and account for about 2−5% of all primary lung tumors. Based on histopathological, biological and clinical criteria PCs are classified as typical or atypical (TPC and APC). The molecular alterations that contribute to PC are debated. We report here on somatic mutations of the MEN1 gene in sporadic TPCs and APCs.
Materials and Methods: We collected formalin-fixed paraffin-embedded (FFPE) blocks of 39 primary sporadic PCs (30 TPCs and 9 APCs) and matched lymph nodal metastases from the Institute of Anatomical Pathology, "S.S. Annunziata" Hospital, Chieti, Italy. Slides and medical records were reviewed for histopathological and clinical features and tumor sections were characterized for chromogranin A, synaptophysin and neuron-specific enolase. Proliferative activity was assessed by quantifying MIB1- or Ki67-stained cells.
Tumor DNA was analyzed along the entire MEN1 coding sequences by DHPLC and direct sequencing.
Results: MEN1 variants were identified in 5 out of 39 cases. Mutations were detected in known "hot spot" regions within exons 2−3 and 10. The pathogenetic variants included the truncating mutation c.427delC (p.Leu143SerfsX184), detected in a TPC, and the missense mutations c.266T>G (p.Leu89Arg), c.646 G>A (p.Ala216Thr) and c.1621 A>G (p.Thr541Ala) respectively identified in 2 APCs and 1 TPC. In addition, the polymorphism c.435 C>T (p.Ser145Ser) was identified in 2 TPCs, including the case that resulted positive for the truncating mutation. Notably, the 4 mutations are not reported in association with PC by Lemos and Thakker (Hum Mutat. 29:22−32, 2008 Review). However, the missense mutation p.Leu89Arg and the polymorphism p.Ser145S were previously identified as somatic variants in glucagonoma and parathyroid tumors.
Conclusions: Our data support the involvement of MEN1 in a subset of sporadic PCs. Further characterization of other genetic alterations, such those in Trop2, p53 and Kras, and LOH (loss of heterozygosity) at the MEN1 locus is in progress. Moreover, we built a tissue microarray resource for the immunohistochemical characterization of PCs and subsequent genotype-phenotype correlations.

9124 POSTER

Phase I trial of sagopilone in combination with cisplatin as 1st-line therapy in patients with extensive-disease small-cell lung cancer (ED-SCLC)

D.C. Christoph[1], T.C. Gauler[1], F. Gamarra[2], H.G. Fuhr[3], J.R. Fischer[4], C. Gonschorek[5], N. Frickhofen[3], R.M. Huber[2], M. Schuler[1], W.E.E. Eberhardt[1]. [1]*University of Duisburg-Essen, Department of Medicine (Cancer Research), Essen, Germany;* [2]*University of Munich, Department of Medicine, Munich, Germany;* [3]*Dr. Horst Schmidt Kliniken, Department of Medical Oncology, Wiesbaden, Germany;* [4]*Clinic Löwenstein, Department of Medical Oncology, Löwenstein, Germany;* [5]*Bayer Schering Pharma AG, Global Clinical Operations, Berlin, Germany*

