showed pronounced tumour regression, causing complete and sustained eradication of the tumour in 3/7 mice. Median survival in the combination group was 45 days after start of treatment, compared to 9 days for untreated mice, 11 days for mice receiving immunotherapy and 17.5 days for mice in the radiation group.
Conclusions: These findings highlight that integration of immunotherapies with standard cancer therapies such as radiation creates highly synergistic anti-tumour effects, that may have the potential to enable long-term survival in cancer patients and ultimately to open a therapeutic avenue to cancer cure.

1254 POSTER

DNA Vaccine Expressing Alpha-fetoprotein With the Degradation Signal From Ornithine Decarboxylase Provides Notable Protective Immunity Against Hepatocellular Carcinoma in Mice

A. Morozov[1], V. Morozov[2], T. Astakhova[3], A. Timofeev[1], V. Karpov[4]. *[1]Engelhardt Institute of Molecular Biology RAS, CSF, Moscow, Russian Federation; [2]Robert-Koch Institute, p13, Berlin, Germany; [3]N.K. Koltsov Institute of Developmental Biology RAS, Biochemistry, Moscow, [4]Engelhard Institute of Molecular Biology RAS, CSF, Moscow, Russian Federation*

Background: Alpha-fetopotein (AFP) is a marker of hepatocellular carcinoma (HCC). DNA vaccines against AFP were shown to generate strong immune response. Previously we demonstrated that DNA vaccine bearing HIV-1 reverse transcriptase (RT) gene and mouse ornithine decarboxylase (ODC) degradation signal at the 3′-end induced a strong Th1 immune response against RT HIV-1 in mice. We proposed that the DNA vaccine bearing AFP which is directed for degradation in proteasome would induce strong CD8+CTL response against tumour cells expressing AFP and might be efficient in preventing HCC.
Materials and Methods: Vectors expressing the following proteins were designed: murine AFP (mAFP), mAFP lacking exportation signal (pΔAFP), mAFP+ODC degradation signal (pAFPODCsignal), mAFP+ODC degradation signal but without exportation signal (pΔAFPODCsignal). After transfection of 293T cells the protein expression was examined by SDS-and Native PAGE and Western blot. The efficacy of proteasomal degradation was evaluated by cycloheximide chase, proteasome inhibition assay and immunofluorescence. Proteins in transfected cells were also examined by confocal microscopy using anti-AFP and anti-calnexin antibodies. Tumours in C57BL mice were induced by subcutaneous admittance of 2×10^5 hepatoma cells from Hepa 1−6 cells line. Vaccine trials were performed on mice. In therapeutic trial [48 animals: 6 groups (8 mice in each)] 14 days after tumour cell challenge mice were vaccinated intramuscularly with 100 μg of plasmid. In “prevention” trial (18 mice: 3 groups) mice were vaccinated four times (50 μg, 2 week intervals) and 2 weeks after the last vaccination were challenged with tumour cells.
Results: All plasmids were well expressed in transfected cells, but only the ΔAFPODCsignal protein degraded fast in the proteasome (half life 1.5−2h). pΔAFPODCsignal was further used in animal trail. No significant protection was demonstrated in the therapeutic experiment. However, preventive vaccination trial yielded 300% reduction in mean tumour volume compared to the control group and 500% reduction compared to the non-immunized group on day 65 after tumour cell challenge.
Conclusions: The ΔAFPODCsignal is fast degrading protein that provokes immune response resulting in retardation of tumour growth in vaccinated animals. We considered pΔAFPODCsignal a promising candidate vaccine against HCC.

