anti-tumor activity of these VLA-4 antagonists through experimental models of hepatic metastasis and subcutaneous xenografts by using both murine B16 melanoma (B16M) cells and primary cultures of human malignant melanoma cells. An in vitro assay based on B16M cell adhesion to immobilized vascular cell adhesion molecule-1 (VCAM-1) substrates was performed in order to calculate the IC50 of the compound. Tumor cell proliferation and hepatic sinusoidal endothelial (HSE) cell migration assays were determined in order to examine the mechanism of action of the VLA-4 antagonists.
Results showed that when mice were treated 3 days/week intraperitoneally with 2.5 mg/kg, metastatic development decreased by 50% and 80% in mice bearing B16M cells and human melanoma cells respectively. In addition, the tumor volume was reduced by 80% and 50% in those mice inoculated subcutaneously with B16M and human melanoma cells, as compared to untreated mice. Histological analysis demonstrated that proliferating KI67 expressing cancer cells, CD31 expressing endothelial cells and smooth-alpha actin expressing myofibroblasts, significantly decreased in metastases and subcutaneous xenografts from mice receiving VLA-4 antagonist. Furthermore, in vitro assays showed that VLA-4 antagonist inhibited B16M cell adhesion to immobilized VCAM-1 in a dose-dependent manner (IC50= 4 μM). Moreover, VLA-4 antagonist inhibited tumor-induced HSE cell migration through collagen type I as well as the tumor cell proliferation in response to vascular endothelial growth factor (VEGF).
In summary, these results demonstrated that small molecule antagonists of VLA-4 possess anti-metastatic, anti-angiogenic and anti-proliferative activity and constitute novel promising agents in the chemoprevention of cancer progression.

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Therapeutic potential of YM155 alone and in combination with chemotherapeutics against human non-small cell lung cancer in carcinoma xenograft models

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Background: YM155 is a novel survivin suppressant currently in phase II trials. Consistent with the evidence that survivin is preferentialy expressed in most human neoplasms and regulates cancer cell proliferation, YM155 shows potent antiproliferative activity against various cancer cell lines and induces cell death preferentially in tumor cells rather than in normal cells. In an established human hormone refractory prostate cancer model, YM155 induces substantial tumor regression without overt toxicities. In this study, we showed the antitumor activity of YM155 alone and in combination with various chemotherapeutics in several established human non-small cell lung carcinoma (NSCLC) xenograft models.
Material and Methods: For each model, male BALB/c nu/nu mice were implanted subcutaneously with 3×10^6 cancer cells and treatment was initiated after the tumors were established (100–200 mm3).
Results: In human NCI-H358 NSCLC xenograft model, continuous infusion of YM155 (3 and 10 mg/kg/day) completely inhibited tumor growth and induced substantial tumor regression with no decrease in body weight and blood cell counts. The antitumor activity of YM155 was more potent than that of cisplatin (3 mg/kg/day, i.v., 5 times weekly), and comparable to paclitaxel (20 mg/kg/day, i.v., 5 times weekly). On the other hand, the MTD of paclitaxel-induced severe systemic toxicities as evidenced by significantly decreased body weight and blood cell counts. In a combination study using an established Calu-6 human NSCLC xenograft model, YM155 in concomitant treatment with paclitaxel, cisplatin, doxorubicin or irinotecan showed substantial tumor regression for longer periods than with each treatment administered singly. Similar findings were observed in the case of sequential treatment of YM155 with carboplatin, vinorelbine or gemcitabine regardless of the dosing sequences. When the combinational efficacy of YM155 plus docetaxel was examined with 18F-FDG-PET imaging, concomitant administration of YM155 and docetaxel significantly inhibited tumor growth and the corresponding intratumoral accumulation of 18F-FDG more extensively when compared with the each treatment administered singly. Consistent with the regression of the tumor volume, the complete inhibition of intratumoral uptake of 18F-FDG was observed only in the combination group.
Conclusions: These results suggest that YM155 is a promising candidate for NSCLC treatment as a novel apoptosis inducer with potent antiproliferative activity and no hematologic toxicity. In addition, YM155 potentiates the antitumor activity of various cytotoxics without an increase in systemic toxicity, which provides a rational approach to combination regimens of YM155 with other chemotherapeutics in clinical tumor treatment.

