the value of p53 activation in preclinical and clinical models before nutlin-3 like drugs are approved. The mechanism by which actinomycin D acts at these doses appears to be by the release of ribosomal proteins that bind to and inhibit MDM2 function. This mechanism explains why the drug can phenocopy the affects of Nutlin3.

42 INVITED

New inhibitors targeting critical cancer dependencies: Progress and challenges

P. Workman. *United Kingdom*

Abstract not received

43 INVITED

Targeting PI3K: where are we?

L. Cantley[1]. [1]*Harvard Medical School, Beth Israel Deaconess Medical Center Division of Signal Transduction, Boston, USA*

Background: The Phosphoinositide 3-Kinase (PI3K) pathway is activated in a large fraction of human cancers due to activating mutations in PIK3CA, PIK3R1 or AKT and loss of function mutations in PTEN or INPP4B. This pathway plays a major role in controlling glucose uptake and metabolism in cancer cells and the ability of these mutations to provide a survival signal is in part due to increased nutrient availability.
Materials and Methods: Mice were genetically engineered to express mutant PIK3CA or to delete PTEN in specific tissues.
Results: Mice with activating mutations in the PIK3CA gene develop cancers that have high rates of glucose uptake and metabolism and pharmacological inhibitors of PI3K block glucose uptake and cause tumor shrinkage. Based on endothelial cell specific deletion of PI3K genes, PI3K signaling is also critical for neovascularization of tumors, raising the possibility that PI3K antagonists could block tumor growth by disrupting the vasculature.
Conclusions: The characterization of drug effects on tumors from genetically engineered mice is likely to provide a background for identifying biomarkers that predict which patients will benefit from treatment with PI3K pathway inhibitors.

Wednesday, 17 November 2010

Poster Sessions

Cancer vaccines

44 POSTER

Vaccination of dendritic cells pulsed with tumor endothelial cells inhibits tumor growth

N. Utoguchi[1], R. Suzuki[1], Y. Oda[1], T. Nomura[1], K. Maruyama[1]. [1]*Teikyo University, Department of Biophamaceutics, Kanagawa, Japan*

Background: Angiogenesis is required for the growth of solid tumors. Therefore, the breaking of tumor-induced endothelial cells (TEC) should be a useful approach for cancer therapy. Endothelial cells (EC) in the angiogenic vessels in solid tumors express proteins on their surfaces that are absent or barely detectable in normal vascular endothelium, including $\alpha v\beta 3$ integrin and receptors for certain angiogenic growth factors. Here we show that immunotherapy of solid tumor using dendritic cells (DC) pulsed with the TEC.
Material and Methods: Human umbilical vein endothelial cells (HUVEC) were cultured with mice tumor cells (B16 melanoma or Colon26 colon carcinoma)-conditioned medium and were used as a model of TEC (mTEC). TEC were isolated by Percoll gradient centrifugation from collagenase digested tumor tissue. Angiotensin-converting enzyme activity and CD34 were used as a marker of EC. Bone marrow-derived murine DC were incubated with lipofectin containing lysate of mTEC or TEC. Mice were immunized by intradermal injection of DC. After one week, B16 cells were injected intravenously, or Colon26 cells were injected intradermaly. Two weeks after the transfer of tumor cells, visible metastatic colonies of B16 on lung were counted, or the volume of Colon26 was measured.
Results: The number of the colonies in the lung was dramatically decreased in the mice immunized with mTEC pulsed DC compared with the mice immunized with none pulsed DC. DC pulsed HUVEC cultured with no tumor-conditioned medium had no inhibitory effect of the lung metastasis. The metastasis of B16 was decreased by the treatment of DC pulsed with the endothelial cells cultured with Colon26-conditioned medium. The colonies of B16 metastasis in lung were inhibited by vaccination of TEC isolated from solid B16 tumor. The tumor volume was also decreased in the mice immunized with Colon26-derived TEC pulsed DC. In mouse dorsal air-sac chamber method, angiogenesis induced B16 cells was inhibited by the treatment of TEC pulsed DC. No significant difference in wound healing (normal physiological angiogenesis) was observed between TEC pulsed DC and control mice.
Conclusions: Vaccination of DC pulsed tumor-induced endothelial cells can inhibit tumor growth and metastasis. Tumor-induced angiogenesis-targeted immunotherapy offers the potential for new approach to treatment of cancer.

