Wednesday 8 November 15:00–16:15

PLENARY SESSION 2

Proffered Papers

26 ORAL

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.

27 ORAL

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

M. De Jonge[1], N. Steeghs[2], J. Verweij[1], J.W.R. Nortier[2], F. Eskens[1], J. Ouwerkerk[2], C. Van Noort[1], P. Carpinelli[3], R. Spinelli[3], F. Bologna[3], H. Gelderblom[2]. *[1]Erasmus University Medical Center – Daniel den Hoed, Department of Medical Oncology, Rotterdam, The Netherlands; [2]Leiden University Medical Center, Department of Clinical Oncology, Leiden, The Netherlands; [3]Nerviano Medical Sciences, Nerviano, Italy*

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.

28 ORAL

Imidazole derivatives with vascular disrupting activity

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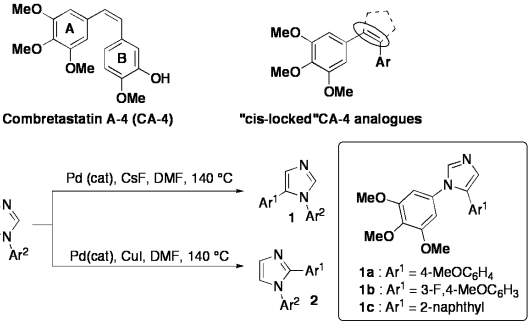
Introduction: Our research group has directed its attention to the identification of structurally new *vascular disrupting agents* (VDAs) which are water soluble or may be converted into water soluble derivatives, possess vascular disrupting activity, and show antitumor activity at non-toxic doses. We 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

60 tumor cell line panel. Similar to CA-4, compounds **1a–c** had a definite cytotoxic activity, displaying MG_MID $LogGI_{50}$ values of −6.59, −7.50 and −7.17, respectively. Docking experiments also showed that the trend of the calculated interaction energies of **1** and **2** with the colchicine binding site on tubulin, which is the target for combretastatins, is similar to that of the *in vitro* $LogGI_{50}$ values of these compounds.
Conclusions: Combretastatin-like imidazole derivatives possess vascular disrupting activity, hence representing promising chemical entities for the design of novel VDA.

29 ORAL

Embryonic stem cell vaccination prevents lung cancer

J. Eaton, R. Mitchell, B. Brewer, E. Krishnan, L. Williams, X. Gao, M. Janjua, H. Bodduluri. *University of Louisville, J. G. Brown Cancer Center, Louisville, KY, USA*

Background: The antigenic similarities between tumor cells and embryos prompted us to test the idea that vaccination with embryonic stem cells (ESC) would prevent tumorigenesis. Here, we report that, in two separate models of lung cancer, vaccination with allogeneic ESC provides protection against tumor outgrowth.
Materials and Methods: C57Bl6 mice were vaccinated s.c. (primary and boost 10 days apart) with live allogeneic ESC alone or with a combination of ESC and a source of GM-CSF (STO fibroblasts retrovirally infected with a GM-CSF retroviral expression vector).
Results: In animals subsequently challenged with transplanted (syngeneic) Lewis lung carcinoma (LLC), prior vaccination with ESC alone or ESC + STO/GM-CSF is 80–100% effective (respectively) in preventing tumor outgrowth. Prevention of tumor growth is primarily due to the activity of cytotoxic T lymphocytes because (1) splenocytes from vaccinated animals are exceptionally active in in vitro tumor cell killing (e.g., 20% kill of LLC at an effector:target ratio of 5:1) and (2) in vivo depletion of CD8+ T lymphocytes completely abrogates the anti-tumor effect of prior vaccination on the outgrowth of implanted LLC. Most importantly, this vaccination strategy prevents the development of lung tumors in a mouse model of carcinogen-initiated lung cancer (3-methylcholanthrene administration followed by repetitive dosing with butylated hydroxytoluene). While 100% of control (unvaccinated) mice developed lung tumors, 60% of ESC vaccinated and 90% of ESC + STO/GM-CSF vaccinated mice remained tumor free after 27 weeks. In over 200 mice vaccinated with ESC we found no evidence of autoimmune disease or significant decline in the numbers of adult pluripotent bone marrow stem cells.
Conclusions: Our results thus far raise the exciting possibility of developing a prophylactic vaccine capable of preventing the appearance of various types of cancers in humans, especially those with hereditary, chronological or environmental predispositions to neoplastic disease.