Background: Despite improvements in the treatment of patients (pts) with ED-SCLC over the last 3 decades, outcomes remain disappointing and there is a need to evaluate innovative and better tolerated therapies. Sagopilone (ZK-EPO), a microtubule-stabiliser, is a novel, fully synthetic epothilone with excellent activity in SCLC cell lines and other tumour models.
Methods: The maximum tolerated dose (MTD) or recommended Phase II dose of sagopilone combined with cisplatin (P) as 1st-line treatment in pts with measurable chemotherapy-naïve ED-SCLC was evaluated (ID 310101; sponsor Bayer Schering Pharma AG). Treatment consisted of a 3h sagopilone infusion followed by a 1h infusion of 75 mg/m^2 P, d1 q3w. Sagopilone dose escalation/de-escalation comprised 12 mg/m^2 (cohort 1), 16 mg/m^2 (cohort 2), 22 mg/m^2 (cohort 3) and 19 mg/m^2 (cohort 4). In each cohort, 6 pts were planned to be treated and dose escalation was to be halted in the event of >1 dose-limiting toxicity (DLT).
Results: As of March 2009, 26 pts (17 male, 9 female) have been treated (6 each in cohorts 1 and 3, and 7 each in cohorts 2 and 4) and preliminary data are available. A median of 4 cycles of sagopilone were administered per pt. No DLTs were observed in cohorts 1, 2 and 4, and 1 DLT (grade 3 bone pain; cycle 1) was reported in cohort 3; the MTD has not been formally reached. The most common drug-related adverse event (AE) was peripheral sensory neuropathy (PNP): grade 1/2 in 12 pts (46%) and grade 3 in 5 pts (19%). No grade 4 PNP was reported. Sagopilone was de-escalated from 22 mg/m^2 (cohort 3) to 19 mg/m^2 (cohort 4) to reduce PNP; pts received a median of 3 and 4 treatment cycles in cohorts 3 and 4, respectively. PNP incidence was similar in both cohorts (5 vs 6 pts), but grade 3 PNP (3 vs 1 pt) and number of pts discontinuing treatment due to PNP (4 vs 2 pts) were lower at 19 mg/m^2. Other common drug-related AEs included grade 1/2 (>25% pts) nausea (46%), vomiting (46%), vertigo (31%) and anorexia (27%), and ⩾grade 3 (>1 pt) leucopenia (12%), fatigue (12%), nausea (8%) and anaemia (8%). The overall response rate was 62%, with responses at all dose levels (including 1 complete and 5 partial responses in 6 evaluable pts at 19 mg/m^2).
Conclusions: Sagopilone ⩽22 mg/m^2 combined with 75 mg/m^2 P shows promising clinical activity and can be safely administered to pts with ED-SCLC, with PNP being the major AE. These results warrant further investigation in Phase II studies using 19 mg/m^2 sagopilone.

9125 POSTER

Can the modified RECIST criteria and EORTC PET criteria predict the postoperative pathologic findings for resectable malignant pleural mesothelioma following neoadjuvant chemotherapy?

T. Mimura[1], H. Watanabe[2], M. Yamanaka[3], M. Satouchi[4], M. Okada[5]. [1]*Hiroshima City Asa Hospital, Department of Surgery, Hiroshima, Japan;* [2]*National Cancer Center Hospital, Division of Diagnostic Radiology, Tokyo, Japan;* [3]*National Kyushu Cancer Center, Institute for Clinical Research, Fukuoka, Japan;* [4]*Hyogo Cancer Center, Thoracic Oncology, Akashi, Japan;* [5]*Hiroshima University, Department of Surgical Oncology, Hiroshima, Japan*

Background: The unique growth pattern of malignant pleural mesothelioma (MPM) presents challenges for clinical investigators evaluating the responses to chemotherapy, which is an important surrogate endpoint for patient benefit, particularly in clinical trials. The applicability of modified RECIST (Response Evaluation Criteria in Solid Tumors) based on the findings on CT images and EORTC (European Organization for Research and Treatment of Cancer) criteria based on the findings on FDG-PET images to resectable MPM would be challenging and significant, but their validity has never been examined.
Materials and Methods: Between May 2006 and November 2008, 13 consecutive patients with resectable pathologically proven MPM were included in this study. All were initially treated with combination chemotherapy including cisplatin. Extrapleral pneumonectomy was successfully performed in all the patients. In addition to modified RECIST (CR; complete response vs PR; partial response vs SD; stable disease vs PD; progressive disease), FDG uptake by the tumor on PET was also evaluated according to the EORTC PET criteria (CMR; complete metabolic response vs PMR; partial metabolic response vs SMD; stable metabolic disease vs PMD; progressive metabolic disease). Also, pathologic findings (NT; no viable tumor vs MR; minimal residual vs GR; gross residual) were reviewed.
Results: According to modified RECIST, in which the definition of measurable lesions is ⩾10 mm in diameter, 7 of the 13 patients investigated had no measurable lesion. Even when the definition of measurable lesions was changed to ⩾5mm, 2 patients had no measurable lesion and 4 had only one lesion. In regard to the response, 4 of 11 patients with any measurable lesions were classified as PR, and 7 were classified as SD, while 8 patients were classified as PMR and 3 were classified as SMD according to the PET findings. Eight patients were classified as GR and 5 as MR. Kappa statistics suggested potential variation between the CT response and the pathologic findings ($\kappa = 0.214$, 95% CI = −0.377–0.806) and between the PET response and the pathologic findings ($\kappa = 0.286$, 95% CI = −0.049–0.620). The proportions of agreement were 53.8% between the CT response and the pathologic findings and 58.3% between the PET response and the pathologic findings.
Conclusions: The modified RECIST criteria as well as EORTC PET criteria did not directly predict the pathologic findings for patients with resectable malignant pleural mesothelioma.

