension and peripheral vascular disease, and at cycle 9 presented with a transient QTc prolongation to 504 milliseconds; however, the patient completed 13 cycles without clinically relevant cardiac events. No grade 2 or more LVEF decreases considered treatment-related or clinically significant cardiac isoenzyme abnormalities were observed.

Pharmacokinetics

Twenty-nine patients were assessable for pharmacokinetics in the single-agent trial, and 25 in the combination trial. CBP501 half-life was 1.2 to 1.7 hours for doses up to 10 mg/m², increasing to approximately 3.5 hours at 25 mg/m². The tendency for longer CBP501 half-life with increasing doses is attributable to the measurability of later time points at higher dose levels; in the lower dose levels, concentrations at 24 hours were generally less than the lower limit of quantification. C_{max} and $AUC_{0-\infty}$ showed dose proportionality over the dose range evaluated on days 1 and 15 for single-agent administration, as did C_{max} on day 1 in combination with cisplatin (Fig. 1). Due to the increase in measured half-life at higher doses, $AUC_{0-\infty}$ had higher values at 25 and 36.45 mg/m² than would be expected from dose proportionality at low doses, but did

show proportionality over the range from 16.2 to 36.45 mg/m². In both studies, interpatient variability within dose levels was moderate, with a coefficient of variation generally in the range 20% to 40%. In the combination study, CBP501 pharmacokinetics at 25 mg/m² were comparable in 7 patients when administered alone on day -7 and on day 1 with cisplatin. No consistent differences were observed between CBP501 PK on days 1 and 15, or between single agent and combination administration (Table 4). Cisplatin pharmacokinetic parameters were consistent with single-agent cisplatin administration (Table 4 and Supplementary Fig. S1).

Efficacy

CBP501 single agent. Among the 30 patients treated, no objective responses were observed. Seven patients experienced stable disease (SD) as best response according to response evaluation criteria in solid tumors (RECIST), including 4 patients with SD lasting at least 3 months. Two of these patients were progression free for over 6 months: 1 patient with ovarian adenocarcinoma previously treated with 4 prior lines of chemotherapy (including gemcitabine, carboplatin, and paclitaxel), received 8 cycles of CBP501 at 3.6 mg/m² before experiencing disease progression; the second patient, with pancreatic adenocarcinoma previously treated with 6 prior lines of chemotherapy (including 5-FU and gemcitabine), received 7 cycles of CBP501 at 12.7 mg/m² before dying of sepsis that was unrelated to study treatment.

CBP501/cisplatin. Evidence of antitumor activity was observed in 12 patients (25%), with diagnoses of ovarian cancer (7 patients, see Supplementary Table S1), mesothelioma (3 patients), salivary gland adenocarcinoma (1 patient), and neuroendocrine tumor (1 patient). Initially, a confirmed partial response (PR) was reported at the 24.3 mg/m² dose level in a patient with synchronous ovarian and endometrial carcinoma. A protocol amendment enlarged the cohort with these diseases, so that a total of 14 ovarian cancer patients were treated, all at the recommended dose of 25 mg/m² CBP501 and 75 mg/m² cisplatin, except 1 patient treated at 36 mg/m² CBP501 and 75 mg/m² cisplatin. These patients were heavily pretreated, with a median of 6 prior lines; 8 of 14 patients were platinum resistant, and 5 of them were platinum refractory. Two (14%) platinum-resistant ovarian cancer patients achieved confirmed PR by RECIST and CA-125; 1 patient, with 3 previous lines of therapy, received 12 cycles and achieved a time-to-progression (TTP) of 8.3 months; the other, with 2 prior lines, received 8 cycles and achieved a TTP of 5.5 months. Five (36%) patients achieved SD > 3 months and 5 patients (36%) achieved a 50% reduction of CA-125, accomplishing the definition of partial response according to Gynecologic Cancer Intergroup (GCIG) criteria. The overall progression-free survival of the ovarian cohort was 5.2 months (95% CI: 1.7–8.8 months).

