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PHASE I OPEN STUDY OF THE EFFECTS OF ASCENDING DOSES OF THE CYTOTOXIC IMMUNOCONJUGATE CMB-401 (HCTM01-CALICHEAMICIN) IN PATIENTS WITH EPITHELIAL OVARIAN CANCER. *A.M. Gillespie, T.J. Broadhead, S.Y. Chan, J. Owen, A. Farnsworth, M. Sopwith and R.E. Coleman. YCRC Dept. Clinical Oncology, Weston Park Hospital, Sheffield, U.K. Dept. Clinical Oncology, City Hospital, Nottingham, U.K. Celltech Therapeutics Ltd., Slough, U.K.*

We have performed a Phase I study of the cytotoxic immunoconjugate CMB-401 (hCTMO1-calicheamicin) in women with epithelial ovarian cancer (EOC). hCTMO1 is a genetically engineered human antibody directed against polymorphic epithelial mucin which binds preferentially to EOC (tumour:blood ratio 8:1 - *Cancer Res 1996;56:5179–518*). The objectives of this two centre study were to identify end-organ toxicities and to establish maximum tolerated dose (MTD). Tumour response was also monitored. 34 patients were recruited with satisfactory WHO performance status, aged 20–75 years and with progressive EOC not amenable to platinum/standard therapy. Patients had received a mean of 3.2 previous chemotherapeutic regimens with a median interval since last chemotherapy of 182 days (range 34–1217). Patients received upto four cycles of a dual infusion of 35mg/m^2 hCTMO1 'pre-dose' followed by ascending doses of CMB-401 - a regimen which minimises drug uptake in normal tissues whilst enhancing delivery to the ovarian tumour. CMB-401 dosing commenced at 2mg/m^2 and progressed via seven cohorts to 16 mg/m^2. CMB-401 was generally well tolerated. Transient malaise and emesis occurred, necessitating routine prophylaxis. WHO grade 3/4 toxicities, irrespective of causality, included: haematological (anaemia 21%, granulocytopenia 9%, thrombocytopenia 9%); liver and renal (transaminases 3%, alkaline phosphatase 6%, urea 3%); sepsis 3%; haemorrhage 6%; nausea/vomiting 76%; pulmonary 6%; conscious state 6%. MTD was defined at 16mg/m^2 by malaise, haematological toxicities and the experience of gastro-intestinal haemorrhage. During the study four patients had a greater than 50% reduction in CA125, and four patients had imaging evidence of reduction in tumour bulk. CMB-401 appears to have an acceptable toxicity profile with initial evidence of activity against EOC. Development will continue in a Phase II study.

*1687

PHASE I DOSE ESCALATION TRIAL OF PRETARGETED RADIOIMMUNOTHERAPY (PRIT) WITH YTTRIUM 90. *A. Murtha, P. Weiden, S. Knox, H. Breitz, M. Goris, D. Axworthy, C. Seiler, P. Beaumier, K. Bryan, J. Reno. Stanford University, Stanford, CA; Virginia Mason Medical Center and NeoRx Corp, Seattle, WA.*

The efficacy of conventional radioimmunotherapy in the treatment of human cancer is limited by inadequate localization of antibody in tumor and toxicity to marrow from circulating radioactivity. PRIT offers the advantages of (1) rapid, efficient, specific, and stable binding of tumor localized antibody receptor, and (2) rapid elimination of radioactivity from the whole body. We pretargeted epithelial tumors with a conjugate of a pancarcinoma-reactive monoclonal antibody (NR-LU-10) and streptavidin to act as a prelocalized, tumor-specific high affinity receptor. Forty-eight hours later the remaining circulating conjugate was cleared with biotinylated human serum albumin. Finally 24 hours later radioactivity was delivered using a small molecule ^{90}Y-DOTA-biotin ligand. After preliminary Phase I studies to optimize the doses and timing of the components of this PRIT regimen, 40 patients with refractory epithelial neoplasms (11 ovary, 10 colon, 9 prostate, 6 breast, 4 misc) were injected with increasing doses of ^{90}Y. Dosimetry estimates for normal tissues and tumor were obtained. Of 33 patients currently evaluable for response, there were 2 partial responses (prostate and ovary), 4 minor responses (2 ovary, 1 colon, 1 prostate) and 9 patients with stable disease. Toxicity has consisted of nausea and vomiting (Grade I/II, 20 pts; Grade III/IV, 3 pts); elevated liver function tests (Grade I/II, 16 pts; Grade III/IV, 2 pts); thrombocytopenia (Grade I/II, 9 pts; Grade III/IV, 7 pts); neutropenia (Grade I/II, 8 pts, Grade III/IV, 4 pts); and diarrhea (Grade I/II, 6 pts, Grade III/IV, 4 pts). The dose limiting toxicity of this PRIT was diarrhea at a dose level of 140 mCi/m^2 ^{90}Y. Phase II trials of ^{90}Y PRIT at 120 mCi/m^2 are planned in patients with prostate, colon or small cell lung cancer.

