by most pts. DLTs consisted mainly of myelosuppression events and appeared to be associated with drug accumulation following repeated dosing. High inter-pt PK variability appeared partially due to 2C19 polymorphism status. Updated data and PK/PG correlative analyses will be presented during the meeting.

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Novel in vivo imaging of acute chemotherapy-induced vascular toxicity

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Background: Chemotherapy may induce deleterious effects in normal tissues, leading to organ damage. Direct vascular injury is the least characterized side effect. Studies performed using organ cultures have shown that doxorubicin induces apoptosis in endothelial cells, leading to impaired vasodilatory response of arteries. Our aim was to establish a real-time, *in vivo* molecular imaging platform for evaluating the potential vascular toxicity of doxorubicin in mice.
Methods: Ovaries served as a prototype for evaluating toxicity in normal tissues. Femoral vasculature was imaged as a control vessel. Mice ovarian perfusion and femoral blood flow were measured in real time during and after doxorubicin administration (8 mg/kg intravenously). Ovarian blood flow was imaged by ultrasound biomicroscopy (Vevo2100) with microbubbles as a contrast agent, and by fluorescence optical imaging system, equipped with a confocal fiber microscope (Cell-viZio). Femoral blood flow was imaged by pulse wave Doppler ultrasound and by Cell-viZio.
Results: Using microbubbles as a contrast agent revealed a 33% ($P < 0.01$) decrease in ovarian perfusion already 3 minutes after doxorubicin injection. The same was true for the femoral arterial blood flow. Cell-viZio imaging depicted a pattern of vessel injury at around the same time after doxorubicin injection: the wall of the large blood vessels was disintegrated whereas the small blood vessels were damaged with malformed walls. The fluorescence signal displayed by the small vessels was nearly diminished.
Conclusions: We have established a platform of innovative high resolution molecular imaging, suitable for the imaging ovaries and blood vessels, that enables prolonged real-time detection of chemotherapy-induced effects in the same individuals. The acute reduction in ovarian and femoral blood flow and the impairment of the blood vessels wall may represent an acute universal doxorubicin-related vascular toxicity, an initial event in organ injury.

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Population pharmacokinetics (PK) and exposure/response relationships of the receptor tyrosine kinase inhibitor E7080 in phase I studies

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Background: E7080 is a once-daily, orally administered, receptor tyrosine kinase inhibitor with anti-angiogenic and anti-proliferative activity. Anti-tumor activity has been reported in phase I studies. Separate dose-finding Phase 1 studies were conducted with continuous once-daily (qd) and twice daily (bid) administration, with empirical maximum tolerated doses (MTDs) at 25 and 10 mg/day, respectively. To aid selection of the dose schedule for further investigation, exposure–efficacy and −safety relationships were evaluated for E7080.
Methods: A population PK model was developed using data from two E7080 dose-finding studies, investigating continuous qd and bid dosing in 28-day cycles (tumor assessments every 2 cycles). Steady-state individual exposure parameters ($C_{max,ss}$, $AUC_{0-24,ss}$, and $C_{min,ss}$) were derived to correspond with starting dose. Logistic regression was used to model the probability of developing the main adverse events, hypertension and proteinuria, in relation to E7080 exposure and ECOG performance status, and the relationship of response (PR or durable stable disease of $\geqslant$23 weeks [dSD]) with E7080 exposure, ECOG performance status and development of hypertension or proteinuria. Progression-free survival (PFS) was modeled as a function of E7080 exposure and other covariates using Cox regression. Disposition for subjects with PK information is presented in the table.
Results: E7080 PK profile was best described by a two-compartment model with sequential zero- and first-order absorption and first-order elimination. All (log-transformed) E7080 steady-state exposure parameters ($C_{max,ss}$, $C_{min,ss}$ and $AUC_{0-24,ss}$) were significant predictors of the probability of developing $\geqslant$grade-2 hypertension ($p < 0.0001$ for all) and proteinuria ($p < 0.05$ for all), whereas dosing frequency and ECOG performance status were not. PFS correlated with increasing E7080 exposure. The probability of tumor responses increased with increasing $C_{max,ss}$ and $AUC_{0-24,ss}$ ($p < 0.01$ for all), while $C_{min,ss}$ and other covariates were not significantly correlated.

	Schedule	
	QD	BID
Response (evaluable subjects, *n*)		
Total	62	35
PR	7	10
dSD	22	9
Safety (subjects experiencing AE $\geqslant$grade 2, *n*)		
Total	81	41
Hypertension	27	21
Proteinuria	21	15

Conclusions: The probability of response and developing hypertension and proteinuria are correlated with E7080 exposure ($C_{max,ss}$ and $AUC_{0-24,ss}$). Based on the higher exposure achieved at the MTD of the once-daily dosing, 25 mg qd was selected for further clinical development.

454 POSTER

A clinical study to characterize the occurrence of mild-to-moderate diarrhea after administration of neratinib either once daily or twice daily for 14 days

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Background: Neratinib (HKI-272 [NER]) is a potent, low molecular weight, orally administered, irreversible pan-ErbB receptor tyrosine kinase inhibitor in development for the treatment of ErbB2-positive breast cancer. We examined whether NER 120 mg twice daily (BID) could reduce the occurrence of diarrhea relative to NER 240 mg once daily (QD), and characterized the pharmacokinetics after single and multiple doses.
Methods: In a randomized, double-blind, parallel-group study, healthy adults aged 18−50 years were eligible to receive NER 240 QD or NER 120 mg BID with a standard meal for 14 days. Severity of diarrhea was graded. Drug was withdrawn in subjects with diarrhea graded at least moderate. Blood samples were obtained through 24 hours postdose on days 1 and 7 for PK analyses of NER and metabolites. ABCG2 genotyping was done on blood. Subjects who had diarrhea graded at least moderate or finished 14 days of dosing were considered evaluable for the primary endpoint.
Results: 50 subjects (48 M, 2 F) aged 19−49 years (median 29.5) were enrolled. 5 subjects discontinued for moderate adverse events (AEs) other than diarrhea. All 50 subjects developed at least mild diarrhea ~4 days into drug administration. The frequency of moderate diarrhea was comparable between regimens: 11/22 (50% [90% CI: 28−72%]) in the QD group and 17/23 (74% [52−90%]) in the BID group. No severe AEs occurred. ABCG2 genotype did not appear to affect the severity or onset of diarrhea that was graded at least moderate. NER 120 mg BID resulted in lower exposures than did NER 240 mg QD: mean (%coefficient of variation [%CV]) for peak plasma concentration (C_{max}) was 37.4 (29%) ng/mL vs 71.8 (34%) ng/mL on day 1 and 49.6 (32%) ng/mL vs 73.1 (35%) ng/mL on day 7, and mean (%CV) area under the concentration-time curve from 0 to 24 hours (AUC_{0-24h}) was 569 (26%) ng·h/mL vs 891 (28%) ng·h/mL on day 1 and 873 (36%) ng·h/mL vs 1060 (25%) ng·h/mL on day 7. Steady-state exposures (AUC_{0-24h}) of NER following 120 mg BID and 240 mg QD on day 7 in this study appeared similar to that previously reported in patients with cancer following the therapeutic dose of NER 240 mg QD with food (AUC_{0-24h}: 939 ng·h/mL; Wong et al. Clin Cancer Res 2009;15(7):2552−8).
Conclusions: NER 240 mg QD and NER 120 mg BID regimens were comparable for severity, frequency, and onset of diarrhea. The observed steady-state exposures of NER in this study appeared consistent with that reported in patients with cancer following the therapeutic dose of NER 240 mg QD with food.