Three patients with malignant pleural mesothelioma showed evidence of activity: 2 pretreated patients treated at CBP501 dose levels of 7.2 and 25 mg/m² received 13 and

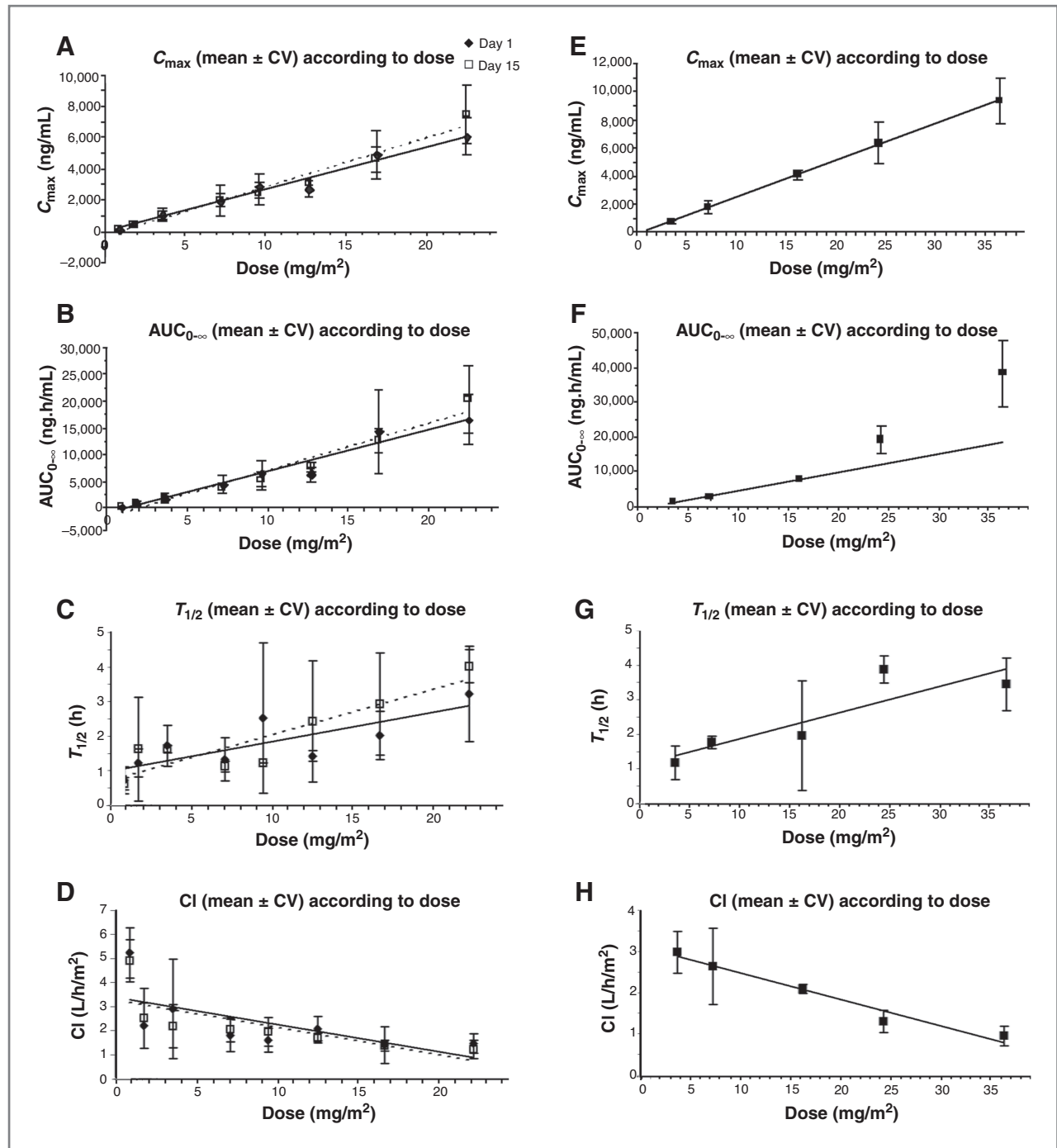


Figure 1. Plot of CBP501 C_{max} , $AUC_{0-\infty}$, $T_{1/2}$, and CI according to dose, in single agent (A–D) and cisplatin combination studies (E–H), respectively. In the single-agent study, PK was assessed on day 1 (\blacklozenge) and day 15 (\square) of the first cycle. Data at each point represent the mean \pm SD of 2 to 9 patients.

12 cycles, respectively, and achieved sustained SD (TTP 11 months) and PR (TTP 9.7 months), respectively; the third patient (16.2 mg/m²) was treated in second line and achieved SD lasting 5 cycles (TTP 3 months). Additional disease stabilization was reported in patients with salivary gland adenocarcinoma (9 cycles, TTP 7 months), and neuroendocrine tumor (6 cycles, TTP 4 months).

