low. CP-4055 and Ara-C plasma concentration decreased rapidly after end of infusion. Plasma concentration of Ara-U was several fold higher than for Ara-C. $t_{1/2}$ Study 1; CP-4055: 0.34h (0.26–0.40), Ara-C: 0.55h (0.38–0.63), Ara-U: 6.73h (5.69–8.38). Study 2: $t_{1/2}$ in same ranges. $C_{max}$of CP-4055 and Ara-C were higher after 30min infusion than after 2h infusion at similar doses.

Conclusion: The plasma concentration and AUC of CP-4055 and Ara-U are broadly linear with increasing doses of CP-4055, independent of the CP-4055 infusion time. The PK parameters display relatively low interpatient variation.

Table 1: PK parameters (mean±standard deviation) at D1 for selected dose levels only.

	Study 1 (30 min)			Study 2 (2h)		
	30 mg/m^2	100 mg/m^2	200 mg/m^2	320 mg/m^2	480 mg/m^2	800 mg/m^2
N(pts)	3	3	6	3	3	1
C_{max} (µg/mL)						
CP-4055	3.3±0.4	11.2±3.3	32.4±6.9	19.9±1.2	40.7±13.2	89.4
Ara-C	0.045±0.005	0.76±0.5	0.64±0.2	0.47±0.08	0.89±0.5	1.2
Ara-U	0.41±0.04	1.6±0.2	3.1±0.5	4.3±0.6	7.3±1.5	15.0
$AUC_{0-\infty}$ (µg-h/mL)						
CP-4055	2.1±0.5	7.2±3.3	23.3±6.0	35.9±6.6	72.3±10.0	164.0
Ara-C	0.054±0.002	0.43±0.2	0.74±0.2	1.0±0.2	2.1±1.0	3.4
Ara-U	3.8±0.7	17.3±4.7	30.0±12.1	40.3±7.9	99.5±32.5	110.5

1495 PUBLICATION

Pharmacokinetics (PK) of AMG 706 on CYP3A activity using oral midazolam and the bioavailability of solid formulations in patients (pts) with advanced solid tumors: results of two phase 1 substudies

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Background: AMG 706 is a potent, oral, multi-kinase inhibitor with both anti-angiogenic and direct antitumor activity achieved by selective targeting VEGF, PDGF, RET, and c-Kit receptors. In vitro, AMG 706 inhibits CYP3A4, 2D6, 2C8, 2C9, and 2C19 (IC_{50} range: 2.0–11.7 µM). Early results from a phase 1 trial of AMG 706 in pts with advanced solid tumors indicated that AMG 706 dosed once daily (QD) provides sustained exposure with no evidence of accumulation or metabolic induction (Rosen ASCO 2005). During this study, the formulation of AMG 706 was changed from capsule to tablet.

Methods: In 2 substudies conducted concurrently in 12 pts, the relative bioavailability of a capsule and tablet formulation of AMG 706 (substudy 1) and the in vivo effect of AMG 706 on CYP3A activity, using oral midazolam as a probe (substudy 2) was evaluated. On day 1, pts received midazolam 2 mg alone. On day 2, pts were randomized (1:1) to receive 100 mg AMG 706 as either a tablet or capsule. After a 1–3 day washout period, pts received 100 mg AMG 706 of the alternate formulation. Subsequently, pts received AMG 706 125 mg QD. On day 21, pts received concomitant midazolam within 5 minutes of consuming AMG 706. Serial 24-hr PK blood collections were drawn for both substudies 1 and 2. Pts fasted for at least 8 hrs before and 2 hrs after dosing on each PK collection day.

Results: Mean (range) age of this cohort was 61.3 yrs (36–90 yrs). In substudy 1, similar plasma concentrations between the tablet and capsule formulation were observed. The estimate geometric mean ratio (tablet:capsule) was 1.02 for AUC and 1.23 for C_{max}. In substudy 2, maximum serum concentrations of midazolam were observed 0.25 to 1 hr after the dose. There was a slightly increased systemic exposure to the second dose of oral midazolam given concomitantly with AMG 706 125 mg. The point estimate (90% CL) for the geometric mean ratio of midazolam serum AUC when midazolam was administrated together with AMG 706 125 mg vs midazolam alone was 1.82 (1.50, 2.22).

Conclusions: The relative bioavailability study (substudy 1) indicated that the PK profiles of the new tablet formulation are comparable to those generated by the capsule formation. In the midazolam study (substudy 2), AMG 706 was found to be a weak inhibitor of CYP3A in humans; therefore, clinically significant interactions of AMG 706 with drugs that are CYP3A substrates are generally not expected.

1496 PUBLICATION

Phase 1 study to determine tolerability and pharmacokinetics (PK) of D0/NDR/02, a novel nanoparticle paclitaxel in patients with locally advanced or metastatic breast cancer (MBC)

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Background: Conventional paclitaxel is formulated in cremophor, which is known to be associated with hypersensitivity reactions and non-linear pharmacokinetics [PK]. DO/NDR/02 is a novel, cremophor free, polymeric, nanoparticle formulation of paclitaxel. A phase I dose escalation study was designed to determine the maximum tolerated dose (MTD) and the safety profile of the formulation in patients with locally advanced or metastatic [MBC] who had failed on anthracyclines or taxanes. The secondary objectives included evaluation of PK and preliminary assessment of efficacy.

Method: DO/NDR/02 was administered in 3-weekly cycles as a one-hour infusion, without premedication, in doses ranging from 135 to 375 mg/m^2, for a maximum of six cycles. Serial blood samples were collected for PK analysis during cycles 1 and 2 and paclitaxel concentrations were determined using a validated HPLC method. The toxicities were graded using NCI CTC version 2.0.

Results: Twenty-five patients who had received prior therapy with either anthracyclines or Taxanes were treated at various dose levels up to 375 mg/m^2. Hypersensitivity reactions were not observed in any patient. The major hematological toxicities have been grade 4 neutropenia (3 out of 123 cycles) two of which occurred at the highest dose of 375 mg/m^2. There was only one incidence of febrile neutropenia at the highest dose. The major non-hematological toxicities were grade 3 infection without neutropenia (n = 1) seen at 135 mg/m^2 and grade 3 diarrhea (n = 2) at 300 and 375 mg/m^2 respectively and grade 3 neuropathy (n = 1 at 300 mg/m^2). The maximum tolerated dose (MTD) was determined to be 375 mg/m^{2}and the dose one level below that (300 mg/m^2) was selected as the recommended phase II dose. Objective responses (OR) were seen in 5 out of 25 (24%) patients. There was no response noted in taxane failed patients. PK analysis showed a linear correlation between the mean AUC and dose, up to 375 mg/m^2.

Conclusions: DO/NDR/02 may be safely administered without any premedications, to a higher dose than cremophor paclitaxel. It has also shown a linear PK profile and encouraging clinical activity in advanced breast cancers. A phase II study to further establish its safety and efficacy is presently being conducted in patients with anthracycline failed MBC.