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Membrane androgen receptor activation triggers down-regulation of PI-3K/AKT/NF-κB activity and induces apoptotic responses via FasL, caspase 3 and Bad in DU145 prostate cancer cells

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Background: Membrane Androgen Receptor (mAR) is a novel, yet unknown G-protein coupled receptor functionally distinct from the classical intracellular Androgen Receptor (iAR). mAR is frequently over-expressed in aggressive prostate cancer and initiates rapid non-genomic signaling resulting in tumor cell death by apoptosis in both iAR-positive and iAR-negative cell lines.
Materials and Methods: Using membrane impermeable conjugates of serum albumin covalently linked to testosterone, we have evaluated the effects of mAR activation on gene products implicated in cell survival and apoptosis in iAR-negative DU145 prostate cancer cells. We have assessed the activity of PI-3K and AKT or NF-κB using either antibodies selective for the activated form of the proteins (p85/PI-3K, Ser473 and Thr308/AKT) or a kit measuring activity of NF-κB's p50 and p65 subunits. Furthermore, we have measured the expression levels of pro-apoptotic FasL, the activity of caspase 3 and the phosphorylation status of Bad upon mAR activation. Actin cytoskeleton disruptors (cytochalasin B) or ROCK inhibitors (Y-27632) previously shown to block mAR-dependent apoptosis were also included as controls.
Results: mAR activation inhibited phosphorylation of the p85 subunit of PI-3K already at 2 hours post stimulation. Similarly, Ser473 andThr308 AKT phosphorylation and NF-κB activity were significantly reduced. Testosterone-albumin conjugates induced apoptotic cell death by activating FasL expression and a FasL blocking peptide was capable of blocking mAR-dependent apoptosis. Caspase 3 activity was strongly increased and Bad was dephosphorylated. Finally, cytochalasin B and Y-27632 were capable of blocking FasL induction and caspase 3 activation in mAR-treated DU145 cells.
Conclusions: Our results provide mechanistic insights on the mAR induced apoptotic regression of prostate cancer cells and corroborate previously published observations on the potential use of mAR agonists as novel anti-tumor agents targeting key survival and apoptotic pathways in prostate cancer cells.

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Updated safety and efficacy data from a first-in-human, first-in-class, phase I study of Hedgehog pathway antagonist, GDC-0449

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Background: Aberrant Hedgehog (Hh) signaling pathway activation via both Hh ligand-independent and ligand-dependent mechanisms has been implicated in a variety of cancers including basal cell carcinomas (BCC) and medulloblastoma. GDC-0449 is a potent oral systemic inhibitor of Hh signal transduction. Efficacy in advanced BCC patients and an unusually long half-life and plasma accumulation of GDC-0449 have been previously reported.
Methods: Pts with advanced solid tumors were enrolled in a phase 1 study to evaluate safety, tolerability PK, and pharmacodynamics at one of 3 dose levels: 150, 270, or 540 mg GDC-0449 orally. Surrogate tissue was assessed for expression levels of Hh target gene, GLI1.
Results: To date, 40 pts have been enrolled (01MAY08 data cutoff date): 150 mg (n = 25), 270 mg (n = 11), 540 mg (n = 4); days on study (range 10+ – 465+ d, median 60 d). There have been no dose-limiting toxicities. Possibly drug-related Gr 1−2 AEs include alopecia, anorexia, arthralgia, dermatitis acneiform, dysgeusia, dyspepsia, fatigue, hypoesthesia, hypomagnesaemia, hyponatremia, madrosis, nausea, skin exfoliation, vomiting, and weight loss. Drug-related reversible AEs of Gr 3 hyponatremia (n = 2) and fatigue (n = 1) were reported. In 12 pts with BCC and medulloblastoma (tumors likely to harbor Hedgehog pathway mutations), 6 PRs (2 RECIST, duration 164+ and 293+ days; 4 clinical exam, duration, 113+ – 214+ d), 2 SDs (duration, 147+, 158+ d), and 1 PD were reported; 3 pts are too early to evaluate. Updated safety and response data for all patients will be reported. GDC-0449 showed a prolonged terminal half-life (>7 days) and drug accumulation, resulting in