of <0.001, 0.014 and 0.003 respectively. However, in the final multivariate Cox regression, N-stage was no longer significant. A comparison was made between three multivariate models each consisting of gender, WHO-performance status, $EQD_{2,T}$ and only one of the following combinations: (1) total tumor volume and PLNS, (2) T-stage and N-stage, (3) UICC overall stage. The AIC of the models was 1965.8, 1989.9 and 2001.2 respectively. It was therefore concluded that model 1 was the best for predicting overall survival.
Conclusions: The best prediction for survival in NSCLC patients treated with (chemo)radiation is based on total tumor volume, number of positive lymph node stations, gender, performance status and equivalent radiation dose corrected for time ($EQD_{2,T}$).

6506 ORAL

A prognostic model based on BRCA1 mRNA expression: a new determinant of outcome in early non-small-cell lung cancer (NSCLC)

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Background: Following surgical resection in operable NSCLC, 5-year survival is 60% in stage I, 39% in stage IIB and 23% in stage IIIA, with relapse commonly as distant metastases. The average benefit of adjuvant chemotherapy is 5%, ranging from nil in stage I to 15% in stage II-IIIA. Caretaker genes involved in keeping genetic alterations to a minimum include the nucleotide excision repair genes ERCC1 and myeloid zinc finger 1 (MZF1), which mediates ERCC1 expression, and other stability genes, such as BRCA1, which control processes involving large portions of chromosomes. Thioredoxin-1 (TRX1) is a redox protein overexpressed in NSCLC that is correlated with poor prognosis, and TWIST contributes to metastasis by promoting epithelial-mesenchymal transition.
Methods: In order to identify p with a high risk of relapse, we investigated the expression of these 5 transcripts in frozen resected tumors from 126 resected NSCLC p by real-time quantitative PCR. Gene expression was normalized using beta-actin and 18SrRNA expression as internal references.
Results: Adenocarcinoma (adeno), 33 p; squamous cell carcinoma (SCC), 93 p. Stage: IA, 18 p; IB, 53 p; IIB, 33 p; IIIA, 22 p. Tumoral transcript expression with ?-actin: ERCC1, 1.23; MZF1, 0.53; BRCA1, 3.65; TRX1, 1.82; TWIST, 7.75. A strong correlation was observed between the expression of ERCC1, MZF1 and BRCA1 ($P < 0.001$). Expression of each of the 5 transcripts was higher in SCC than in adeno ($P < 0.001$). Median survival (MS): low ERCC1 (<1.5) = not reached (NR), high ERCC1 = 33 months (m) ($P = 0.21$); low MZF1 (<0.5) = NR, high MZF1 = 33 m ($P = 0.04$); low BRCA1 (<5) = NR, high BRCA1 = 22 months (m) ($P = 0.01$); low TRX1 (<0.8) = NR, high TRX1 = 39.5 m ($P = 0.02$); no differences in MS according to levels of TWIST. In a multivariate Cox model for survival, BRCA1 and stage emerged as independent prognostic variables (Table). The prognostic value of BRCA1 has been validated in a separate set of 58 NSCLC p.

		HR	95% CI	p
Stage	IA-IB	1		
	IIA-IIIA	1.75	1.02−3.06	0.04
BRCA Level	<5	1		
	>5	1.77	1.02−3.06	0.04

Conclusion: Increased BRCA1 is associated with shorter survival, and BRCA1 assessment could be useful for customizing adjuvant chemotherapy.

6507 ORAL

Phase III study of IV vinflunine (VFL) versus IV docetaxel (DTX) in patients (pts) with advanced or metastatic non-small cell lung cancer (NSCLC) previously treated with a platinum-containing regimen

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Background: VFL is a novel microtubule inhibitor of the vinca alkaloid class with clinical activity in NSCLC (J. Bennouna, BJC, 2006). Single-agent safety and efficacy of VFL and DTX were compared in 2nd line NSCLC.
Methods: Open-label, multi-centre, randomised, Phase III study in platinum pre-treated advanced/metastatic NSCLC pts; 550 pts were to be randomised to receive VFL (320 mg/m^2, 20' infusion) or DTX (75 mg/m^2, 1-hour infusion with dexamethasone over 3 days) every 3 weeks. The primary endpoint was to compare PFS, with a non-inferiority analysis based on a 10% difference (types I/II error rates: 5%/20%); response, stable disease, overall survival and safety were assessed (RECIST and NCI CTC [version 2.0] respectively).
Results: From 06/03 to 03/05, 551 pts were randomised (VFL: 274; DTX: 277) and 547 treated (411 men, 136 women; median age 61 y [range 21−83]; ECOG PS 0−1: 89%; metastatic: 90%). All pts were platinum pre-treated, in combination with a vinca alkaloid (22%), paclitaxel (21%), gemcitabine (48%) or other excluding DTX (9%). A total of 950 [1−20] and 1025 [1−18] cycles were given with VFL and DTX respectively.
Safety: Grade 3/4 toxicities (VFL vs DTX): neutropenia (33% vs 30%), anaemia (8% vs 3%), thrombocytopenia (2% vs <1%), febrile neutropenia (3% vs 5%), fatigue (10% vs 6%), vomiting (2% vs 1%), abdominal pain (4% vs <1%), constipation (7% vs <1%) and all grades >0: alopecia (20% vs 35%), nail disorders (1% vs 5%), injection site reaction (25% vs 1%), peripheral neuropathy (11% vs 15%), diarrhoea (6% vs 12%) were observed.
Efficacy: Efficacy endpoints were similar): median PFS (2.3 vs 2.3 months, HR: 1.004 [0.841−1.199]), response rate (4.4% vs 5.5%), stable disease (36.0% vs 39.6%), median overall survival (6.7 vs 7.2 months, HR: 0.973 [0.805−1.176]). No significant difference was observed in the rate of Patient Benefit (PB) and Quality of Life (QOL)(FACT-L) assessment between the VFL and the DTX arms.
Conclusion: Vinflunine 320 mg/m^2 every 3 weeks was found to be similar in terms of efficacy to docetaxel 75 mg/m^2 when administered every 3 weeks in patients previously treated with a platinum-containing regimen for advanced NSCLC patients. PB and QOL were also comparable for the two study treatments. Manageable but different toxicity profiles were observed in either arm allowing a good median relative dose intensity >98%. Therefore, vinflunine offers a new treatment option for patients with advanced NSCLC in the second line setting.

