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

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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

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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

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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