Wednesday 8 November 15:00–16:15

PLENARY SESSION 2

Proffered Papers

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Phase Ib and pharmacodynamic study of the MEK inhibitor AZD6244 (ARRY-142886) in patients with advanced solid malignancies

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AZD6244 is an orally bioavailable, selective and potent inhibitor of MEK1/2 with pre-clinical activity in human tumor models at nanomolar concentrations. AZD6244 has been investigated in a 2-part Phase I study to assess safety, pharmacokinetics (PK), pharmacodynamics (PD) and biological efficacy in patients (pts) with advanced solid malignancies. The Phase 1a study has been previously reported [Chow, 2005] and was useful in determining the MTD (200 mg) and the safety of the compound when given in continuous 28-day cycles. In part B, pts were randomized to receive 100 or 200 mg doses BID for 28-day cycles, with a target of enrolling 50% melanoma pts. In addition to confirming a sustainable dose for further investigation, part B examined PK and target modulation, as assessed by ERK phosphorylation (pERK) in peripheral blood mononuclear cells (PBMCs) and pERK and Ki67 in pre- and post-dose tumor biopsies. Thirty four pts were treated in Phase 1b, with the most common tumor types being melanoma, breast, and colorectal. The adverse event profile was similar to 1a (in decreasing frequency) rash, diarrhea, nausea, peripheral edema, vomiting, and elevated liver enzymes. Though 200 mg was initially determined as the MTD in phase 1a, the incidence, duration and severity of adverse events in the expanded population suggested that dose was too high for continuous dosing. By contrast, the 100 mg dose was well-tolerated over prolonged periods of dosing. Evaluable paired pre- and post-dose (4 hours post-dose on ~Day 15) tumor biopsies were obtained from 17 pts: 29% melanoma and 71% other tumors, 82% of the samples at the 100 mg dose. Formalin-fixed, paraffin embedded tissue samples were evaluated by immunohistochemistry for pERK (score range 0–400) and proliferative index (range 0–100%). After treatment, tumor pERK staining was reduced, with a gmean reduction in nuclear staining of −83% (CI: −57%, −93%). Proliferative index (Ki-67) showed a gmean reduction of −46% (CI: −17%, −65%). Genetic analysis of the tumor samples is ongoing to determine the presence or absence of the V600E bRaf and 7 commonly occurring K-ras mutations. After 15 days of BID dosing, trough plasma concentrations of AZD6244 were approximately 400 ng/mL, with a strong correlation between plasma concentrations of AZD6244 and inhibition of pERK in PBMCs. Importantly, the trough plasma concentration of 400 ng/mL corresponded to 35%-44% inhibition of pERK. Of 31 pts assessable for clinical response, 14 (45%) had stable disease (SD) after 2 months. Of these, 9 pts (29%) [6 of 13 melanoma patients (46%), 1 breast cancer, 1 NSCLC, and 1 thyroid cancer] had SD lasting for $\geqslant$ 5 months. These results demonstrate that a dose of 100 mg of AZD6244 (ARRY-142886) is well-tolerated, is associated with a profound inhibition of pERK and good knockdown of Ki67, and produces a high incidence of long-lasting stable disease. This dose has therefore been selected for Phase 2 studies.

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Phase I dose escalation study of the aurora kinase inhibitor PHA-739358 administered as a 6-hour infusion on days 1, 8 and 15 every 4 weeks in patients with advanced/metastatic solid tumors

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Background: Aurora proteins belong to a family of 3 serine/threonine kinases that are key regulators of different steps in mitosis. Aurora kinases have been found to be implicated in tumor genesis and over expressed in cancer.

Materials and Methods: Objectives of this trial are to determine the maximum tolerated dose (MTD) and dose limiting toxicities (DLTs) during the first cycle of treatment, to evaluate the safety and pharmacokinetics (PK) profiles, to document antitumor activity and evaluate histone H3 phosphorylation in skin biopsies. DLTs are defined as grade (G) 4 neutropenia >7 days, febrile neutropenia, neutropenic infection, G $\geqslant$3 thrombocytopenia ($\geqslant$7 days or with bleeding), G $\geqslant$3 non-hematological toxicity except inadequately treated nausea/vomiting or diarrhea, and two-week delay in starting cycle 2. Sequential cohorts of 3–6 patients (pts) are treated per dose level (DL).