*1688

N7: COMBINATION CHEMOTHERAPY, RADIOIMMUNOTHERAPY AND ADJUVANT ANTIBODY THERAPY FOR HIGH-RISK NEUROBLASTOMA (NB). *N.K. Cheung, B. Kushner, M. LaQuaglia, K. Kramer, S. Gollamudi, G. Heller, D. Wuest, M. Byrnes, W. Gerald, S. Yeh, R. Finn, S. Larson, I. Cheung, N. Rosenfield, S. Abramson, R. O'Reilly. Memorial Sloan-Kettering Cancer Center, New York, NY.*

N7 protocol builds on the N6 approach (JCO 12:2607, 1994, 40% progression-free (PF) survivors at 66 mo median followup) which utilizes dose-intensive cyclophosphamide (CPM), doxorubicin, Cisplatin and VP-16 to achieve rapid cytoreduction, plus 400 mg/m^2 anti-G_{D2} monoclonal antibody 3F8 to eradicate microscopic disease. Distinct from N6, the addition of 20 mCi/kg of ^{131}I-3F8 replaces conventional myeloablative chemotherapy/TBI. Complete primary tumor resection is integrated with 7 courses of chemotherapy: #1, #2, #4, and #6 include CPM 70 mg/kg/d ×2 (with mesna) and 72-hr continuous infusion of doxorubicin 75 mg/m^2 plus vincristine 2 mg/m^2; #3, #5 and #7 contain Cisplatin 50 mg/m^2/d ×4 and VP-16 200 mg/m^2/d ×3. Courses start when ANC reaches 500/μL and platelet counts exceed 100k/μL. G-CSF is given 24 hrs after chemotherapy until ANC recovers to >500/μL. 21 Gy is administered to the primary and metastatic sites to ensure local control. Among 24 consecutive patients (pts) newly diagnosed at >1 y of age (median age 3 y, 22 stage 4, 2 stage 3U with MYCN amplification) most had metastases to marrow (17/24) and bones (18/24). Thirteen pts had elevated serum ferritin >142 ng/ml; 11 MYCN amplification ≥10 copies, and 8 with serum LDH > 1500 IU/mL. 16 pts have completed chemotherapy achieving CR/VGPR in 15/16. 12 pts have completed ^{131}I-3F8, and 8 pts all treatment. 20 pts (83%) are PF (median followup 12.3 mon, 2 CNS relapse, 2 PD on therapy). Compared to N6, peripheral neuropathy was decreased. Acute toxicities of 3F8 were pain, fever and urticaria; thyroid was protected during ^{131}I-3F8 treatment by SSKI, Cytomel and perchloracap. All pts required intensive antibiotic, nutritional and blood transfusion support. Optimally-timed 3F8 treatment for in vivo and in vitro purging will allow earlier harvest of CD34+ stem cells and accelerate the eradication of microscopic disease.

*1689

RANDOMIZED PHASE II STUDY OF ALL-TRANS RETINOIC ACID (ATRA) ± α INTERFERON (IFN) IN SQUAMOUS CELL CARCINOMA (SCC). *C. Domenge, A.Le Cesne, P. Pautier, A. Kramar, T.Le Chevalier, N. Bouvet, L. Thill, B. Escudier. I.G. Roussy, Villejuif and Roche Company, France.*

Based on previous in vitro and in vivo data demonstrating synergy between IFN and retinoids in SCC, we designed a randomized phase II study comparing ATRA alone or associated with IFN in metastatic patients (pts) with SCC of head and neck (HNC), lung (NSCLC) and cervix cancers (CC). *Methods:* pts were randomly treated with either ATRA, 45 mg/m^2/d p.o. for 7 d every other week, or ATRA (same regimen) plus subcutaneous IFN (Roferon, Roche) 9.10^6 IU 3 times a week, every week, until progression of the disease or unacceptable toxicity. Tumor evaluation was repeated every 6 weeks. *Results:* 48 pts have been enrolled in this study. All the pts with NSCLC and CC had been previously treated, while all but 2 pts with HNC were untreated. As initially designed, an interim analysis after enrollment of 18 pts in each arm demonstrated the lack of response in the ATRA alone arm; we thus stopped this arm and are continuing the study as a phase II study of ATRA + IFN association. Tolerance was satisfactory, and toxicity was mainly attributable to IFN. ATRA induced around 50% of skin toxicity ≤ grade 2 and few cases of mild hypertriglyceridemia. Among 30 pts treated in the combined arm (HNC = 15, NSCLC = 8, CC = 7), we observed 2 responses in HNC (1 CR and 1 PR) but none in NSCLC and CC. The 2 responders were previously untreated and had lung metastases. *Conclusion:* ATRA alone is not active in SCC. Moreover, despite some minor activity in non pretreated HNC, ATRA combined with IFN is poorly efficient in SCC.