45 POSTER

Preliminary results of a phase 1 study of intravenous administration of GL-ONC1 vaccinia virus including green-fluorescent protein real time imaging in patients with advanced cancer

J. Vitfell-Pedersen[1], E.M. Karapanagiotou[2], S. Alam[1], M. Puglisi[1], L. Britton[1], S. Sassi[1], D. Mansfield[3], T. Yap[1], J. De-Bono[1], K. Harrington[2]. [1]*Royal Marsden Hospital, Drug Development Unit, Sutton, United Kingdom;* [2]*Royal Marsden Hospital, Head and Neck Unit, Chelsea, United Kingdom;* [3]*Institute of Cancer Research, Cell and Molecular Biology, Chelsea, United Kingdom*

Background: GLV-1h68/GL-ONC1 is a genetically engineered vaccinia virus attenuated by insertion of the ruc-gfp (a luciferase and green fluorescent protein fusion gene), beta-galactosidase (LacZ) and beta-glucuronidase (GusA) reporter genes into the *F14.5L, J2R* (thymidine kinase) and *A56R (*hemagglutinin) loci respectively. Impressive anti-tumour activity was observed in preclinical models.
Material and Methods: GL-ONC1 was administered as an intravenous infusion in escalating doses (1×10^5, 1×10^6, 1×10^7, 1×10^8 and 1×10^9 plaque forming units) with three patients in each cohort on day 1 of a 28 day cycle for the first 5 cohorts. Cohort 6−7 will receive $1{,}667\times10^7$ and $1{,}667\times10^8$ pfu on days 1−3 and cohort 8 will receive 1×10^9 for 5 consecutive days. Green-fluorescent protein (GFP) imaging was performed at baseline and during each cycle on patients with superficial or mucosal lesions. Endpoints were safety, tolerability, viral replication, tumour delivery, neutralizing antibody development, anti-tumour activity and recommendation of dose for future trials.
Results: To date, 15 patients (11 males, median age 57 years) have been treated with no dose limiting toxicities (DLT) observed. Toxicities were mild (grade 1 or 2) including fatigue (n = 3), fever (n = 7), rigor (n = 1), myalgia (n = 2), flu-like symptoms (n = 2), vaccinia rash (n = 2), anemia (n = 2), oily skin/hair (n = 1) and moderate leukocytosis (n = 1). The rash comprising of vaccinia pustules was asymptomatic in one patient (grade 1) and symptomatic with itching and discomfort in the other patient (grade 2). In both patients the rash appeared in cycle 1 during the first week and resolved without treatment at the end of cycle 1. It was positive for GL-ONC1 viral plaque assay (VPA) and GFP expression. VPA of blood, urine, stool and sputum were negative for viral shedding in all except one patient which had positive viral shedding in blood, rash, stool and sputum. Blood (1 pfu) was only positive for viral shedding on day 2. Highest amount was seen in sputum (120 pfu) on day 9; all viral shedding were negative by day 13. There was an increase in neutralizing anti-GL-ONC1 antibodies in all but one patient. Best response was stable disease by RECIST observed in four patients for 3 to 6 months but one patient received 8 months of treatment.
Conclusion: GL-ONC1 is well tolerated with minimal toxicity and preliminary evidence of anticancer activity.
Trial is sponsored by Genelux. Trial identifier NCT00794131.

46 POSTER

Immunotherapy with the toll-like receptor 9 agonist MGN1703 in patients with metastatic solid tumors − clinical efficacy and immunological results of a phase I study

M.R. Weihrauch[1], M.S. von Bergwelt-Baildon[1], U. Hacker[1], H. Richly[2], U. Holtick[1], M. Tschaika[3], M. Schmidt[3], B. Wittig[4], B. Nokay[2], M.E. Scheulen[2]. [1]*University of Cologne, Department I for Internal Medicine, Cologne, Germany;* [2]*University of Essen, Department of Medicine (Cancer Research), Essen, Germany;* [3]*Mologen AG, Berlin, Germany;* [4]*Charité Universitätsmedizin Campus Benjamin Franklin, Institute for Molecular Biology and Bioinformatics, Berlin, Germany*

Background: MGN1703 is a novel synthetic DNA-based immunomodulator, which acts as a toll-like receptor 9 agonist. The antineoplastic activity of MGN1703 has been previously shown *in vitro* and in several animal models. In this clinical phase I study patients with metastatic cancer without further treatment options were treated with MGN1703.