9126 POSTER

Bi-weekly paclitaxel-gemcitabine in patients with small-cell lung cancer resistant to previous platinum and etoposide-based chemotherapy

A. Martinez Bueno[1], X. Mielgo Rubio[1], E. Iruarrizaga Ovejas[1], S. Sergio Carrera[1], A. Ruiz de Lobera Martinez[1], R. Casas Cornejo[1], R. Fernandez Rodriguez[1], J. Ferreiro Quintana[1], D. Ballesteros Quintanilla[1], J.M. Mañé Martinez[1]. [1]*Cruces Hospital, Medical Oncology, Barakaldo-Vizcaya, Spain*

Background: Patients with small-cell lung cancer (SCLC) resistant or refractory to cisplatin- based chemotherapy (progression during or within 3 months after the last course) have a poor prognosis. In this setting topotecan is the most commonly used agent with high hematological toxicity. We analyzed the efficacy and toxicity profile of a combination of Paclitaxel and Gemcitabine in a bi-weekly regimen in patients with small-cell lung cancer previously treated with a combination of etoposide and platinum-based chemotherapy.
Materials and Methods: Twenty-eight patients were enrolled with the following characteristics: median age: 60 (range 39−76); gender: 26 male/2 female; performance status (PS) 0/1/2/3:10/10/7/1 respectively; all were platinum-refractory or resistant (progression during the first line or within 3

months since the last course). Treatment consisted of Paclitaxel (80 mg/m^2) and Gemcitabine (1250 mg/m^2) on days 1 and 15 in a 4-week cycle. Treatment was held until progression or unacceptable toxicity.
Results: 145 cycles were administered (median 2 cycles: range 1−6). The overall disease control rate was 35.7%: 3 partial responses (10.7%) and 7 stable disease (25%). Median time to progression was 15 weeks (95% CI 5.4−24.5) and median overall survival was 21 weeks (95% CI 5.4−36.5). Treatment was well tolerated: nausea/vomiting, neurotoxicity and asthenia were the most common non hematological toxicity (grade 2/3/4: 3/0/0, 1/4/0 and 8/1/0, respectively); neurotoxicity was related to a mild-moderate increment of previous treatment toxicity. Neither febrile neutropenia nor mielotoxicity grade IV were recorded. Anemia was the only grade 3 hematological event (grade 2/3/4 anemia 4/1/0, neutropenia 0/0/0, thrombocytopenia (2/1/0). Only one toxicity-related death was registered, due to gastric perforation. Ps was the only factor affecting survival among all analyzed (age >65, gender, PS, LDH, NSE, metastases vs. thoracic disease).
Conclusions: Bi-weekly Paclitaxel-Gemcitabine regimen is active in patients with small-cell lung cancer resistant/refractory to platinum-etoposide, with a favorable toxicity profile and easy management.

