untreated patients with extensive-disease (ED) SCLC has not been established.
Purpose: To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of amrubicin and carboplatin in ED-SCLC.
Patients and Methods: Eligibility criteria were chemotherapy-naive ED-SCLC patients, performance status 0−1, age <75, and adequate hematological, hepatic, and renal function. Patients received escalating amrubicin doses under a fixed target AUC 5 of carboplatin (Chatelut formula). Amrubicin and carboplatin were administered by intravenous (i.v.) infusion on days 1, 2, and 3, and day 1, respectively. The initial dose of amrubicin was 30 mg/m^2, and the dose was escalated to 35 and 40 mg/m^2.
Results: Sixteen patients were enrolled and 15 eligible patients were evaluated. One of 6 patients in level 1, 1 of 6 in level 2, and 3 of 3 in level 3 experienced DLT. The presentation of DLTs included neutropenia, leukopenia, thrombocytopenia, febrile neutropenia, and liver dysfunction. The MTD doses of amrubicin and carboplatin were determined as 40 mg/m^2 and AUC 5. Evaluation of responses were 2CR, 9PR, 3SD, and 1PD (response rate 73%), and the median survival time was 13.6 months.
Conclusions: A dose of 35 mg/m^2 amrubicin and carboplatin AUC 5 were recommended. This regimen is associated with an acceptable tolerability profile, and warrants evaluation in the phase II setting.

9118 POSTER

Effect of chemotherapy (CT) in patients (pts) with resected small-cell (SCLC) or large-cell neuro endocrine carcinoma (LCNEC)

N. Abedallaa[1], L. Tremblay[2], C. Baey[3], D. Fabre[4], D. Planchard[1], J.P. Pignon[3], J. Guigay[1], J.C. Soria[1], B. Besse[1]. *[1]Institut Gustave Roussy, Department of Medicine, Villejuif, France; [2]Hôpital Laval, Thoracic Oncology, Quebec, Canada; [3]Institut Gustave Roussy, Department of Statistics, Villejuif, France; [4]Centre Chirurgical Marie Lannelongue, Department of Thoracic Surgery, Plessis-Robinson, France*

Background: CT and concurrent radiotherapy is the current standard of treatment for limited-stage (LS) SCLC. The role of surgery is limited and remains a matter of controversy. Surgical resection of undiagnosed lung lesion may lead to unintentional removal of SCLC. The benefit of peri-operative CT in resected SCLC or large cell neuroendocrine tumors is unknown.
Material and Methods: This retrospective analysis included LS-SCLC and LCNEC surgically removed between 1979 and 2007 at Surgical Centre Marie Lannelongue. Logrank test was used to compare overall survival.
Results: Among 74 total pts identified, 29 pts (25 male, 4 female, median age of 64 years) underwent surgery (S) and 45 (38 male, 7 female, median age of 58 years) underwent surgery plus chemotherapy (S+C). Four and 21 pts had pre- and post-operative radiotherapy respectively. Pathological diagnosis was as follow: (1) group S: 25 SCLC, 4 LCNEC, 15 pN0 and 10 pN+, and only 2 resections were incomplete (2) group S+C: 34 SCLC, 11 LCNEC, 15 pN0, 27 pN+ and only 3 resections were incomplete. CT was preoperative in 9 pts and postoperative in 37 pts; 62% of the pts received etoposide/platinum, 13% platinum/other agent, 25% other. 15 pts were excluded from the survival analysis, 3 pts alive whose follow-up did not exceed 6 months, 12 pts died within 6 months postoperative, including 4 within 1 month in group S. Among the patients alive at 6 months or followed at least 6 months (n = 59), 33 died, with an overall median follow-up of 5.8 years (range 0.6−19.6). It is 4.5 years (1.4−7) for the group S and 5.8 years (0.6−19.6) for the group S+C. The median survival of the group S (n = 20) and S+C (n = 39) were 2.3 and 6.1 years respectively. The hazard ratio of death was 0.48 (95% CI [0.24–0.99], p = 0.04) for the group S+C compared to the group S. The overall survival at 3 years was 48% in the group S compared to 59% in the group S+C.
Conclusion: These results suggest that peri-operative chemotherapy may be beneficial in pts with resected SCLC or LCNEC.

