efficacy against cDDP resistant tumor cells, the synergy of the two drugs in preclinical models and their generally non-overlapping toxicity profiles.
Methods: Patients (pts) with advanced/metastatic solid tumors, relapsing after chemoradiotherapy or surgery plus radiotherapy (RT), were sequentially allotted to dose levels (DL) 1, 2 and 3 of B (5, 7 and 9 mg/m^2, respectively) and fixed dose of cDDP (75 mg/m^2) given IV every 3 weeks. Cohorts of 3 to 6 pts were treated. DLTs were defined as grade (G) 4 neutropenia for $\geqslant$7 days, febrile neutropenia (FN), neutropenic infection, G 4 thrombocytopenia for $\geqslant$7 days or associated with bleeding, any G 3/4 non-hematological toxicities, and 2-week delay in starting cycle 2 due to toxicity.
Results: 21 pts (11 males), median age 61 years [40−76], were treated. Primary tumor types included 15 squamous cell carcinoma (11 head and neck, 4 uterine cervix), 2 leiomyosarcoma, and 4 others. At study entry 8 pts had locally recurrent and 13 had metastatic disease. Median ECOG-PS was 0. All pts had at least one prior therapy: 1 pt had RT, 2 surgery plus RT, 4 surgery plus chemotherapy (CT), 2 RT and CT, 12 surgery plus RT and CT (most consisting of platinum-based combination therapy). Five pts were treated at DL1, 10 at DL2 and 6 at DL3. DLTs consisted of 1 FN, and 1 G 3 asthenia lasting 11 days in 1 pt each at DL3. DL2 was then expanded to 6 pts; none of them experienced DLTs. This cohort was again expanded to 10 pts for completing PK evaluations at the recommended dose. None of these pts experienced DLTs. G 3/4 treatment related toxicities at DL1 were neutropenia in 4 out of 5 pts, thrombocytopenia in 2 pts and FN in 1 pt; at DL2 they consisted of neutropenia in 8 out of 10 pts and in 1 pt vomiting and diarrhoea; at DL3 they were neutropenia in 5 out of 6 pts, thrombocytopenia in 4 pts, fatigue and FN in 2 pts each and anemia in 1 pt.
Conclusions: The recommended dose/schedule of 7 mg/m^2 of B and 75 mg/m^2 of cDDP/q3w is safe and all toxicities (essentially hematologic) were easily manageable. Further investigations of the combination in phase II trials should be warranted. To date 10 pts received 4 or more cycles and 5 of them are still under treatment. Complete results including PK will be presented.

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Sunitinib combined with modified (m) FOLFOX6 chemotherapy in patients with advanced solid tumors: a phase I study

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Background: Sunitinib malate (SUTENT®; SU) is an oral, multi-targeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, FLT3 and RET. It is approved internationally for the treatment of advanced RCC and imatinib-resistant or -intolerant GIST. It inhibits angiogenesis pathways, which may improve antitumor activity when combined with FOLFOX. This phase I, open-label, dose-finding study investigated the safety, PK and efficacy of SU combined with mFOLFOX6 in patients (pts) with advanced solid tumors.
Patients and Methods: Successive cohorts of 3–6 pts received mFOLFOX6 in 2-wk cycles with escalating doses of SU (37.5 and 50mg/d) on 3 different dosing schedules: 2 wks on, 2 wks off (2/2); 4 wks on, 2 wks off (4/2); or continuously. The primary endpoint is the maximum tolerated dose (MTD) of SU in combination with mFOLFOX6 with each schedule of SU. Secondary endpoints include the antitumor activity and PK of this combination regimen.
Results: Twenty-one pts have been enrolled on the 3 SU dosing schedules, of whom 13 on the 2/2 schedule are evaluable (4 at 37.5 mg/d, 9 at 50 mg/d). Eight pts discontinued treatment due to disease progression; the remaining 5 completed 8 cycles of therapy and enrolled in a continuation study. Dose-limiting toxicities (DLTs) occurred in none of the pts at 37.5 mg/d and in 3 pts at 50 mg/d (1 grade 4 neutropenia, 2 grade 4 thrombocytopenia). As the 2 cases of thrombocytopenia occurred in heavily pretreated pts, the protocol was amended to limit prior chemotherapy. Four pts were enrolled under the amendment at 50 mg/d with no further DLTs reported. Based on these results, the MTD of SU on schedule 2/2 in combination with mFOLFOX6 was determined to be 50 mg/d. Two pts (1 with ovarian cancer and 1 with pancreatic cancer) achieved a confirmed PR. There were no PK-mediated drug–drug interactions for SU, its metabolite and oxaliplatin.
Conclusions: SU 50 mg/d on a 2/2 schedule with mFOLFOX6 in pts with advanced solid tumors who had not been heavily pretreated with chemotherapy was safe and well tolerated. Durable PRs were observed with this regimen. Patient enrollment continues at 50 mg/d 4/2 and 37.5 mg/d continuously, as well as at 50 mg/d 2/2 in pts with advanced colorectal cancer, to confirm the safety and antitumor efficacy of this combination regimen.

