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A phase I safety, pharmacokinetic and pharmacodynamic study of carfilzomib, a selective proteasome inhibitor, in subjects with advanced solid tumours

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Background: Carfilzomib (CFZ) is a structurally- and mechanistically-novel proteasome inhibitor of the peptide epoxyketone class that exhibits a high level of selectivity for active sites within the proteasome. This phase I study assessed the maximum tolerated dose (MTD), pharmacokinetics (PK), and pharmacodynamics (PD) of CFZ dosed on D1, D2, D8, D9, D15 and D16 of a 28 day cycle in patients (pts) with advanced solid tumors. The starting dose of 20 mg/m^2 was the MTD established in the phase 1 hematologic malignancy study and has demonstrated anti-tumor activity in myeloma and NHL.
Material and Methods: Pts failing $\geqslant$ 2 prior treatments were enrolled in this 3+3 dose escalation study. Cycle 1 D1, D2 dosing in all cohorts was at 20 mg/m^2. Subsequent dose cohorts were at 20, 27, or 36 mg/m^2. MTD was defined as the highest dose level at which $\leqslant$33% of subjects experience a dose limiting toxicity (DLT) during the first 28-day cycle. PK measurements of CFZ were drawn in C1. For PD, constitutive proteasome and immunoproteasome inhibition in red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs) were assayed in C1 and 2.
Results: 14 pts, 8 male/5 female, mean age 59 years (range 36−75), received a total of 27 cycles of CFZ at dose levels of 20/20 mg/m^2 (n = 3), 20/27 mg/m^2 (n = 4), and 20/36 mg/m^2 (n = 7). Median cycles given was 2 (range 1 to 5). At 20/36 mg/m^2, 1 of 6 evaluable pts had a DLT (Grade 3 fatigue) and established the MTD. Common adverse events were fatigue (36%), headache (29%), diarrhea (21%), nausea (21%), and constipation (21%). Notable was the absence of grade > 1 peripheral neuropathy. One renal cancer pt who had failed two multi-targeted antiangiogenesis inhibitors and an mTOR inhibitor has a confirmed partial response (>80% reduction) after 5 cycles. Two pts (mesothelioma and small cell lung cancer) had SD for >3 months. PK on C1D16 at the 36 mg/m^2 MTD showed C_{max} of 4080$\pm$1828 ng/mL, AUC_{inf} of 42173 $\pm$15319 ng$_*$min/mL and a short $T_{1/2}$ of 36 $\pm$ 18 min. On C1D1 post 20 mg/m^2 (n = 12), the chymotrypsin-like activity of both the constitutive proteasome and the immunoproteasome was potently inhibited; 80$\pm$4% and 81$\pm$5% in blood and PBMCs, respectively. Less inhibition of trypsin-like and caspase-like activities was observed. Recovery of activity in PBMCs occurred between cycles.
Conclusions: CFZ 20/36 mg/m^2 is well tolerated when administered IV on a QDx2 weekly schedule in pts with solid tumors, with preliminary evidence of antitumor activity. PD analysis supports inhibition of the proteasome chymotryptic site as the predominant mechanism. The phase 2 portion of the trial is currently enrolling.

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Pharmacokinetic (PK) and pharmacodynamic (PD) phase I study of an oral c-Met inhibitor ARQ197 reaches maximum tolerated dose (MTD) in a twice daily (bid) dosing schedule