9119 POSTER

Reciprocal CD4+ T cell balance of Th17 and Treg in small cell lung cancer reflects disease stage

T. Miyabayashi[1], H. Kagamu[1], K. Koyama[1], S. Miura[1], S. Watanabe[1], H. Tanaka[2], J. Tanaka[2], H. Yoshizawa[2], I. Narita[3]. *[1]Niigata University, Graduate School of Medical and Dental Sciences, Respiratory Medicine, Niigata, Japan; [2]Niigata University, Medical and Dental Hospital, Bioscience Medical Research Center, Niigata, Japan; [3]Niigata University, Graduate School of Medical and Dental Sciences, Division of Repiratory Medicine, Niigata, Japan*

Background: Small cell lung cancer (SCLC) possesses high tendency to disseminate. However, SCLC patients with paraneoplastic syndrome mediated by immunity against onconeural antigens remain in limited-stage disease (LD) without distant metastases. Cumulative evidence regulates that a balance between immune and regulatory T cells (Treg) determines the magnitude of immune responses to not only self-antigens but also tumor-associated antigens. The purpose of this study was to elucidate the immunological balance induced in SCLC patients.
Materials and Methods: We analyzed T cells in the peripheral blood of 35 consecutive SCLC patients, 8 long-term survivors, and 19 healthy volunteers.
Results: Purified CD4$^+$ T cells with down-regulated expression of CD62L (CD62L^{low}) produced IFN-g, IL-4, and IL-17, thus, considered to be immune effector T cells (Teff). Significantly more Teff numbers were detected in LD-SCLC patients than that of extended-stage (ED) SCLC. By contrast, induction of CD62L^{high}CD25$^+$ CD4$^+$ Treg was significantly higher in ED-SCLC patients. Long-term survivors of SCLC maintained a high Teff to Treg ratio, whereas patients with recurrent disease exhibited a low Teff to Treg ratio. Teff in LD-SCLC patients included more IL-17-producing CD4$^+$ T cells (Th17).
Conclusion: These results show that CD4$^+$ T cell balance may be a biomarker that distinguishes disease stages and predicts recurrence. This study also suggests the importance of inducing effector CD4$^+$ T cells, particularly Th17 cells, while eliminating Treg to control systemic dissemination of SCLC.

9120 POSTER

Second-line amrubicin vs topotecan in extensive-disease small cell lung cancer (ED-SCLC) sensitive to first-line platinum-based chemotherapy: updated results of a randomized phase 2 trial

R. Jotte[1], P.R. Conkling[2], C. Reynolds[3], C. Shah[4], M. Galsky[5], L. Klein[6], J.F. Fitzgibbons[7], R. McNally[8], J.W. Oliver[9], M. Renschler[9]. *[1]Rocky Mountain Cancer Centers US Oncology, Medical Oncology, Denver, USA; [2]Virginia Oncology Associates US Oncology, Medical Oncology, Norfolk, USA; [3]Ocala Oncology Center US Oncology, Medical Oncology, Ocala, USA; [4]SUNY Upstate Medical University, Medical Oncology, Syracuse, USA; [5]Comprehensive Cancer Centers Of Nevada US Oncology, Medical Oncology, Las Vegas, USA; [6]Cancer Center and Hematology Specialists of Chicagoland US Oncology, Medical Oncology, Niles, USA; [7]Sacred Heart Medical Center US Oncology, Medical Oncology, Spokane, USA; [8]Celgene Corporation, Biostatistics, Summit, USA; [9]Celgene Corporation, Clinical Development, Summit, USA*

Background: Amrubicin (AMR) is a 3rd-generation synthetic anthracycline and potent topoisomerase II inhibitor that has shown an improved early cardiac safety profile relative to other anthracyclines. We compare the efficacy and safety of AMR for 2nd-line treatment of ED-SCLC sensitive to 1st-line chemotherapy with that of topotecan (Topo).
Methods: Randomized, phase 2, open-label, multicenter study (NCT 00319969). Eligible pts had ED-SCLC sensitive to 1st-line platinum-based chemotherapy (recurrence or progression ⩾90 days from completion of 1st-line treatment), ECOG PS ⩽2, and only 1 prior therapy. Pts were randomized (2:1) to IV AMR 40 mg/m^2/d (days 1−3) or IV Topo 1.5 mg/m^2/d (days 1−5) q21 days until progression, unacceptable toxicity, or withdrawal. The primary endpoint was overall response rate (ORR, by RECIST). Secondary endpoints were time to progression (TTP), progression-free survival (PFS), overall survival (OS), and safety. Left ventricular ejection fraction (LVEF) in AMR pts was measured by ECHO or MUGA at baseline (BL), cycles 3, 6, then every 2 cycles, and end of treatment.