29LB1 Late Breaking ORAL

Final safety, pharmacokinetic and antitumor activity results of a phase I study of YM155, a novel survivin inhibitor, when administered by 168 hour continuous infusion

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Background: Targeting the inhibitor of apoptosis proteins (IAPs) is a novel anticancer therapeutic strategy. Survivin is a key member of the IAP family, selectively expressed in most solid tumors but not expressed in most normal tissues. YM155 is an imidazole bromide derivative selected via high throughput screening, which inhibits survivin mRNA transcription and protein expression and showed potent (nM) anti-proliferative activity in a broad spectrum of preclinical models. In vivo, YM155 exhibited high distribution in tumor tissue and induced major tumor regressions (including complete remissions) in lymphoma, lung and prostate xenografts.
Material and Methods: This classical "3+3'' dose-escalation study aimed to determine the maximum tolerated dose (MTD) of 168 hour continuous IV infusion of YM155 every 3 weeks, to evaluate toxicity, characterize the pharmacokinetics and observe anti-tumor activity. Additional patients (pts) were added to fully characterize toxicities at the MTD. Pharmacokinetic sampling was performed during cycles 1 and 2.
Results: A total of 41 pts (M/F: 31/10, median age 61, range 28−78) with performance status of 0–2 were treated at 4 dose levels [1.8 mg/m^2/day (N = 8), 3.6 (6), 6.0 (2) and 4.8 (25)]. Most common tumor types were prostate (9), and colorectal (5) carcinomas and NHL (5). Dose-limiting toxicities (DLTs) were encountered at 6.0 mg/m^2/day (reversible renal tubular necrosis with grade 3 mucositis in one pt and increased serum creatinine in one pt). The MTD was established at 4.8 mg/m^2/day. Serious adverse events related to YM155 included: one grade 4 transient neutropenia, 2 grade 3 mucosal inflammations and 1 grade 3 renal tubular necrosis. Common grade 1–2 toxicities were pyrexia, arthralgia, nausea, fatigue and diarrhea. At MTD, median clearance was 45.6 L/hr with a median steady state concentration of 7.67 ng/mL and a median terminal half-life of 24 hours. Three pts with NHL (2 chemotherapy refractory intermediate grade B-cell, and 1 follicular B-cell NHL) had PRs. One of these pts had near CR and subsequently went onto BMT and is currently in remission for 14+ months. The 2 other NHL pts remain on YM155 (75 and 57 weeks respectively) with sustained PRs. Two HRPC pts exhibited PSA response and one NSCLC pt had a minor response.
Conclusion: YM 155, the first survivin inhibitor, was well tolerated at the MTD of 4.8 mg/m^2/day × 7 days and exhibited anti-tumor activity in 5 pts. Broad phase 2 evaluation is ongoing.

Wednesday 8 November 16:30–18:15

PLENARY SESSION 3

Antibody versus small molecule inhibitors of receptor tyrosine kinases

30 INVITED

Combination of monoclonal antibodies and Tyrosine Kinase Inhibitors with the same target

J. Baselga. *Spain*

Abstract not received.

31 INVITED

Combination of monoclonal antibodies against RTKs

S. Kelsey. *Genentech BioOncology, BioOncology, South San Francisco, CA, USA*

Monoclonal antibodies directed against receptor tyrosine kinases or their ligands have the attribute of being relatively specific for the intended target, which may be construed as an advantage or a disadvantage depending on the context in which they are being used. The target specificity may often be associated with a preferential toxicity profile; on the other hand the inability to target more than one kinase may result in differential efficacy. The favorable tolerability of monoclonal antibodies combined with their discrete specificity has both required and enabled preclinical and clinical studies of antibody combinations. Antibodies to many RTKs and their ligands have either entered or are soon to enter clinical development; most notably antibodies to HER2, EGFR (HER1), VEGF and KDR, PDGFR, HGF and MET, as well as antibodies directed against other cellular targets which might act synergistically with RTK inhibition, such as CD20 and death receptors DR4 and DR5. This presentation will review the preclinical rationale and overview some of the key clinical efficacy data obtained to date with combinations of therapeutic monoclonal antibodies in oncology. In addition, some of the perceived limitations to combination therapy with monoclonal antibody therapy will be discussed.

32 INVITED

Multitargeted molecules versus combined Tyrosine Kinase Inhibitors

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The present abstract aims at proving a theoretical framework for discussing the specific advantages and disadvantages of multi-targeted agents as compared to the combination of single targeted drugs. Key-points that need to be addressed are: structural and chemical issues, metabolism, toxicity, efficacy, resistance and pragmatic issues.
Structural and chemical issues: Most tyrosine kinase inhibitors (TKI) have a propensity to hit multiple targets. Imatinib was initially described as a selective agent, albeit it inhibits in fact at least 3 TKs (BCR-ABL, KIT and PDGFR). Dasatinib binds to 74 of 148 kinases recently screened at 10 micromolar.
Metabolism: Drug interaction between different TKI can be related to their absorption and/or metabolism. Several TKI can inhibit PGP pumps involved in drug absorption and elimination. Sorafenib, valatinib, erlotinib, gefitinib,