9127 POSTER

The role of thymidylate synthase (TS) and excision repair cross-complementing group 1 (ERCC1) immunohistochemical expression in malignant pleural mesothelioma patients treated with pemetrexed and carboplatin

P. Zucali[1], A. Destro[2], G.L. Ceresoli[1], L. Gianoncelli[1], E. Lorenzi[1], F. De Vincenzo[1], M. Simonelli[1], L. Giordano[3], M. Roncalli[2], A. Santoro[1].
[1]Istituto Clinico Humanitas, Department of Medical Oncology and Hematology, Rozzano Milano, Italy; [2]Istituto Clinico Humanitas, Department of Human Pathology, Rozzano Milano, Italy; [3]Istituto Clinico Humanitas, Biostatistic Unit, Rozzano Milano, Italy

Background: The combination cisplatin-pemetrexed has recently become the standard of care in the first-line treatment of malignant pleural mesothelioma (MPM). In unfit patients, carboplatin frequently substitutes cisplatin. However, today there are no data about pemetrexed and/or cisplatin/carboplatin predictors of response in MPM patients. The goal of this study is to retrospectively correlate the expression of ERCC1 and TS in tumor specimens by immunohistochemistry with the outcomes of a series of MPM patients treated with carboplatin plus pemetrexed in first line setting.
Material and Methods: TS and ERCC1 expression was detected by immunohistochemistry in tumor specimens of 71 patients. Sections of 2μm were stained with mouse monoclonal antibodies directed against ERCC1 (1:50; clone8F1; Santa Cruz) and TS (clone106; 1:100; DAKO). To evaluate the proteins staining (for TS cytoplasmatic and nuclear; for ERCC1 nuclear) the percentage of positive tumor cells was considered and a proportion score was attributed (TS: 0 $\leqslant$5%, 1 6−29%, 2 $\geqslant$30%; ERCC1: 0 $\leqslant$10%, 1 11−50%, 2 >50%). This proportion score was then multiplied by the staining intensity (1+, 2+, 3+) to obtain a final semiquantitative score (FSC).
Results: The increasing FSC of TS (TS-FSC) correlated with a minor probability of disease control (partial response plus stable disease) (OR = 1.57; p = 0.012). Comparing TS-FSC$\geqslant$4 vs TS-FSC$\leqslant$1 progression of disease was significantly increased (OR = 14.4; p = 0.005). The increase of TS-FSC was significantly correlated with a shorter PFS (HR = 1.23; p = 0.004) and OS (HR = 1.21; p = 0.02). In a model corrected for disease control, TS-FSC remained significant correlated with PFS (HR = 1.24; p = 0.005). There was not a significant correlation between ERCC1 expression and disease control, PFS, and OS. Interestingly, ERCC1 was expressed with a percentage $\geqslant$10% in 83.1% of tumor specimens, and with an intensity $\geqslant$2+ in 61.7%.
Conclusions: Immunohistochemical TS expression seems to be able to predict the clinical outcomes in MPM patients treated with carboplatin plus pemetrexed. Despite the absence of significant correlation with clinical outcomes, the high ERCC1 expression observed could explain the low response rate of MPM to platinum compounds. Further prospective studies are needed to confirm these results.

9128 POSTER

Advanced poorly differentiated neuroendocrine carcinoma arising from miscellaneous organs was less sensitive to chemotherapy and had poorer prognosis than advanced small-cell lung carcinoma

T. Terashima[1], C. Morizane[2], S. Iwasa[2], A. Hagihara[2], Y. Kojima[2], S. Kondo[2], H. Ueno[2], N. Hiraoka[3], S. Kaneko[1], T. Okusaka[2]. *[1]Kanazawa University Hospital, Gastroenterology, Kanazawa, Japan; [2]National Cancer Center Hospital, Hepatobiliary and Pancreatic Oncology, Tokyo, Japan; [3]National Cancer Center Research Institute, Pathology, Tokyo, Japan*