1255 POSTER

Outcomes in Patients 70 Years and Older Enrolled in Phase I Studies at Vall D'Hebron University Hospital

R. Morales Barrera[1], O. Castillo-Fernández[2], I. Braña[1], R. Dienstmann[1], J. Cortes[1], E. Felip[1], J.M. Del Campo[1], J. Carles[1], J. Rodon[1], J. Tabernero[1]. *[1]Vall d' Hebron University Hospital, Medical Oncology, Barcelona, Spain; [2]National Oncology Institute, Medical Oncology, Panama, Panama*

Background: Patients aged ⩾70 years are generally underrepresented in cancer clinical trials and little is known about outcomes in this population in phase I trials.
Methods: Data were collected from 246 eligible patients treated in Phase I trials with multiple agents between 2005 and 2007. We compared results between two subgroups: pts <70 years (n = 97) and pts ⩾70 years (n = 49) using Fisher, Mann-Whitney U, Kaplan Meier and log rank tests.
Results: Median age was 61.7 years. 20% patients were ⩾70 years. There were no differences in baseline and treatments characteristics between both groups (gender, ECOG PS, previous treatment lines, metastatic sites, Royal Mardsen Hospital Prognostic Score Index, time to diagnosis of advanced disease and phase I trial enrolment, treatment duration, type of trial − single agent or combination). Toxicity was the main reason for discontinuation of treatment in 6% of patients ⩾70 years versus 8.6% the younger patients (p = 0.40). Partial response/stable disease as best response was 47% in <70 years and 51% en ⩾70 years (p = 0.39). Median survival in elderly patients was 34.9 weeks (CI 14.3–53.4) and in younger patients was 40.4 weeks (CI 31.0–49.7) log rank test=0.13. Analysis of the elderly patient cohort found that those that had received more than three previous lines of therapy (HR 2.0, 95% CI 1.11–3.74), had lung metastasis (HR 1.89 95% CI 1.03–3.48), and high white blood cell count (⩾10,500/mm$^{3)}$ (HR 3.7 95% CI 1.36–10.15) were associated with worse outcome.
Conclusion: Elderly patients suitable for Phase I studies have similar outcomes as compared to younger patients. Age by itself should not be an absolute contraindication to enrol patients in Phase I trials.

1256 POSTER

Evaluation of Enrollment in Oncology Phase I Clinical Trials

A.J. van der Biessen[1], M.A. Cranendonk[1], B. van der Holt[2], J. Verweij[1], M.J.A. de Jonge[1], R.H.J. Mathijssen[1]. *[1]Erasmus MC University Hospital, Medical Oncology, Rotterdam, [2]Erasmus MC University Hospital, Trials and Statistics, Rotterdam, The Netherlands*

Background: Trial participation of cancer patients (pts) lacking standard treatment options is crucial for the development of new anti-cancer drugs. The main reasons to participate are hope for remission or even cure. The aim of this study was to increase insights into motives and other variables influencing pts to participate in phase I oncology trials.
Methods: Over 2 years, all pts with advanced solid tumours, referred to our outpatient clinic to be informed about phase I trials, were included. Pts were seen by a staff-physician or nurse practitioner during a 40-min intake and if applicable, they received written information about a phase I study. During (a) successive visit(s), patient and physician decided if he/she was or was not willing and able to participate. In our evaluation, we included the following variables: ways of referral, distance from residence to hospital, tumour type, time since primary diagnosis, number of prior treatments (both regular and experimental), WHO performance status at visits, age, gender, and marital status. In addition, specific reasons for refusing informed consent were scored. Data were first compared between patients who did, or did not, give informed consent to participate in a trial. Next, the same analyses were performed, restricted to patients who gave informed consent, and data were compared between patients who actually did or did not start phase I treatment.
Results: Between Oct 2008 and Dec 2010, a total of 366 pts (189 men, 177 women) were evaluated, with a median age of 59 years (range, 18−78), and median WHO performance of 1. Most tumours originated from the GI tract (45%). Of all pts 71% was treated before, with a median of 2 treatment lines (range, 1−7). Informed consent was not signed by 146 pts (40%) of which 54% refused mostly because of disappointing expectations of the treatment, and fear for side effects/condition. Patients already treated with multiple lines gave informed consent more often than others (P < 0.001). After signing informed consent another 10% was not eligible according to protocol criteria and 7% due to clinical deterioration. Finally 43% participated in a phase I trial.
Conclusion: Despite specific referral to our hospital, more than half of all pts that were informed about a phase I trial finally did not participate. Reasons for both participating and not participating were quite diverse. Possibly, enrollment can be increased by referral to a dedicated and experienced trial-team.

