and weight loss 7C10 was humanized and h7C10 shares the same *in vivo* properties as 7C10. The present results indicate that the humanized anti-IGF-IR antibody h7C10 has a great potential for cancer therapy.

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A phase Ib study of pertuzumab (P), a recombinant humanized antibody to HER2, and capecitabine (C) in patients with advanced solid tumors

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Background: P represents the first in a new class of targeted therapeutics known as HER dimerization inhibitors (HDIs). It blocks ligand-associated heterodimerization of HER2 with other HER-kinase family members (HER1, HER3 and HER4), and thereby inhibits intracellular signaling through MAPkinase and PI3kinase. This phase Ib study of the combination of P and C is being performed to determine the maximum tolerated dose (MTD), to assess the safety profile and dose limiting toxicities (DLTs), to evaluate if there is pharmacokinetic (PK) interaction of the combination and to determine any anti-tumor activity.
Patients and Methods: DLT is assessed in cycle 1 and is defined as: non-hematological toxicity $\geqslant$ grade 3, grade 4 neutropenia of > 7 days, thrombocytopenia grade 4 or any thrombocytopenia requiring platelet transfusion, any subjectively intolerable toxicity felt to be related to either one of the compounds. If DLT is observed in $\geqslant$ 2 pts out of 6 pts at a dose level, the MTD has been exceeded. Selection criteria are: performance status (PS) ECOG 0 or 1, measurable or evaluable disease, baseline LVEF $\geqslant$ 50%, adequate bone marrow-, hepatic- and renal function, no prior therapy with C, other oral fluoropyrimidines or infusional 5-FU > 48 hrs, no history of cardiac failure or poorly controlled cardiovascular disease. Patients are treated with a fixed dose of 1050 mg of P administered as an IV infusion on day 1, and C administered orally bid on days 1–14, q 3 weeks. In combination with P, three dose levels of C are explored: 825, 1000, and 1250 mg/ m* bid.
Results: To date, a total of 7 pts (2 male/5 female) have been included. Mean age 59 years (range 39–68), ECOG PS 0/1: 4/3 pts. Tumor types: breast, ovarian, hepatocellular, colorectal, prostate, fallopian tube and pancreatic cancer. To date, 5 pts have been treated at dose level 1 and 2 pts at dose level 2. A total of 16 cycles have been administered, median 2 (range 1–5). No DLTs have been observed. Most frequent toxicities included: diarrhea, hand-foot syndrome and asthenia, all of grade 1 or 2, in 44%, 31% and 44% of cycles, respectively. Other toxicities were nausea, vomiting, anorexia and mucositis, all of grade 1, in 6% of cycles each. Preliminary data of 2 pts in the first cohort suggest that PK parameters of C are not altered in combination with P. Tumor assessment has been performed in 5/7 pts: 3 pts had stable disease and 2 progressed.
Conclusion: MTD is to be determined and recruitment is ongoing. Results will be updated at the meeting.

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A trivalent bispecific fusion protein produced in myeloma cells for improved pretargeting and therapy of CEA-expressing cancers