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Background: ARQ197 is a selective non-ATP competitive small molecule inhibitor of c-Met, a receptor tyrosine kinase implicated in tumor growth, metastasis and angiogenesis. A previous phase I study of ARQ197 did not reach MTD and a recommended phase 2 dose (RP2D) of 120 mg bid was established based on PK data (Rosen et al, AACR-NCI-EORTC Conference 2007 abstract B91).
Methods: ARQ197 was administered orally bid to advanced cancer patients (pts) using a 3+3 phase I dose escalation design. Mandatory paired tumor biopsies were taken for total and phosphorylated c-Met and FAK analyses by immunohistochemistry, and for c-Met amplification by fluorescent in situ hybridization and mutation analysis by sequencing. Circulating endothelial cell (CEC) enumeration was undertaken.
Results: 18 pts (10 males; mean age 56) received ARQ197 at 100, 200, 300 and 400 mg bid. PK data revealed that the mean C_{max} increased linearly from 100 mg to 400 mg bid. The mean $AUC_{0-12\,h}$ also increased linearly to 300 mg bid, but the increase to 400 mg bid was two-fold and appeared non-linear. Mean values for $t_{1/2}$, Cl/F and Vz/F remained relatively constant up to 300 mg bid; however at 400 mg bid, a longer mean $t_{1/2}$ and lower mean Cl/F were observed, suggesting saturation of ARQ197 clearance mechanisms. Two pts demonstrated dose limiting toxicities (DLTs) of CTCAEv3 grade (G)3 febrile neutropenia at 400 mg bid, one of whom also had reversible G3 palmar-plantar erythrodysesthesia and mucositis lasting 2 weeks. This established the MTD of ARQ197 at 300 mg bid. Other toxicities included G1−2 fatigue, nausea, vomiting and diarrhea. One pt each at 100, 200 and 300 mg bid with high baseline phosphorylated c-Met and FAK expression had substantial declines post ARQ197, confirming target inhibition. To date, 7 of 11 pts have demonstrated declines in CEC counts post therapy of up to 100%, suggesting antiangiogenic activity for ARQ197. Prolonged disease stabilization was observed in 5 pts for up to 32+ weeks. Tumor regression was observed in a metastatic gastric cancer pt who remains on study.
Conclusions: PK increased linearly up to 300 mg bid. Two DLTs were observed at 400 mg bid, establishing the MTD and new RP2D of ARQ197 at 300 mg bid. ARQ197 inhibited tumor c-Met and FAK phosphorylation with minimal toxicity up to 300 mg bid and decreased CEC counts. Further evaluation of antiangiogenic activity with dynamic contrast-enhanced magnetic resonance imaging at the MTD dose of ARQ197 is ongoing in 20 pts.

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Operation strategy of Phase I trials

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Background: Phase I trials is solely adaptive. The Continual Reassessment Method (CRM) enables to update an assumed dose-response model with each patient's response in Bayesian fashion while conventional design requires three patients to decide to escalate dose or add another three patients, otherwise terminate the trial. A modified CRM with two or three patients' cohort has also been proposed. The TIme To Event CRM (TITE-CRM) is also proposed and has been applied to some trials which are interested in late onset toxicity. Compared with ordinal CRM and conventional design, the advantage of rapid accrual of patients was empathized. However, drop-out due to low efficacy or non dose limiting toxicity (DLT) in the study is inevitable and censoring mechanism for the above reason is dose-dependent in TITE-CRM while most of cyto-toxic drugs are evaluated with in one or two cycle to evaluate toxicity.
Some clinicians think investigators must wait for each patient's response concerning patient accrual. Those who believe so think the CRM is inferior to the conventional design in terms of patients' accrual speed. They are afraid they could not catch eligible patients while one patient is being treated in the trial.
In Bayesian sense any patients should be treated at the most promising dose level based on the all of the cumulative information including the ongoing trial. So we think at most three patients can be observed simultaneously as conventional design does. When one of these patients completes a defined cycle for treatment, the next dose level can be determined by CRM. This operation strategy with CRM design can be expected more rapid patients accrual than conventional design because it does not wait for other patient's response in a cohort.
Material and Methods: We evaluated the advantage of this operation strategy compared with conventional design quantitatively. The simulation study of 10,000 times is typical one of Queuing theory in Operational Research. In the simulation setting we assumed 24 eligible patients will arrive in a year. The time windows to evaluate toxicity vary from 1 week to 16 weeks.
Result: Our simulation result suggests that the proposed operation strategy is superior in terms of time to accomplish the target sample size, availability of beds, percentages of patients who enrolled in all of arrived patients.
Conclusion: The CRM which allows at most three patients treated simultaneously is strongly recommended in a certain situation. We have also confirmed feasibility of the design in UGT0601 trial with CPT-11 for individualized dosing based on genotype.