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A phase I study of IMGN388, an antibody drug conjugate targeting α_v integrin, in patients with solid tumors

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Background: IMGN388 is a novel antibody–drug conjugate (ADC) composed of an α_v integrin-targeting fully human antibody and the maytansinoid, DM4, attached via a covalent bond. Its target is expressed in a wide variety of solid tumors and also on endothelial cells in the process of forming new blood vessels. In preclinical testing, IMGN388 has both anti-angiogenic and direct cytotoxic effects with strong activity against human xenograft lung, colon, pancreatic, ovarian and breast tumors in nude rat models.
Methods: In this first-in-human, phase I dose-escalating study, IMGN388 is administered to patients with advanced solid tumors using a standard 3 + 3 design. The primary study objectives are to establish the maximum tolerated dose and evaluate the safety and pharmacokinetics (PK) of IMGN388 when given intravenously every 3 weeks. Secondary objectives include evaluation of pharmacodynamics, immunogenicity and preliminary activity.
Results: A total of 35 patients (14M, 21F, median age = 63) have received the study drug at doses ranging from 5–160 mg/m^2. Most adverse events (AEs) have been Grade 1 or 2; the most common related events include nausea (26%), vomiting (23%), headache (13%), anorexia (13%), diarrhea (6%), fatigue (6%) and peripheral neuropathy (6%). There have been no related grade 4 AEs. One patient had grade 3 nausea/vomiting. One dose-limiting toxicity has been observed; grade 3 headache with confusion 24 hours after the first infusion of IMGN 388 at a dose of 45 mg/m^2. Subsequent patients have received steroid prophylaxis and no further grade 3/4 headache has been noted. There has been no evidence of human anti-human or anti-maytansinoid antibody formation (data available for doses up to 105 mg/m^2). Preliminary PK reveals an elimination phase $t_{1/2}$ of approximately 28 hrs; maximal plasma concentration increases in a generally dose-proportional manner. Five patients (breast, prostate, neuroendocrine, and 2 NSCLC) treated at doses $\geqslant$ 45 mg/m^2 have acheived stable disease for $\geqslant$4 cycles; two of these patients remain on therapy in cycles 6 and 8, respectively.
Conclusions: IMGN388 has been well tolerated at the doses tested. Dose escalation is ongoing. Updated results including α_v integrin expression data by immunohistochemistry will be presented.

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Mesenchymal stromal cells enhance the malignant potential of human colorectal cancer cells by inducing epithelial–mesenchymal transition (EMT)-related phenomena

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Background: Mesenchymal stromal cells (MSCs) are recruited to primary and metastatic sites of several tumour types, including colorectal cancer (CRC), and might contribute to tumour progression. The actual role played by MSCs and the mechanisms underlying MSC-tumour interactions remain to be clarified. We investigated the effects of human bone-marrow-derived MSCs (BM-MSCs) on CRC, *in vitro* and *in vivo*.
Material and Methods: Human established CRC cell lines were cultured in the presence or absence of BM-MSCs, in direct contact or in transwell plates. After a five day culture, tumour cell proliferation was assessed by differential cell counts, surface molecule expression was analyzed by flow cytometry, and production of soluble factors in culture supernatants was measured by Raybio antibody array® and ELISA. Tumour cells, sorted upon co-culture by flow cytometry, were evaluated for the expression of EMT-related genes by quantitative PCR and for *in vitro* invasiveness, by chemoinvasion assay. Furthermore, their tumorigenicity was assessed upon injection in NOD/SCID mice and developing tumours were analyzed by immunofluorescence.
Results: MSCs significantly increased tumour cell proliferation and decreased CD44 expression, independently of cell-to-cell contact. Analysis of co-culture supernatants revealed higher amounts of IL-6, MCP-1, RANTES and Angiogenin, in comparison to supernatants derived from single cultures. Moreover increased expression of several EMT-related genes, including SNAI2, TWIST, N-Cadherin, was detected on CRC cells sorted upon co-culture as compared with controls. Importantly, CRC cells co-cultured with MSCs showed higher invasive behaviour *in vitro*, than CRC cells cultured alone. No significant changes were observed in tumorigenicity. However, tumours originated from tumour cells co-cultured with MSCs showed a significantly higher vessel density as compared to controls.
Conclusions: MSCs reduce adhesiveness, induce expression of EMT-related genes and increase proliferation, invasiveness and angiogenic potential of CRC cells. These effects might contribute to CRC progression and spreading.

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The role of epithelial to mesenchymal transition (EMT) in the establishment of colorectal liver metastases. A potential source of prognostic biomarkers

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Background: Understanding of the biological processes involved in the development of metastatic cancer continues to develop, and the importance epithelial to mesenchymal transition (EMT) is well established. Several markers of EMT are recognised including various cytokines, transcription factors and markers of cell adhesion. Colorectal cancer will commonly metastasize to the liver but why some primary and secondary cancers behave in a more aggressive way is not fully understood.
Materials and Methods: A series of 20 colorectal liver metastases (LM) were obtained from surgical resection specimens, as well as 13 unmatched colorectal primary cancers (CPCs). Normal tissue was also retrieved from colon and liver. The expression of 13 key EMT genes were quantified by RT-PCR.
Results: LM samples were initially grouped according to the size and by number of synchronous metastases, being known predictive factors of recurrence and survival in LM. However, EMT profiles were similar across these groups. We then grouped LM by the Dukes stage of the primary cancer from which it arose, with Dukes A and B (LMAB) together (localised) and C and D (LMCD) together (metastatic biology). We saw that LMAB had up-regulation of EMT markers compared to LMCD with a significant increase in vimentin, s100a4 and TGFβ1 ($p < 0.05$).
When LMAB were compared to normal colon a strong EMT profile was seen, with significant down-regulation of E-cadherin and up-regulation of MACC1, HGF2, c-Met, Snail, vimentin, s100a4 and TGFβ1.
LMCD demonstrated a less robust profile with significantly reduced E-cadherin and raised cMET and MACC1, but reduced Slug and MMP-2.
In CPCs we found that EMT profiles were similar in Dukes AB (CPC AB) and Dukes CD (CPC CD) cancers, with both up-regulating MACC1 and c-Met. E-cadherin reached significant down-regulation in CPC AB and MMP2 was down-regulated in CPC CD.
When LMAB was compared to CPC AB we saw up-regulation of EMT markers in LMAB reaching significance for TGFβ1 and approaching significance in vimentin ($p = 0.056$) and s100a4 ($p = 0.073$). LMCD and CPC CD had very similar profiles.
Conclusions: LM are likely to arise from an aggressive sub-population of low stage CPC and this aggressive phenotype can be detected by EMT profiling. As expected, low stage CPCs selected from the general population do not express such an aggressive phenotype.
EMT markers may have a role in detecting aggressive primary cancers in low stage disease that may benefit from adjuvant treatment.

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Protease nexin 1 cleavage by MMP-9 modulates prostate cancer cell proliferation and tumorigenesis via regulation of the hedgehog pathway

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Background: The Hedgehog (HH) pathway is implicated in the growth and metastasis of prostate cancer cells. We report that increased expression of protease nexin 1 (PN1), an extracellular matrix (ECM) protein and serine protease inhibitor, reduces HH mediated signalling by reduction of the HH ligand, Sonic. We also show that PN1 levels are regulated by MMP-9 mediated cleavage.
Methods: Alterations in PN1 and MMP-9 in metastatic prostate cell lines PC3 were used to determine their effect on Hedgehog signalling. We used intraprostate injection followed by magnetic resonance imaging and