1257 POSTER

Phase I Safety and Tolerability Study of Olaparib (AZD2281) in Combination With Liposomal Doxorubicin (PLD) in Patients With Advanced Metastatic Solid Tumours

C. Sessa[1], R. von Moos[2], T. Digena[1], G. Del Conte[3], L. Viganò[3], E. Gallerani[1], R. Cathomas[2], A. Fasolo[3], D. Schneider[4], L. Gianni[3]. *[1]Oncology Institute of Southern Switzerland, Bellinzona, [2]Kantonsspital Graubünden, Chur, Switzerland; [3]San Raffaele Institute, Department of Medical Oncology, Milan, Italy; [4]AstraZeneca AG, Zug, Switzerland*

Background: Olaparib (O) is an orally active PARP inhibitor shown to be an active and well-tolerated monotherapy in patients with *BRCA*-mutated ovarian and breast cancer.
Methods: Phase I, open-label, ascending (3+3 design) dose cohort study evaluating the safety and tolerability of O combined with PLD (ClinicalTrials.gov NCT00819221). Patients (Pts) with advanced metastatic solid tumours received oral O bid in combination with PLD (40 mg/m^2 IV every 28 days). O 50 mg (for 7 days) was assessed followed by parallel

escalation of the O dose (100, 200 and 400 mg) and dosing duration (28-day cycle), ie the 7-day schedule was tested first and, if proven tolerable, the same dose given for 28 days and a higher dose given for 7 days were assessed concurrently, in separate cohorts. Primary objective was to determine the MTD of O combined with PLD based on treatment-related DLTs occurring during the first 28-day treatment cycle. Secondary and exploratory objectives included assessment of O PK alone and in combination with PLD, and antitumour activity. Interim review was for safety and efficacy.
Results: At 2 March 2011, 44 pts (male/female 2/42; ECOG performance status 0/1, 77%/23%) were enrolled and received treatment with O and PLD 40 mg/m^2 (n = 3 O 50 mg 7 days; n = 3 O 100 mg 7 days; n = 4 O 100 mg 28 days; n = 3 O 200 mg 7 days; n = 7 O 200 mg 28 days; n = 12 O 400 mg 7 days; n = 3 O 400 mg 28 days). Primary tumour sites were ovarian (28), breast (13), and small-cell lung cancer, prostate/colon, unknown (1 each). Cycle 1 DLTs occurred in 2/42 evaluable pts: grade 3 stomatitis (O 200 mg 28-day cohort), grade 4 thrombocytopenia (O 400 mg 7-day cohort). All pts experienced at least 1 AE; overall the most commonly reported were stomatitis (73%), nausea (61%) and asthenia (46%). Treatment-related AEs, CTCAE grade $\geqslant$3 AEs and serious AEs were reported for 93%, 46% and 9% of pts, respectively. Two AEs had an outcome of death and were considered related to combination treatment by the investigator: pneumonitis (O 100 mg 28-day cohort); pneumonitis, pneumonia and dyspnoea (O 200 mg 28-day cohort). Both pts had different confounding factors which may have contributed to the events of pneumonitis. No dose-dependent increase in AEs was observed. Efficacy and PK results will be reported.
Conclusions: At this interim review, the per-protocol MTD of O in combination with PLD 40 mg/m^2 every 28 days was not reached using O 400 mg bid continuously (the RD for O monotherapy). Accrual is completed.

