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

(3.1%). The most common tumour types in which CR/PR were reported were renal cancer (18%), non small-cell lung cancer (16%), colorectal cancer (15%) and breast cancer (11%). In the subgroup of drugs for which the MTD was reached, signs of efficacy were observed at 0−50%, 50−90%, 90–110%, and >110% of the MTD in respectively 15%, 17%, 34% and 30% of patients (unknown in 6% of cases). Finally, only 27 out of the 86 clinical situations (31%) in which signs of efficacy in specific tumour types were observed at doses <110% of the MTD were subsequently evaluated in phase II/III clinical trials.
Conclusion: Antitumour activity infrequently occurs in phase I trials of molecularly targeted agents evaluated as single agents. A substantial proportion of drugs do no pursue clinical development in specific tumour types even though signs of efficacy have been observed in the phase I setting.

1261 POSTER

Long-term Protective Effects of the Angiotensin Receptor Blocker Telmisartan on Epirubicin-induced Inflammation, Oxidative Stress and Myocardial Dysfunction

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Introduction: Chronic inflammation, oxidative stress and renin-angiotensin system (RAS) play a significant role in chemotherapy-induced cardiotoxicity (CTX): telmisartan (Tel), an antagonist of angiotensin II type-1 receptor, was shown to be able to reduce anthracycline (ANT)- induced CTX.
Patients and Methods: We carried out a phase II placebo-controlled randomized trial, to assess the possible role of Tel in the prevention of the cardiac sub-clinical damage induced by epirubicin (EPI). Forty-nine patients (mean age $\pm$ SD 53.0$\pm$8 years), cardiovascular disease-free with cancer at different sites and eligible for EPI- based treatment, were randomized to one of two arms: Tel n = 25; Placebo (PLA) n = 24. A conventional echocardiography equipped with Tissue Doppler Imaging, Strain and Strain Rate (SR) was performed as well as serum levels of proinflammatory cytokines IL-6 and TNF-a and oxidative stress parameters reactive oxygen species (ROS) and glutathione peroxidase (GPx). All assessments were carried out at baseline, every 100 mg/m^2 of EPI dose and 12 month-follow up (FU).
Results: A significant reduction of the SR peak both in the TEL and PLA arm was observed at t_2 (cumulative dose of 200 mg/m^2 of EPI) in comparison to t_0. Conversely, at t_3 (300 mg/m^2 EPI), t_4 (400 mg/m^2 EPI) and 12 month-FU, the SR increased reaching the normal range only in the Tel arm, whilst in the PLA arm the SR remained significantly lower as compared to t_0 (baseline). The differences between SR changes in the PLA and Tel arm were significant from 300 mg/m^2 EPI (t_3) up to 12 month-FU. Serum levels of IL-6 increased significantly in the PLA arm at 200 mg/m^2 EPI (t_2) in comparison to baseline but remained unchanged in the Tel arm. The same trend was shown by ROS levels which significantly increased at t_2 versus baseline in the PLA arm, whilst remained unchanged in the Tel arm. The mean change of ROS and IL-6 at t_2 was significantly different between the 2 arms. In the present study, we confirm at 3 month-FU the trend toward a decrease of ROS and IL-6 from t_2 in the PLA arm.
Conclusions: Our results suggest that Tel is able to reverse the acute (early) EPI-induced myocardial dysfunction and to maintain later a normal systolic function up to 12 month-FU. These effects are likely to be due to different mechanisms: RAS blockade and prevention of chronic inflammation/oxidative stress.
This study was partially funded by AIRC (Associazione Italiana Ricerca per il Cancro)- project number 8679.