DNA damage response and DNA repair biomarker study

Several markers relevant to repair of cisplatin-induced DNA damage (32–34) were analyzed immunohistochemically among tumors of 10 ovarian cancer patients treated at the MTD in the combination study. Markers related to homologous recombination repair included Rad51,

Table 4. Pharmacokinetic parameters (mean and coefficient of variation) of CBP501 and cisplatin

Dose level, mg/m ²	Day	N assessable patients	C _{max} , μg/mL		T _{1/2} , h		AUC _{0-∞} , μg h/mL		Cl, L/h/m ²	
CBP501 in the single-agent study										
0.9	1	4	0.12	7	0.7	56	0.18	21	5.24	20
	15	3	0.14	14	0.6	29	0.19	19	4.91	18
1.8	1	3	0.52	37	1.2	34	0.91	35	2.20	43
	15	3	0.48	43	1.6	94	0.87	54	2.51	50
3.6	1	4	1.06	26	1.7	35	1.78	30	2.91	71
	15	3	1.07	36	1.6	7	1.88	45	2.18	41
7.2	1	3	1.92	51	1.3	48	4.39	38	1.8	37
	15	3	2.01	19	1.1	14	3.66	23	2.04	25
9.6	1	3	2.89	27	2.5	87	6.48	37	1.60	31
	15	2	2.41	30	1.2	0	5.14	31	1.95	31
12.7	1	3	2.73	19	1.4	11	6.34	21	2.08	24
	15	3	3.08	4	2.4	73	7.66	12	1.68	12
16.9	1	2	4.92	31	2	35	14.26	55	1.40	55
	15	3	4.64	18	2.9	51	12.60	18	1.37	17
22.5	1	7	6.08	20	3.2	43	16.51	28	1.46	28
	15	5	7.49	25	4	12	20.23	31	1.21	32
CBP501 in the combination study										
3.6	1	6	0.72	19	1.19	41	1.21	17	2.98	17
7.2	1	3	1.73	28	1.79	10	2.72	35	2.64	35
16.2	1	2	4.05	9	1.98	81	7.75	5	2.09	5
24.3	1	9	6.33	24	3.92	10	19.23	21	1.30	21
36.45	1	5	9.38	17	3.49	22	38.47	25	0.95	25
Total plasma platinum										
50	1	3	2.62	5	34.3	9	79.02	25	0.63	25
75	1	24 ^a	3.68	17	34.8	105	120.29	79	0.62	79
Platinum ultrafiltrate										
50	1	3	1.34	21	7.6	22	3.90	4	0.01	4
75	1	26 ^b	2.17	43	8.7	47	5.35	28	0.01	28

^aFor 4 patients, half-life could not be determined, and thus neither could AUC_{0-∞} or Cl.

^bFor 2 patients, half-life could not be determined, and thus neither could AUC_{0-∞} or Cl.

BRCA1, ATM, FANCD2 and MUS81 (35). XPF and polη were evaluated as markers of nucleotide excision repair and translesion synthesis, respectively (36, 37). ATM and phospho-MAPKAP-K2, which phosphorylates CDC25C at Ser²¹⁶ (11), were used to assess the DNA damage response. For each of the 8 biomarkers tested, a dynamic range of expression (assessed by QIM score) was detected across the samples tested (test samples and the TMA). Test samples did not cluster within the larger continuum of samples, so the range of expression mirrored that within the TMA population, as shown for Rad51 and phospho-MAPKAP-K2 (Fig. 2A and B).

Among the markers for homologous recombination, FANCD2 and MUS81 showed no apparent correlation with response to the cisplatin/CBP501 combination. However, for Rad51, BRCA1, and ATM, patients whose best response was progressive disease (PD) tended to have higher QIM scores than patients who achieved PR or SD. This was particularly true for Rad51, where there was no overlap

between QIM scores of patients who derived clinical benefit and those who did not (Fig. 2A and Supplementary Table S2). Similar trends were also observed for the DNA repair pathway biomarkers XPF and Polη (Supplementary Table S2). Additionally, expression of phospho-MAPKAP-K2, activity of which may be inhibited by CBP501, also tended to be higher in patients with PD (Fig. 2B and Supplementary Table S2). Finally, an average of QIM scores for Rad51, BRCA1, ATM, XPF, polη, and phospho-MAPKAP-K2 yielded composite scores that tended to be higher in patients with PD (Fig. 2C and Supplementary Table S2). Taken together, these data suggest that compromised DNA repair and DNA damage response pathways may predict response to the cisplatin/CBP501 combination.