1258 POSTER

Phase I Clinical Trial of a Genetically Modified Oncolytic Vaccinia Virus GL-ONC1 With Green Fluorescent Protein Imaging

A. Biondo[1], J.V. Pedersen[1], E.M. Karapanagiotou[2], N. Tunariu[3], D. Mansfield[4], S. Sassi[5], J. Corral[1], T.A. Yap[1], J.S. de Bono[1], K.J. Harrington[6]. *[1]Royal Marsden Hospital/The Institute of Cancer Research, Drug Development Unit, Sutton, [2]Royal Marsden Hospital/ The Institute of Cancer Research, Head and Neck Unit, London, [3]Royal Marsden Hospital/ The Institute of Cancer Research, Clinical MRI Unit & Drug Development Unit, Sutton, [4]The Institute of Cancer Research, Targeted Therapy Team, London, [5]Royal Marsden Hospital/ The Institute of Cancer Research, Joint Department of Physics, Sutton, [6]Royal Marsden Hospital/ The Institute of Cancer Research, Head and Neck Unit & Targeted Therapy Team, London, United Kingdom*

Background: GL-ONC1 is a genetically engineered vaccinia virus attenuated by insertion of the *RUC-GFP* (*Renilla* luciferase and *Aequorea* green fluorescent protein fusion gene), beta-galactosidase (*lacZ*) and beta-glucuronidase (*gusA*) reporter genes into the *F14.5L*, *J2R* (thymidine kinase) and *A56R* (hemagglutinin) loci, respectively. A phase I clinical trial of intravenously administered GL-ONC1 was pursued to evaluate safety, tolerability, tumour delivery, neutralizing antibody development and anti-tumour activity.
Methods: GL-ONC1 was to be administered to patients with advanced solid tumours at escalating doses (1×10^5, 1×10^6, 1×10^7, 1×10^8, 1×10^9, 3×10^9 plaque-forming units (pfu) on day 1; 1.667×10^7 and 1.667×10^8 pfu on day 1−3; 1×10^9 pfu on day 1−5 of a 28-day cycle) using a 3+3 dose escalation design. Green fluorescent protein (GFP) imaging was performed on superficial and mucosal tumour lesions at baseline and after each cycle, and on GL-ONC1-related skin rashes. Optional paired tumour biopsies were obtained for pharmacodynamic and viral delivery evaluation.
Results: To date, 24 patients (males 18, median age 60 years) have been treated. One of six patients at the 1×10^9 pfu dose level developed a dose-limiting, short-lived, grade 3 rise in aspartate transaminase levels after a single infusion. This patient with metastatic colorectal adenocarcinoma had a subsequent initial fall in CEA and stable disease by RECIST at 8 weeks. Other commonly reported adverse events (grade 1/2) included pyrexia (n = 12), musculoskeletal pain (n = 7), fatigue (n = 7), nausea (n = 5), and vomiting (n = 4). One patient developed a left common femoral artery embolism of uncertain causality (grade 3). Two patients developed skin rash (grade 1 and grade 2, respectively) during the first week of treatment, which appeared green by GFP imaging and were positive to viral plaque assay (VPA). The rash resolved spontaneously by the end of cycle 1. VPA of blood, urine, stool and sputum were negative for viral shedding in all but one patient who had positive shedding for 11 days. Increased neutralizing antibody titres were detected in all tested patients apart from one. Best response by RECIST was stable disease at 24 weeks (n = 3) and 8−12 weeks (n = 5). Tumour biopsy analyses are ongoing.
Conclusions: GL-ONC1 administered intravenously is well tolerated with preliminary evidence of anti-tumour activity.

1259 POSTER

A Phase II Study of Cisplatin Plus S-1 in Patients With Carcinomas of Unknown Primary Site

A. Tsuya[1], T. Kurata[2], A. Tamiya[3], I. Okamoto[2], N. Sugimoto[4], K. Matsumoto[5], I. Goto[6], N. Yamamoto[1], M. Fukuoka[7], K. Nakagawa[2]. *[1]Shizuoka Cancer Center, Division of Thoracic Oncology, Sunto-gun, [2]Kinki University School of Medicine, Department of Medical Oncology, Osakasayama-shi, [3]National Hospital Organization Kinki-Chuo Chest Medical Center, Department of Thoracic Oncology, Sakai, [4]Osaka Medical Center for Cancer and Cardiovascular Diseases, Department of Clinical Oncology, Osaka, [5]Hyogo Cancer Center, Medical Oncology Division, Akashi, [6]Osaka Medical College, Division of Pulmonary Medicine, Osaka, [7]Izumi Municipal Hospital, Cancer Center, Osaka, Japan*