Backgroud: Neuroendocrine carcinoma is a fairly rare, heterogeneous disease entity, and no standard treatment has been established. The chemotherapy regimen for small-cell lung carcinoma (SCLC) has been adopted for extended or recurrent poorly differentiated neuroendocrine carcinoma (PDNEC) because they share many pathological features and aggressive clinical behavior. However, PDNEC may differ from SCLC with respect to sensitivity to anticancer agents and outcome. The aim of this study was to clarify the efficacy of standard SCLC regimens when used to treat PDNEC arising from various organs and to compare the outcome with that of SCLC.
Materials and Methods: We retrospectively reviewed the medical records of 982 patients with a proven diagnosis of neuroendocrine tumor between January 2000 and October 2008 at the National cancer center hospital of Japan. The inclusion criteria were chemotherapy-naïve patients with extended or recurrent PDNEC who had been treated by a combined regimen consisting of cisplatin and etoposide (PE regimen), cisplatin and irinotecan (IP regimen), or carboplatin and etoposide (CE regimen). We investigated patients background, treatment efficacy, and the outcome of the patients according to the organ that was the site of the primary lesion.
Results: There were 145 patients who met the above criteria, 41 with PDNEC and 104 with SCLC. The primary site of the PDNEC were gastrointestinal (GI) tract in 18 patients (GI group), hepatobiliary and pancreatic region in 16 patients (HBP group), and another site in 7 patients (other group). Median age was 63.0 (27−84) years, and 108 patients (75%) were male. The response rate of the SCLC patients was 83%, and the response rate of the PDNEC patients was 31%: 38% in the GI group, 13% in the HBP group, and 67% in the other group. Overall survival of the SCLC was 417 days and overall survival of the PDNEC was 281 days: 452 days in the GI group, 237 days in the HBP group, and 270 days in the other group. A multivariate analysis demonstrated that poor performance status, liver involvement, and PE regimen were independent unfavorable prognostic factors.
Conclusions: Extended or recurrent PDNEC, especially in the HBP group, was less sensitive to chemotherapy and had a poorer outcome than SCLC. The greater tendency to metastasize to the liver may have affected the outcome in the HBP group.

9129 POSTER

Outcomes of malignant pleural mesothelioma patients treated with second-line chemotherapy (SL): a retrospective analysis of 161 patients

M. Garassino[1], A. Moretti[1], M. Cinquini[2], M. Tiseo[3], G. Michetti[4], E. Collova[5], A. Follador[6], N. La Verde[7], G. Farina[7], P. Zucali[8].
[1]Fatebenefratelli and Ophthalmic Hospital, Oncology, Milano, Italy; [2]Mario Negri, New Drug Development Strategies Lab., Milano, Italy; [3]Maggiore hospital, Oncology, Parma, Italy; [4]Ospedali Riuniti, Oncology, Bergamo, Italy; [5]Hospital, Oncology, Legnano, Italy; [6]Hospital, Oncology, Udine, Italy; [7]Fatebenefratelli and Opthalmic, Oncology, Milano, Italy; [8]Humanitas, Oncology, Rozzano, Italy

Background: Malignant pleural mesothelioma (MPM) is a disease with a poor prognosis. While a standard first-line therapy (FL) using platinum pemetrexed based regimens is available, no certainty in second-line treatment (SL) exists. In fact, at present, it is unclear whether a SL chemotherapy might improve the outcome and what is the best schedule to be used. For this aim we analyzed the clinical outcomes of patients who received SL treatment for MPM.
Matherials and Methods: Retrospectively we reviewed all consecutive patients who progressed after FL and received a SL treatment in 7 italian institutions. In our analysis we divided patients in four subgroups, according to the type of SL treatment: 1) Platinum-based rechallenge, 2) pemetrexed-based rechallenge 3) not platinum based chemotherapy (vinorelbine, gemcitabine, antracyclines, taxanes) and 4) biological agents. Our endpoints were Overall survival (OS), Progression free survival (PFS) and Response Rate (RR). Survival curves were designed with Kaplan-Meier method and Log Rank was used for testing differences.
Results: We analyzed 414 patients of whom 161 received a SL. Patients characteristics were: male 63%; median age 62.5 years (range: 41−79).