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Background: A novel trivalent bispecific agent for improved pretargeted delivery of radionuclide payloads carried by bivalent haptens to tumors expressing carcinoembryonic antigen (CEA) has been produced in myeloma cells. Pretargeting with BS14HP, a trivalent bispecific fusion protein expressed in *Pichia pastoris*, which binds divalently to CEA, resulted in a 3-fold increase in tumor uptake of radio-peptide as compared to constructs with monovalent CEA binding. Here, a construct similar in design to BS14HP was produced in myeloma cells.
Methods and Results: hBS14 is an 80-kDa recombinant fusion protein consisting of two heterologous polypeptide chains associated non-covalently to form two binding sites for CEA from the variable domains of hMN-14 (a humanized anti-CEA antibody; labetuzumab) and one binding site for histamine-succinyl-glycine (HSG) from the variable domains of h679 (a humanized anti-HSG antibody). The V-domains were engineered into a single DNA construct that was stably transfected into SP2/0 cells. Bispecificity was demonstrated on BIAcore using an HSG-coupled sensor chip by measuring the additional increase in response units upon successive injections of hBS14 followed by an anti-id antibody to hMN-14. SE-HPLC analysis of the binding between CEA and hBS14 demonstrated two functional CEA binding groups of hBS14. The efficacy of hBS14 for tumor pretargeting was evaluated in CEA-expressing GW-39 human colonic tumor-bearing nude mice using a bivalent HSG hapten (IMP-245) labeled with ^{99m}Tc. Forty-eight hours after mice were given the hBS14, the ^{99m}Tc-peptide was administered. Animal groups were then imaged at 1, 3, and 24 h, or necropsied at 1, 4, or 24 h. Excellent high contrast images were obtained as early as 1 h after injection of ^{99m}Tc peptide, with tumor uptake at 21% [$\pm$ 2.5] ID/g while other tissues such as liver (1.1%ID/g) and blood (1.6%ID/g) showed very low activity. Although IMP-245 is excreted very rapidly by urinary clearance, tumor/kidney ratios were 2.7 [$\pm$ 0.5] allowing for clear delineation of the tumor compared to the kidney. Image contrast improved over time with only tumor signal detectable after 24 h.
Conclusion: These results indicate that hBS14 is an attractive candidate for use in a variety of pretargeting applications, particularly tumor therapy with radionuclides and drugs. The very early visualization of tumors suggests that this technique could be used with SPECT and PET imaging systems with a suitably radiolabeled peptide. [Supported in part by PHS grant EB002114.]

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Peptide-targeted alpha-radiation for melanoma therapy

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A unique combination of a melanoma targeting peptide and an α-particle-emitting radioisotope were investigated for their melanoma therapy potential. The alpha-emitting radionuclide ^{212}Bi was targeted to melanoma tumors by the DOTA-ReCCMSH peptide, which binds melanocortin-1 receptors expressed on melanoma cells. Radiotherapeutic treatment of relatively radio-resistant melanoma cells with peptide targeted alpha particles is attractive due to the high linear energy transfer properties of alpha radiation: dense ionization with irreparable DNA double strand breaks, lack of oxygen effects and enhanced efficiency by cell internalization of peptide. The DOTA-ReCCMSH peptide was radiolabeled with ^{212}Pb in a 0.05 M NaOAc solution at pH 5.5 at 85ºC for 45 min. The ^{212}Pb[DOTA]-ReCCMSH product was purified by reverse phase high performance chromatography and stabilized in buffered saline with ascorbic acid. Lead-212 ($t_{1/2}$=10.6 h) is the parent of ^{212}Bi ($t_{1/2}$=60.6 min) that decays to stable ^{208}Pb via an alpha beta decay sequence. The radioisotopes were eluted from a ^{224}Ra-^{212}Pb/^{212}Bi radionuclide generator. Biodistribution and therapy studies were performed in a B16/F1 melanoma bearing C57 mouse flank tumor model.
Biodistribution studies demonstrated that the radiolabeled peptide rapidly accumulated in the tumor reaching a maximum level of 13.49% injected dose per gram (ID/g) at 5 min. Tumor activity levels remained constant over 4 hrs then gradually declined to 4.59% ID/g 24 h post injection. Normal organ disappearance was rapid as the peptide is primarily cleared by the kidneys. The radiation dose delivered to the tumor was estimated to be 61 cGy/uCi ^{212}Pb administered.
Therapy studies were performed in tumor bearing mice 4 days post melanoma cell implantation when tumors were palpable. Groups of mice (n=8–10) were given 50, 100 and 200 uCi of ^{212}Pb[DOTA]-ReCCMSH or a saline placebo via the tail vein. The mice tolerated all dose levels with no observable signs of acute toxicity. Survival data were evaluated according to the method of Kaplan and Meier. Placebo treated mice had a 14.6 day mean survival. Treatment with 50 uCi and 100 uCi doses extended mean survival to 22.0 days (p=0.004) and 28.0 days (p=0.002), respectively. The 200 uCi treatment group exhibited the best survival statistics (45.0 days mean survival, P=0.01). Forty-four percent of the mice receiving a 200 uCi dose and twenty percent of the mice from the 100 uCi treatment group were free of tumor and survived the entire 100 day study. These striking results highlight the therapy potential of peptide-targeted α-radiation for malignant melanoma.