Background: Carcinomas of unknown primary site (CUP) represent a group of heterogeneous tumours and accounts for about 5% of all cancer patients. The prognosis of CUP is generally poor with a median overall survival time (OS) of 6 to 13 months, and no standard chemotherapy has been established. S-1 is a new oral fluoropyrimidine and shows broad efficacy for many carcinomas. Therefore, we conducted a phase II study of novel combination chemotherapy using cisplatin (CDDP) plus S-1 in pts with CUP to evaluate the efficacy and safety.
Methods: The treatment schedule included CDDP (60 mg/m^2) given intravenously on day 8, and S-1(40 mg/m^2) given orally twice a day on days 1−21. This schedule was repeated every 5 weeks. The primary endpoint was objective response rate, and secondary endpoints included safety, OS, and 1-year survival rate.
Results: A total of 46 chemotherapy naïve patients were enrolled. Median age of patients was 63 years (range 31−84). There were twenty-five male. Twenty-three patients had adenocarcinoma, fourteen had squamous cell carcinoma, three had poorly differentiated carcinoma, and three had poorly differentiated adenocarcinoma. Eighteen patients presented with lymph nodes metastasis only. Twenty-two patients presented with lymph nodes and multiple organ metastases. The median number of courses was four. The overall response rate and the disease control rate were 41.3% and 80.4%, respectively (CR/PR/SD/PD/NE; 2/17/18/7/2). The median progression-free survival time and the overall survival time were 7.5 months and 17.4 months, respectively. The most common grade 3 or worse adverse events were hematologic toxicities. Non-hematologic toxicities were generally mild. Neutropenia, thrombocytopena, and febrile neutropenia occurred in 28.3%, 13%, and 2.2%, respectively.
Conclusion: This study demonstrated the efficacy and safety of CDDP plus S-1 combination chemotherapy in patients with CUP. Because of its high response rate, good survival rate, and mild toxicities, this treatment may be one of the standard first-line therapies for patient with CUP.

1260 POSTER

Preliminary Signs of Efficacy Reported in Monotherapy Phase I Cancer Clinical Trials of Molecularly Targeted Agents and Correlation With Further Clinical Development

J. Arrondeau[1], X. Paoletti[2], S. Pop[1], P. Tresca[1], V. Diéras[1], C. Le Tourneau[1]. *[1]Institut Curie, Medical Oncology, Paris, [2]Institut Curie, Biostatistics, Paris, France*

Background: Although the primary objective of phase I cancer clinical trials is primarily the safety, clinical efficacy is often highly expected in order to decide further clinical development of anticancer agents.
Methods: In this study, phase I cancer clinical trials evaluating molecularly targeted agents as monotherapy published in English over the last decade were retrieved. In each trial were recorded the occurrence of complete/partial responses (CR/PR) according to RECIST and WHO criteria, along with other signs of efficacy, including minor responses (MR), decrease in serum markers (such as PSA) and responses on PET scan or DCE MRI. A search on PubMed and www.clinicaltrials.gov was then performed to evaluate the proportion of cases in which efficacy was reported that were subsequently evaluated in phase II/III trials in tumour types in which antititumour activity was observed in the phase I trial.
Results: Hundred and sixty eight phase I trials evaluating 116 different molecularly targeted agents involving 6,050 patients were reviewed. The maximum tolerated dose (MTD) was reached in 126 of the 168 trials (75%). CR/PR were observed for 53 out of the 116 molecularly targeted agents (46%), in 90 out of the 6,050 patients included (1.5%) of all included patients. When MR, decrease in serum markers and responses on PET scan or DCE MRI were also taken into account, signs of efficacy were reported for 55 agents (48%), in 182 out of the 6,050 patients included