Discussion

Cancer cell-selective G₂ checkpoint abrogation following cisplatin by CBP501, a synthetic peptide inhibitor of

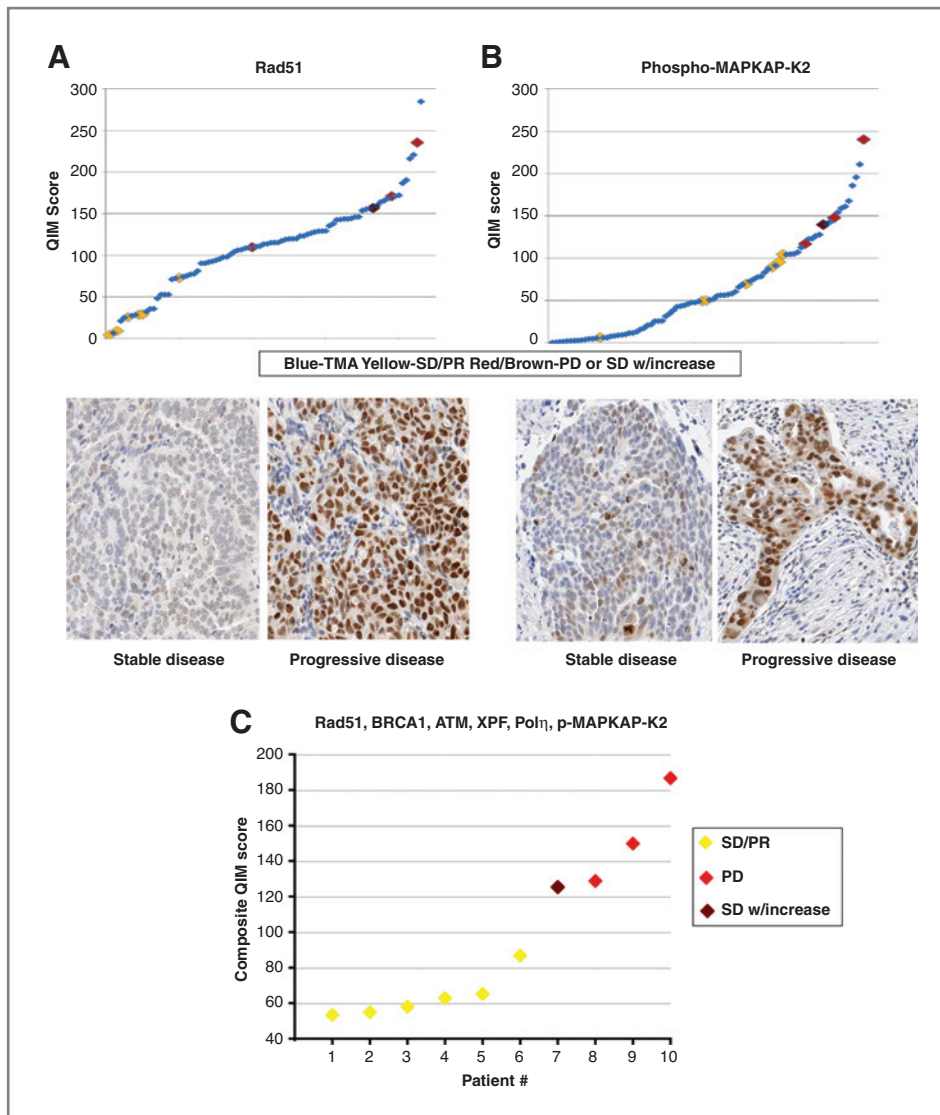


Figure 2. DNA repair and DNA damage response biomarkers in archival tumor samples from ovarian cancer patients. A (top graph), plot of Rad51 QIM scores for patient samples in the TMA (blue), samples from patients with progressive disease (PD, red or SD with increased tumor volume, brown) and samples from patients with stable disease or partial response (SD/PR, yellow). Bottom, representative Rad51 immunohistochemical stains from 2 patients, with stable disease and progressive disease, respectively. B (top graph), plot of phospho-MAPKAP-K2 QIM scores for patient samples in the TMA (blue), samples from patients with progressive disease (PD, red or SD with increased tumor volume, brown) and samples from patients with stable disease or partial response (SD/PR, yellow). Bottom, representative phospho-MAPKAP-K2 immunohistochemical stains from 2 patients, with stable disease and progressive disease, respectively. C, plot of composite QIM scores for the 6 biomarkers for patients with progressive disease (PD, red or SD with increased tumor volume, brown) and stable disease or partial response (SD/PR, yellow).

CDC25C Ser²¹⁶ phosphorylation, prompted a development program intended to exploit tumor-intrinsic G₁ checkpoint defects and optimize combination therapies. On the basis of weak activity of CBP501 in several pre-clinical models (28), intrinsic DNA damage that can occur in genetically unstable tumor cells, and the need to evaluate CBP501 alone in this first-in-human experience, we conducted a phase I single-agent trial. To translate the synergism of CBP501 and cisplatin, a phase I combination study was also conducted.