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Difluorodeoxyuridine (dFdU) plasma concentrations with weekly low dose gemcitabine during chemoradiation in head and neck cancer patients

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Background: Gemcitabine (dFdC) is an active antitumor agent with radiosensitizing properties. However, dFdC is rapidly metabolised by deoxycytidine deaminase to dFdU which has little antitumor activity on its own but is a potent radiosensitizer in vitro even at low concentrations ($\pm$2500 ng/ml for 24 hrs; Pauwels et al Cancer Cemother Pharmacol 2006, 58, 219). In contrast to dFdC, dFdU is detectable in plasma of patients treated with dFdC for a prolonged period of time (>24 hrs). In head and neck cancer (HNC) patients, chemoradiation with weekly dFdC results in excellent local control rates; however, it is associated with substantial mucosal and skin toxicities (Specenier et al; ASCO 2006, abstract 5547).
Aim: To investigate whether relevant plasma levels of dFdU can be detected during chemoradiation with weekly low dose of dFdC.
Methods: dFdC was administered weekly at three dose levels (10, 50 and 100 mg/m^2) along with conventional radiation therapy.
Plasma concentrations of dFdU were determined daily after the first administration (cycle 1) and before each weekly administration, thereafter. A high-performance liquid chromatographic method has been used and validated for the determination of dFdU in human plasma. Floxuridine (5-fl-2'-deoxyuridine) was used as an internal standard. Tetrahydrouridine was used to prevent the deamination of dFdC to dFdU after sampling. The limit of quantitation was about 50 ng/ml for dFdU. Within-run and between-run precisions were less than 10% and average accuracies were between 90% and 110%.
Results: Three patients were sampled at each dose level (only 2 presently available at 100 mg/m^2). dFdU AUCs, peak and trough concentrations are summarized in the table.

	Weekly dFdC dose (mg/m^2)			p-value
	10	50	100	
dFdU AUC day 1−5 (ng $\times$ min/ml), cycle 1	2.7×10^6	7.6×10^6	9.8×10^6	0.069
dFdU concentration (ng/ml) at 24 hrs, cycle 1	692	1819	2225	0.077
dFdU trough concentration (ng/ml) cycle 1	<50	455	694	0.034
dFdU trough concentrations (ng/ml) > cycle 1	458	549	658	0.101

All values are medians of available data.

Conclusion: During chemoradiation with weekly low dose dFdC, its potent radiosensitizing metabolite dFdU remains detectable at potentially radiosensitizing concentrations. A significant interpatient variation is observed.

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The pharmacokinetic and tolerability profile of once-daily oral ZD4054 in Japanese and Caucasian patients with hormone-refractory prostate cancer

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Background: ZD4054 is a specific endothelin A receptor antagonist in development for the treatment of cancer. To investigate potential