Poster Presentations (Mon, 26 Sep, 14:00−16:30) **Regulatory/Trial Methdology/Pharmacy**

1300 POSTER

Non-Inferiority Cancer Clinical Trials (NIFCT) Often Rely on Large Upper Boundaries

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Background: NIFCT are time and resource-consuming studies whose main purpose is deliver treatments that are either more convenient to patients, less toxic or cheaper in comparison to similarly efficacious standard of care (SOC). Here, we sought to evaluate the characteristics and the purpose of NIFCT.
Methods: We performed a systematic review of NIFCT of cancer-directed therapy and supportive care (SC) agents in oncology which were either published in the PubMed in the last 10 years or as ASCO abstracts (last 5 years). Study characteristics, data on primary endpoint and sponsorship were extracted; authors' conclusions (positive, negative, neutral, implied positive, not reported) and study purpose were independently analyzed and classified by two blinded investigators.
Results: 76 of 163 studies were eligible (34 abstracts and 42 full articles): 32(42%) were partially or entirely sponsored by industry while 21 (28%) did not report source of funding; 18 (24%) were SC trials, followed by breast, colorectal and lung cancer trials (12 each; 16%). The median number of patients per arm was 478 (40–3148). The most common primary endpoint was overall survival (N = 19; 25%), followed by progression free survival and response rate (N = 14 each; 18%). Sixty percent of NIFCT were positive as per the primary endpoint. For trials with a pre-specified absolute non-inferiority margin, the median absolute difference was 12.5% (range 4−25%). For trials that used a pre-specified Hazard Ratio for non-inferiority, the median upper boundary was 1.25 (range 1.10–1.50). The purpose of NIFCT was clear in all studies: 23(30%) offered more convenient schedule, 17(22%) showed similar efficacy without any clear advantage against SOC, 12(16%) described less toxic drugs, and 12(16%) used lower doses. Despite the fact that 12 studies were clearly negative, authors' conclusions were either clearly positive or implied positive in 8 instances. Response rate was more associated with a positive conclusion reported by authors when compared to other study endpoints (p = 0.018).
Conclusion: While most NIFCT of cancer therapeutics report positive results many use large pre-specified difference margins. Studies that use response rate as their primary endpoint tend to report more favorable conclusions. Their most frequent purposes were to test more conveniently administered drugs or to show similar efficacy to SOC.

1301 POSTER

Assessment of Progression-free Survival as a Surrogate Endpoint for Overall Survival in Patients With Metastatic Renal Cell Carcinoma

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Background: Among surrogate endpoints for overall survival (OS) in oncology trials, progression-free survival (PFS) is increasingly taking the lead. Although there have been some empirical investigations on inter-dependence of OS and PFS in different tumour types, new ways to model and interpret this inter-dependence are scarce, and only limited evidence is available for metastatic renal cell carcinoma (mRCC).
Methods: We assessed the relationship between PFS (the primary endpoint) and OS in 750 patients with treatment-naïve mRCC randomized 1:1 to receive sunitinib (SU) or interferon-alfa (IFN) in a pivotal phase III study, pooling data for all available patients across treatment arms. Kaplan–Meier curves for OS were fit to three groups of patients based on PFS: PFS <10.2 weeks (<33.3 percentile); 10.2 $\leqslant$ PFS <34.6 weeks (33.3-to-66.6 percentile); and PFS $\geqslant$ 34.6 weeks (>66.6 percentile). A parametric model to failure-time data was also fit to the same set of patients. We used the difference between OS and PFS as the outcome to remove inherent dependencies between PFS and OS. By excluding PFS time from OS time we obtain a distinct measure of survival beyond PFS, i.e. post-progression survival (PPS).
Results: Non-parametric Kaplan–Meier analysis indicated that incremental PFS may be associated with longer PPS; curves for OS according to duration of PFS were statistically significantly different (log-rank test, P < 0.0001). The parametric model clearly demonstrated that longer PFS was significantly predictive of longer PPS (P < 0.001). Estimated median PPS time was linked to a particular PFS time. For example, for PFS of 20 weeks, the median PPS time was 43.9 weeks (95% confidence interval [CI]: 40.1, 48.1); for PFS of 60 weeks, the median PPS time was 57.9 weeks (95% CI: 50.3, 66.7).
Conclusions: In this study, for patients with mRCC randomized to either sunitinib or IFN, a discernible and quantifiable relationship was found between PFS and PPS time. This suggests that PFS can be used as a surrogate measure for OS in mRCC, although more research is needed to generalize this finding beyond this particular study. This novel statistical approach enriches the interpretation and understanding of that relationship, with potential implications for clinical trial design.