As predicted by preclinical toxicology (30, 31), CBP501 was frequently associated with HRS in humans. This was attenuated, but not prevented by diphenhydramine, dexamethasone, ranitidine, and loratadine. The allergic reaction dictated the dose-escalation process in both studies, appeared dose dependent, and was not associated with respiratory or hemodynamic problems. It is likely that this noncytolytic histamine-release activity is related primarily

to the presence of the basic arginine amino acid residues in the structure of CBP501 (38, 39).

Assessment of cardiac parameters was carried out because the initial repeat-dose toxicology studies reported treatment-related minimum to mild, focal, and multifocal myocardial fibrosis in the hearts of rats treated at 0.5 mg/kg, associated with nonspecific histamine-release events (31). Subsequent cardiovascular safety pharmacology studies confirmed that the effects of CBP501 are attributable to induction of histamine release rather than a direct effect on cardiac tissues (31). The lack of clinically significant adverse findings after extensive cardiac monitoring suggests that there is minimal risk of cardiotoxicity associated with CBP501 treatment. In summary, aside from HRS, CBP501 was well tolerated, without enhancement of toxicities usually associated with cisplatin.

CBP501/cisplatin showed promising evidence of activity in platinum resistant or refractory ovarian cancer and

mesothelioma. The biomarker study using archival specimens was conducted on a small sample of tumors from patients with ovarian cancer. Expression of markers of DNA repair tended to be higher in patients whose best response was PD and lower in patients who achieved PR or SD. Although we cannot rule out the possibility that these markers simply predict outcome to cisplatin alone, the results suggest that the addition of CBP501 is unlikely to overcome intact DNA repair pathways, at least in tumors where expression of DNA repair proteins is robust. In such tumors, repair may occur even if there is G₂ checkpoint abrogation.

Of note, the presence of germline BRCA1 or BRCA2 mutation did not correlate with patient outcome in the small group examined. One patient with BRCA1 mutation, who experienced substantial radiographic progression between cycles 2 and 3, had a lower BRCA1 QIM score than other progressors, but a high Rad51 QIM score and a high composite score. Another patient with BRCA1 mutation, whose tumor was not analyzed, progressed after 2 cycles. In these heavily pretreated patients, BRCA1 reversion mutation following prior cisplatin exposure is a possibility (40). A third patient with a BRCA1 alteration of unknown significance achieved partial response, and another patient with BRCA2 mutation had stable disease; both of these patients had low Rad51 QIM scores (Supplementary Table S2).

Interestingly, high levels of phospho-MAPKAP-K2 expression were also found in patients with PD. Because CBP501 is expected to inhibit the ability of this kinase to phosphorylate CDC25C at Ser²¹⁶, clinical benefit from the cisplatin/CBP501 regimen may have been expected irrespective of expression of this marker. Rather, the data suggest that high expression of MAPKAP-K2 may overcome the ability of intratumoral CBP501 to augment cisplatin-mediated cytotoxicity.

It has recently been reported that CBP501 can enhance the intracellular concentration of cisplatin 1.5- to 3.9-fold in a variety of cancer cell lines, including mesothelioma and MIA PaCa2 pancreatic cancer cells (29), suggesting another basis for the synergism of these agents. Increased intracellular cisplatin in the presence of CBP501 has been associated with increased platinum-DNA adducts (29), which would be expected to increase, not decrease G₂ accumulation in the absence of checkpoint modulation. Therefore, proof-of-mechanism for CBP501-mediated G₂ checkpoint abrogation will be critical in future studies and will require assessment of checkpoint cascades and CDC25C Ser²¹⁶

phosphorylation in paired pre- and posttreatment biopsy samples. Nonetheless, the increase in intracellular cisplatin and associated DNA damage together with reduced checkpoint function mediated by CBP501 may make its combination with cisplatin particularly compelling.

Ultimately, proof-of-principle will require randomized studies. To this end, the favorable safety and signs of enhancement of the activity of cisplatin have prompted further trials in which pemetrexed has been added (41, 42). There are currently 2 ongoing phase II randomized programs in patients with malignant pleural mesothelioma and nonsquamous non-small cell lung carcinoma (NSCLC), respectively, combining CBP501 with cisplatin/pemetrexed versus treatment with cisplatin/pemetrexed alone. Finally, results of the biomarker study suggest that it may be most appropriate to study the impact of addition of CBP501 in tumors with compromised DNA repair and DNA damage response pathways.

Disclosure of Potential Conflicts of Interest

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Clinical Cancer Research

Phase I Studies of CBP501, a G₂ Checkpoint Abrogator, as Monotherapy and in Combination with Cisplatin in Patients with Advanced Solid Tumors

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