43% and 44% of pts receiving AMR or Topo, respectively, and 4 AMR pts (5%) died of neutropenic infection. Changes in LVEF from BL were minimal even in 13 pts who received cumulative AMR doses >1000 mg/m^2.
Conclusion: AMR significantly improves ORR vs Topo and has acceptable tolerability as 2nd-line therapy in pts with sensitive ED-SCLC. AMR has an improved early cardiac safety profile relative to other anthracyclines, but long-term effects are unknown.

9121 POSTER

Amrubicin monotherapy in patients with extensive disease small cell lung cancer (ED-SCLC) refractory to first-line platinum-based chemotherapy: final results of a phase 2 trial

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Background: Amrubicin (AMR) is a 3rd-generation synthetic anthracycline and potent topoisomerase II inhibitor. It is approved in Japan for treatment of NSCLC and SCLC. Literature indicates that SCLC patients (pts) who are refractory to 1st-line chemotherapy are unlikely to respond to additional chemotherapy and their expected median survival is 3−5 mos. This phase 2 open-label trial (NCT 00375193) evaluated the efficacy and safety of AMR monotherapy for treatment of pts with refractory ED-SCLC.
Methods: Pts with ED-SCLC refractory to 1st-line platinum-based chemotherapy (progression [PD] during therapy or relapse $\leqslant$90 days of treatment end) and ECOG performance status (PS) $\leqslant$2 were eligible. Pts received IV AMR 40 mg/m^2/day $\times$3 days every 21 days until PD, unacceptable toxicity, or withdrawal. The primary endpoint was overall response rate (ORR, CR+PR; by RECIST), with a goal of demonstrating an ORR $\geqslant$18%. Secondary endpoints included time to progression (TTP) duration of response (DR), progression-free survival (PFS) and overall survival (OS). Left ventricular ejection fraction (LVEF) was measured by ECHO or by MUGA at baseline, cycles 3, 6, then every 2 cycles, and end of treatment.
Results: 75 patients enrolled; median age was 63 years (range 43−88) and 17% were PS 2. Median time from end of 1st-line therapy to PD was 1.3 mos. Six pts died or discontinued before receiving AMR; the remaining 69 pts (92%) received a median of 4 AMR cycles (range 1−12). The primary endpoint was met: ORR was 21% (16/75, 95%Clopper-Pearson lower bound 13.9%), including 1 CR (1%) and 15 PR (20%). Stable disease (SD) was achieved by 30 (40%) pts. Of note, 7 pts with SD or PD as best response to 1st-line therapy achieved a PR with AMR treatment. Median DR was 4.3 months (95% CI 3.1, 5.8 mos), TTP was 3.8 mos (95% CI 2.7, 4.2 mos), PFS was 3.3 mos (95% CI 2.5, 4.0 mos), and OS was 6.1 mos (95% CI 4.9, 7.2 mos). Changes from baseline LVEF were similar across cumulative dosing groups, including in 4 pts who received cumulative AMR doses >1000 mg/m^2. The most common grade 3 or 4 adverse events were neutropenia (67%), thrombocytopenia (41%), and leukopenia (35%). Eight pts (12%) experienced febrile neutropenia. Twenty-six pts (38%) required dose reductions.
Conclusions: AMR shows promising activity in pts with refractory ED-SCLC, with an ORR of 21% and an acceptable safety profile.

9122 POSTER

Phase I study with pemetrexed, cisplatin and concurrent radiotherapy in limited-stage small cell lung cancer (LS-SCLC)

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Background: The activity of the combination of pemetrexed and cisplatin (P/Cis) in extensive stage (ES) SCLC (Socinski et al, JCO 2006) coupled with its radiosensitizing properties provided the rationale for this study. The study was stopped early based on interim results of the GALES trial in December 2007, showing inferior activity of P/carboplatin compared to etoposide/carboplatin in ES-SCLC.
Materials and Methods: Treatment-naïve patients (pts) with a diagnosis of LS-SCLC, without cytologically-proven malignant pleural effusion, were entered. This was an open-label, dose-escalation study, with 3−6 pts to be treated in each of the 4 planned cohorts (Coh): escalating pemetrexed doses (400−500 mg/m^2) and 75 mg/m^2 Cis administered intravenously for four 21-day cycles, concurrent with thoracic radiotherapy (TRT) 50 to 62 Gy starting at cycle 2. Endpoints were determination of recommended dose, maximum tolerated dose (MTD), dose-limiting-toxicity (DLT), acute and late toxicities and best overall response.
Results: A total of 9 pts were entered, age 50−80 years, 6 male, 3 female, 2 with ECOG performance status (PS) 0 and 7 with PS 1. The study was stopped too early to assess recommended dose or MTD. Three pts in Coh 2 discontinued due to adverse events after 1 or 2 treatment cycles (renal failure, femoral artery occlusion, peripheral sensory neuropathy). There was no DLT during TRT up to 6 weeks after treatment, 3 Coh 2 pts were replaced as they were not evaluable for DLT. Four pts experienced at least one possibly drug-related serious adverse event: one in Coh 1 (oesophagitis grade 2, anaemia grade 3, diverticulitis, malaise) and three in Coh 2 (sensory neuropathy grade 3, nausea, fatigue, anorexia, dehydration, femoral artery occlusion). One patient experienced oesophagitis grade 3 but was able to complete treatment without delay in TRT. There was no febrile neutropenia and no toxic death.

The most common (>1) related CTC grade 3/4 toxicities

CTCAE grade 3/4	Cohort 1 P 400 mg/m^2* (N = 3)	Cohort 2 P 500 mg/m^2* (N = 6)
Anorexia	2	1
Lymphopenia	1	2
Dehydration	1	1
Neutropenia	1	1
Thrombocytopenia	2	0

*plus 75 mg/m^2 Cis, 50 Gy TRT

The best overall response in Coh 1 was 2 partial responses (PR), 1 progressive disease (PD) and in Coh 2 was 1 PR.
Conclusions: Although the recommended dose of P/Cis and TRT could not be assessed, these data show that the combination of systemic doses of 75 mg/m^2 Cis and 500 mg/m^2 P concurrent with 50 Gy TRT is well tolerated. Pemetrexed is the first 3rd generation cytotoxic found to be tolerable at full dose with concurrent radiotherapy.

9123 POSTER

Screening of lung carcinoids for somatic mutations of MEN1 gene

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Background: Pulmonary carcinoids (PC), that occur sporadically and rarely in association with multiple endocrine neoplasia type 1 (MEN1) are relatively rare neoplasms that express neuroendocrine markers

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)

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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?

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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

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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