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Triterpene extract of Ganoderma lucidum inhibits proliferation of pre-malignant human prostate cells by regulation of epithelial mesenchymal transition

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Background: Prostate cancer is the leading cancer diagnosed in men. Ganoderma Lucidum (GL), a well known medicinal fungus, has been widely used in the treatment and prevention of many diseases, including cancer, in Asian countries. The triterpene extract of GL, has been identified as an important active ingredient possessing anti-cancer activities, through, as yet an unknown mechanism of action. The aims of our current research were to characterise the inhibitory activity of triterpene extracts of GL in pre-malignant prostate cell lines (PINs) as a potential model of chemoprevention and to investigate the mechanism of action of triterpene.
Materials and Methods: Effects on growth of PIN cell lines were measured using an "in vitro" fluorometric cell viability assay and "in vivo" growth assays. Invasive behaviour of PIN was assessed "in vitro" by using a wound healing assay, and cell branching, in a matrigel invasion assay. The effect on angiogenesis was assessed by measuring formation of tubules by human endothelial cells. To identify the cellular targets of triterpene, two-dimensional gel electrophoresis was used, and proteins showing differential expression were identified by mass spectrometry. Effects on protein expression and gene regulation were further confirmed by western blotting, quantitative RT-PCR and luciferase reporter assay.
Results: The triterpene extract of GL inhibited the "in vitro" proliferation of PINs with an IC_{50} ranging from 38.8 μg/ml to 118.8 μg/ml. In addition, triterpene (at the IC_{25}) significantly suppressed angiogenesis (>95% inhibition, $p < 0.0001$), migration (76% inhibition, $p < 0.001$) and invasion of PIN ($p < 0.001$). From proteomic analysis, two potential target proteins identified included the epithelial–mesenchymal transition (EMT) marker vimentin and the glycolytic enzyme enolase α. The down-regulation of vimentin and up-regulation of enolase α were further confirmed by western blotting. The possible role of triterpene in regulation of EMT markers including vimentin, E-cadherin and N-cadherin were also demonstrated by quantitative RT-PCR of PIN cells collected from a cell branching assay. Additionally, triterpene was found to down-regulate the protooncogene c-myc, a downstream target of enolase α.
Conclusion: These findings suggest that the triterpene extract of GL could be a promising new agent in prevention of prostate cancer by regulation of EMT and c-myc.

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Phase Ib study of plitidepsin with bevacizumab in refractory solid tumor patients (pts)

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Background: Plitidepsin (APL) is a new marine compound that induces apoptosis by increased oxidative stress and JNK pathway activation, it also, decreases both vascular endothelial growth factor (VEGF) and its receptor (VEGFR-1) mRNAs. APL, recommended dose (RD) is 5 mg/m^2/days 1 & 15 every four weeks (q4wk) when used alone for solid tumors or hematological malignancies.
Methods: Pts with advanced refractory solid tumors, adequate organ function and Eastern Cooperative Oncology Group performance status (ECOG PS) $\leqslant$ 1 received escalating doses of APL: 2.8, 3.8 and 4.8 mg/m^2 followed by fixed doses of bevacizumab (BEV) (10 mg/kg) on days 1 and 15 q4wk.
Results: 12 pts are evaluable; 50% are males with median age 54 years (r: 26−70) and 3 prior lines of therapy (r:1−6).
A median of 2 cycles was given (r: 1−7+). Relative dose intensity was 100% and 98% for APL and BEV, respectively. APL 4.8 mg/m^2 + BEV 10 mg/kg is the maximum tolerated dose (MTD), with 2/6 patients experiencing dose limiting toxicities (DLTs) [grade (G) 3 fatigue, myalgia and transaminase increase] and the RD is APL 3.8 mg/m^2 + BEV 10 mg/kg, with no pts experiencing DLTs out of 3 pts treated. Tolerance was good and toxicity was mild. No G4 events occurred. G3 toxicity was transient alanine aminotransferase (ALT) increase (n = 3), fatigue, myalgia, nausea and vomiting (n = 1 each). 4 pts are still ongoing, with 1 disease stabilization (> 6+ months) observed in a refractory renal cancer patient.
Pharmacokinetic (PK) parameters were similar to those already published for both drugs given as single agents. No relevant PK interactions were observed.
Conclusions: APL + BEV can be safely combined at almost 100% of their single-agent RD. RD is APL 3.8 mg/m^2 + BEV 10 mg/kg/d1 & 15 q4wk. Toxicity is very mild, with almost no G3/4 events observed. No PK interactions were observed or expected. Prolonged disease stabilizations are still ongoing. Further studies of this combination in specific solid tumor types are warranted.

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Anti-cancer activity of onconase, a cytotoxic amphibian ribonuclease, in combination with standard of care agents in non-small cell lung tumorgraft models

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Onconase is a cytotoxic amphibian ribonuclease and the smallest member of the RNAse A superfamily. It has been shown to possess anti-tumor activity in many preclinical studies where it demonstrates a high selectivity for cancer cells and potent anti-tumor activity. Onconase is currently being evaluating in phase I/II trials. The current study was initiated in order to identify clinical indications and drug combinations that can be pursued for the development of the compound. Biomerk Tumorgrafts™ are human solid tumors passed as heterogeneous whole-tumor fragments in immunocompromised mice and not cell line xenografts. Biomerk Tumorgraft models derived from individual patients with non-small cell lung cancer (NSCLC) were treated with Onconase combined with either cisplatin or a carboplatin–pemetrexed doublet. Results demonstrated that Onconase displays an additive and/or synergistic effect with the combinations tested. Specifically, tumor growth inhibition increased from 33−42% following treatment with carboplatin–pemetrexed to 67−85% with carboplatin–pemetrexed plus onconase, suggesting at least an additive effect. Further evaluation of Tumorgraft samples is ongoing in order to identify potential biomarkers of response that can be applied to the clinical development of Onconase with a particular focus on miRNAs. Given that Biomerk Tumorgraft models may be more predictive of clinical outcomes than traditional xenograft models, these results suggest that Onconase in combination with standard of care agents such as cisplatin and/or carboplatin + pemetrexed may be applied clinically with the potential for greater success. Overall, the application of Biomerk Tumorgraft™ models has the potential to accelerate and enhance the further development of Onconase.

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First-in-man phase I study of PM01183 using an accelerated titration design

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Background: PM01183 is a new minor groove DNA-binder with antitumor activity within nanomolar range against several tumor cell lines. This first-in-man study began in March 2009 to define the phase II recommended dose (RD).
Methods: Patients (pts) with solid tumors with adequate organ function and performance status were treated at 10 dose levels (DLs), from 0.02 mg/m^2 to 5 mg/m^2 with a 1-hr infusion every 3 wks, using an accelerated titration design. Dose escalation (100%, 50% or 25%) was done according to prior worst drug-related toxicity observed.
Results: 22 pts were treated and evaluable, 16 were males, median age was 62 (33−77). Pts received a median of 3 prior chemotherapy lines (1−6). Most pts had colorectal (59%) or pancreatic/biliary tract (23%) cancer. A median of 2 cycles (1−8) was given. DL9 (5 mg/m^2) was the maximum tolerated dose (MTD), with 1/2 pts having dose-limiting toxicities (DLTs). DL10 (4 mg/m^2/7 mg flat dose) was defined as the RD, as 4/7 pts had