and severe hematologic toxicities. Final results of the PK and PD will be reported.
Conclusions: CFZ is active as a single agent in relapsed solid tumors demonstrating PR in both renal (clear cell) and SCLC; and SD >16 wks in mesothelioma, ovarian, renal and NSCLC. The 20/36 mg/m^2 QDx2 dose schedule was well tolerated and lacks severe myelosuppression, hepatotoxicity and neuropathy which make CFZ an attractive agent to combine with traditional or novel targeted agents. In addition, further dose escalation is underway.

Poster presentations (Mon, 21 Sep, 09:00–12:00)
Drug development – Preclinical

1208 POSTER

Toxicity of systemic administration of blank and paclitaxel-loaded lipid nanocapsules in mice

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Background: Lipid nanocapsules (LNCs) are very promising nanocarriers (size ranging from 25 to 100 nm) containing lipophilic drugs such as paclitaxel or etoposide. The authors describe the first blank and paclitaxel-loaded LNCs preclinical toxicological studies in mice.
Materials and Methods: The study was performed on 55 nm-diameter LNCs on female Swiss mice (7 weeks; 20–22 g). LNCs formulations or saline serum were slowly injected in the lateral tail vein during a short inhalational anaesthesia induced by isoflurane. The experimental protocols were approved by the Pays-de-la-Loire ethic committee. Repeated dose toxicity studies corresponding to 12 mg/day from Day 1 to Day 5 were performed in 3 groups: blank LNCs, paclitaxel-loaded LNCs and saline serum. At Day 12, gross or histological analyses of vital organs such as liver, spleen, kidneys and lungs, complete blood counts, biological analysis (ion counts, ALAT, total bilirubin, creatinine and C-Reactive protein) were performed. Maximum tolerated dose (MTD) and 50% lethal dose (DL50) were assessed for high concentration blank LNCs and paclitaxel-loaded LNCs (12, 24, 48, 96, 192 and 288 mg/kg) in comparison with Taxol® (commercial formulation diluted at 1.2 mg/ml in saline) and saline serum in accordance with Irwin Test.
Results: No mortality was observed in repeated dose toxicity studies. Weight increase was similar in both groups. At Day 12, no abnormality was observed during autopsy. The mean weight of the organs of interest was similar ($p > 0.05$). Histological studies revealed that the livers, spleens and kidneys were normal. Complete blood counts, natremia, kaliemia, chloremia, ALAT, total bilirubin, serum creatinine and C-Reactive protein in serum were similar in both groups ($p > 0.05$). For Taxol®, MTD and DL50 were equal to 12 mg/kg and 19.5 mg/kg, respectively. MTD and DL50 of paclitaxel-loaded LNCs was equal to 96 mg/kg and 216 mg/kg. MTD of blank LNCs was equal or superior to 288 mg/kg.
Conclusion: This study demonstrates for the first time the good tolerance of systemic administration of blank and paclitaxel-loaded LNCs in mice. A five-day i.v. injection schedule does not induce any histological or biochemical significant abnormality in Swiss mice. In comparison with paclitaxel-solvent formulation Taxol®, the paclitaxel-loaded LNCs dispersion tolerance in mice was increased such that the LD50 and MTD were eightfold and eleven fold than the commercial formulation, respectively. The entrapment of paclitaxel in LNCs induces an improvement of its therapeutic index in comparison with Taxol®.

1209 POSTER

SU14813 induces mitotic catastrophe in a wide-spectrum of tumour models independently of the expression of active receptor tyrosine kinase targets

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Background: Receptor Tyrosine Kinases (RTKs) have emerged as clinically valuable drug target molecules for treating different types of cancer such as Chronic Myeloid Leukemia, Gastrointestinal Stromal Tumors and Metastasic Renal Cell Carcinoma among others. SU14813 is a novel broad-spectrum receptor tyrosine kinase inhibitor for multiple membrane RTKs such as FLT-3, VEGFR, KIT, EGFR or PDGFR, derived from the same molecular library than Sunitinib®. This new molecule has shown potent antiangiogenic and antitumoral properties, however the complete molecular mechanisms involved in its antitumoral activity, in vivo and in vitro, still remains unclear.
Methods: After incubating A549, SK-UT-1 and Jurkat cells for 24–72 hours with 1–100 μM of SU14813, western blotting, flow cytometry and citotoxicity assays were performed in order to address the possible mechanism of action associated to SU14813.
Results: SU14813 induces in multiple cell lines the formation of huge cells with numerous micronucleus. This morphological event is accompanied by an increased percentage of cell death in time. This process has been already defined as the failure of the cells to go through a complete mitosis or mitotic catastrophe, after DNA damage. In this context the cell cycle deregulation induced by SU14813 is associated with significant changes on the expression of pivotal proteins that control cellular mitosis such as cdc2, Cyclin B1 and Retinoblastoma (Rb). Moreover we show in this study how cells with defective p53 or Rb are more sensitive to SU14813-induced mitotic catastrophe and or cell death.
Conclusion: We present, to our knowledge, SU14813 as the first Tyrosine Kinase Inhibitor (TKI) that induces mitotic catastrophe (1–100 μM) in different tumor models in vitro. This cellular event is associated with changes in the activity of mitotic regulators and could play an essential role in the antitumoral activity observed in "in vivo" models treated by this compound. Moreover we do not discard that another TKIs may also act by deregulating mitotic exit depending on the dose. This work opens the possibility of combining SU14813 with inhibitors of Aurora Kinase B.

1210 POSTER

Novel nanoparticle fusion protein achieves normal P21 delivery to p53/p21 mutated tumors resulting in their eradication

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Background: Novel applications of nanotechnology present us with new opportunities and the potential to design new as well as enhance the effectiveness of current cancer treatments.
Material and Methods: We report here the creation and application of a nanoparticle fusion protein driven by the Antennapedia protein as a "Trojan horse" able to penetrate the cell membrane and intracellular compartments of cancer cells in order to deliver normal p21 to the nucleus, a known tumor suppressor protein. The fusion protein has been validated in multiple tumor models in nude mice.
Results: The fusion protein (TR1), consisting of Antennapedia and normal p21 has the ability to interfere with the cell cycle, and more specifically to antagonize and block the interaction between cyclins and cyclin-dependent kinases. TR1, has been validated in multiple tumor models *in vivo* and has demonstrated its therapeutic potential. Additionally, it is non-immunogenic and nontoxic.
Cell-based studies have shown its effectiveness in a range of human tumor types, whilst iv administration resulted in a time- and dose-dependent uptake into all tissues including regions of restricted drug delivery and access, such as the brain.
Restoration of p21 function in tumors devoid of endogenous activity resulted in growth arrest and, in combination with conventional chemotherapy, in complete tumor eradication.
Conclusions: Evaluation of this novel strategy is currently being initiated in a phase I clinical trial designed to determine, pharmacokinetics, safety profile and as to whether it has an anticancer effect in humans as it has in mice.