Response	AMR (n = 50) n (%)	Topo (n = 26) n(%)
ORR*	22 (44)	3 (12)
CR	6 (12)	1 (4)
PR	16 (32)	2 (8)
SD	11 (22)	10 (39)
PD	13 (26)	9 (35)
N/A†	4 (8)	4 (15)

*AMR vs Topo, p = 0.005; †8 pts (4 each group) discontinued or died before first response assessment.

Results: 76 pts were randomized to AMR (n = 50) or Topo (n = 26). AMR was given for a median of 6 cycles (range 1−16); Topo 3 cycles (1−16). AMR significantly improved ORR vs Topo (p = 0.005 Table), including in older (⩾65 yrs) pts: 46% vs 7%, respectively. Median TTP was 5.6 mos (95% CI 2.8, 6.9) with AMR vs 3.0 mos (95% CI 1.4, 4.4) with Topo. Median PFS was 4.6 mos (95% CI 2.1, 6.1) with AMR vs 3.3 mos (95% CI 2.2, 5.4) with Topo. Median OS was 9.3 mos (95% CI 5.8, 12.2) with AMR vs 7.7 mos (95% CI 4.5, 14.0) with Topo. The most common grade ⩾3 AEs with AMR vs Topo were neutropenia (61% vs 78%), thrombocytopenia (39% vs 61%) and leukopenia (39% vs 39%). Dose reductions were required in

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

D.S. Ettinger[1], R. Jotte[2], P. Lorigan[3], V. Gupta[4], L. Garbo[5], D. Spigel[6], A.Z. Dudek[7], R. Salgia[8], R. McNally[9], M. Renschler[10]. *[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Medical Oncology, Baltimore, USA; [2]Rocky Mountain Cancer Centers US Oncology, Medical Oncology, Denver, USA; [3]Christie Hospital NHS Foundation Trust, Medical Oncology, Manchester, United Kingdom; [4]St Joseph Oncology US Oncology, Medical Oncology, St. Joseph, USA; [5]New York Oncology Hematology US Oncology, Medical Oncology, Albany, USA; [6]Sarah Cannon Cancer Center, Medical Oncology, Nashville, USA; [7]Masonic Cancer Center University of Minnesota, Medical Oncology, Minneapolis, USA; [8]University of Chicago, Medical Oncology, Chicago, USA; [9]Celgene Corporation, Biostatistics, Summit, USA; [10]Celgene Corporation, Clinical Development, Summit, USA*

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)

V. Surmont[1], K. Nackaerts[2], S. Senan[3], C.J. Kraaij[4], N. Chouaki[5], R.J. van Klaveren[6], J. Vansteenkiste[7], E.F. Smit[8]. *[1]UZ Gent, Respiratory Medicine/Thoracic Oncology, Gent, Belgium; [2]University Hospital Gasthuisberg Leuven, Pulmonology, Leuven, Belgium; [3]Vrije Universiteit Medical Center, Radiation Oncology, Amsterdam, The Netherlands; [4]Eli Lilly, Oncology, Houten, The Netherlands; [5]Eli Lilly, Radiation Oncology, Paris, France; [6]Erasmus Medical Center/Daniel den Hoed Cancer Clinic, Thoracic Oncology, Rotterdam, The Netherlands; [7]University Hospital Gasthuisberg, Pulmonology, Leuven, Belgium; [8]Vrije Universiteit Medical Center, Pulmonology, Amsterdam, The Netherlands*

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

S. Veschi[1], G. Aceto[1], S. Magnasco[2], R. Lattanzio[3], M.C. Curia[3], D. Angelucci[2], R. Mariani-Costantini[3], P. Battista[1]. *[1]University "G. d' Annunzio", Department of Human Movement Sciences, Chieti Scalo, Italy; [2]"S.S. Annunziata" Hospital, Institute for Pathological Anatomy, Chieti Scalo, Italy; [3]Center for Sciences on the Ageing (CeSI) "G. d'Annunzio" University Foundation and University "G. d'Annunzio", Department of Oncology and Neurosciences, Chieti Scalo, Italy*

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