Results: To date 31 pts were included in 6 DLs (45, 90, 135, 190, 250 and 330 mg/m^2 by 6 hr infusion). Omission of one dose due to G3 uncomplicated neutropenia observed at day 15 in 2 pts at 250 mg/m^2 led to modify the criteria for dosing on days 8 and 15 and the definition of the DLT; the drug could be safely infused in 6 further pts at this same DL. At 330 mg/m^2 G3 neutropenia was only reported in 1 out of 3 pts. One DLT consisting in a G2 hypertensive episode occurred in 1 pt at 90 mg/m^2; a G1 transient episode happened once in 1 pt at 190 mg/m^2; for both pts further infusions did not lead to similar events. No G $\geqslant$3 non-hematological toxicities were reported. Other G 1 and 2 toxicities included nausea, anorexia and diarrhea. Seven pts presented with a stable disease, lasting $\geqslant$7 months in 3 pts treated at 190/250 mg/m^2. PK parameters show dose linearity for the DLs explored and do not differ between days 1 and 15; plasma clearance is moderate (around 0.40 L/h/kg) and the terminal half-life about 20 hours. Modulation of histone H3 phosphorylation occurred from 190 mg/m^2.

Conclusions: This regimen and schedule is well tolerated. The MTD has not been reached and dose escalation continues. Modulation of histone H3 phosphorylation occurred from 190 mg/m^2. For the studied DLs, PK parameters are dose and time independent and are characterized by a low variability. Clinically relevant stable diseases have been reported.

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Imidazole derivatives with vascular disrupting activity

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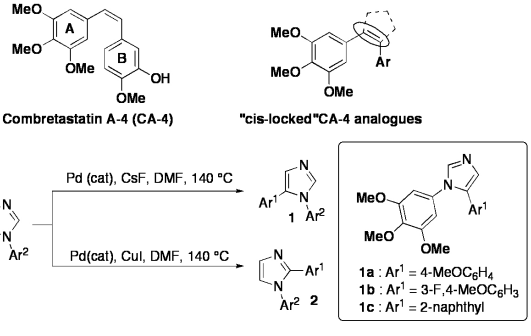
Introduction: Our research group has directed its attention to the identification of structurally new *vascular disrupting agents* (VDAs) which are water soluble or may be converted into water soluble derivatives, possess vascular disrupting activity, and show antitumor activity at non-toxic doses. We prepared 1,5- and 1,2-diaryl-1*H*-imidazoles of general formula **1** and **2**, respectively, which can be considered as *cis*-locked analogues of combretastatin A-4 (CA-4), a natural tubulin-binding VDA. We became interested in the imidazole core since its basic nitrogen atom may lead to compounds which can easily be formulated as water-soluble salts. Moreover, since the 3,4,5-trimethoxyphenyl substituted A ring of the CA-4 seems to be essential for the activity of this natural product, we maintained this moiety in compounds **1** and **2** and evaluated the effect due to the replacement of the B-ring of CA-4 with a variety of aryl substituents.

Material and Methods: Imidazoles **1** and **2** were prepared using the innovative synthetic protocols we recently developed. The vascular disrupting activity of some selected compounds was evaluated in vitro on HUVEC, and in vivo on experimental tumors.



Results: Compounds **1a–c** caused profound changes in the morphology of endothelial cells (ECs) (IC_{50} = 6.5, 30.9 and 38.8 μM, respectively). Interestingly, in comparable experimental conditions, **1a** – but not **1b** and **1c** – induced changes in the shape of ECs at concentrations that did not affect their proliferation. By immunohistochemistry we confirmed the ability of **1a** to cause depolymerization of microtubules in ECs. We next analyzed the ability of the compounds to induce necrosis of experimental tumors in vivo, the hallmark of vascular disrupting activity. Following a single treatment, compounds **1a–c** caused massive central necrosis of tumors. They were also subjected to primary cytotoxicity screening against the NCI