Oral presentations (Wed, 26 Sep, 09.00−11.00)
Lung cancer (2)

6508 ORAL

CP-751,871, an anti-IGF-IR antibody, in combination with paclitaxel and carboplatin or paclitaxel and carboplatin alone as first-line treatment for advanced non-small cell lung cancer (NSCLC): A phase Ib/randomized phase II, non-comparative, open label trial

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Background: CP-751,871 is a fully human, IgG2 monoclonal antibody against the IGF-IR active in preclinical models of NSCLC. We report the

results of an ongoing phase Ib/II study in ten centers to evaluate the safety and efficacy of the combination of paclitaxel (T), carboplatin (C) and CP-751,871 (I) in advanced NSCLC.
Methods: Phase Ib was an open-label dose-escalation study of T (200 mg/m^2), C (AUC of 6) and CP-751,871 (0.05−10 mg/kg) every 3 weeks for up to 6 cycles in patients with advanced solid malignancies; pts with response or stable disease could receive extended CP-751,871 therapy. The ongoing phase II is an open label, randomized (2:1), non-comparative study of TCI and of TC alone. Only treatment-naive NSCLC pts (stage IIIB or IV) are eligible in phase II. The statistical hypotheses are 28% (null) versus 40% (response of interest).
Results: Following informed consent and screening, 7 cohorts with a total of 30 pts, including 23 NSCLC pts, were enrolled in phase 1b. No dose limiting toxicities were identified and the recommended phase 2 dose cohort of 10 mg/kg was extended to 12 pts. One case of grade 3 GGT elevation attributed to CP-751,871 was reported. An interim analysis for futility has been conducted at 73 pts enrolled in phase II: 48 treated with TCI; 25 with TC. TCI was well tolerated. All causality grade 3, 4 toxicity included (TCI, TC): hyperglycemia (20%, 10%), fatigue (15%, 8%), neutropenia (13%, 20%) and neuropathy (10%, 4%).Twenty-two pts receiving TCI (46%) and 8 pts on TC alone (32%) had objective responses. Furthermore, 14 out of 27 TCI pts (52%) with non-adenocarcinoma responded to treatment. In addition, a PR was observed in 1 out of 4 TC pts who elected to receive single agent I after progression on TC alone.
Conclusions: CP-751,871 appears safe in combination with TC. Interim TCI activity warranted further investigation. An additional 83 pts are being enrolled in the phase II part to further assess the safety and efficacy of this combination treatment.

6509 ORAL

Management of hypertension (HTN) in patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) receiving first-line cisplatin and gemcitabine with bevacizumab or placebo – results from randomised phase III trial BO17704

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Background: The addition of bevacizumab (B, Avastin®) to carboplatin/paclitaxel (CP) significantly improved overall and progression-free survival (PFS) compared with CP in patients (pts) with advanced non-squamous NSCLC in a phase III trial [Sandler et al. NEJM 2006]. The incidence of grade 3−4 HTN observed in E4599 was 0.7% in the placebo-containing arm and 7.5% in B-containing arm. Study BO17704 investigated the use of B (7.5 or 15 mg/kg q3w) in addition to cisplatin/gemcitabine (CG) for the first-line treatment of pts with locally advanced, metastatic or recurrent non-squamous NSCLC.
Methods: Eligibility criteria included histologically or cytologically documented previously untreated locally advanced, metastatic or recurrent non-squamous NSCLC; ECOG PS 0–1; adequate haematological, renal and liver function; no brain metastases; no history of recent CTC grade $\geqslant$2 haemoptysis. Between 2/2005 and 8/2006, a total of 1043 pts were randomised to 3 treatment groups. All pts were to receive up to 6 cycles of C 80 mg/m^2 day 1 and G 1,250 mg/m^2 days 1 and 8 every 3 wks, plus placebo (n = 347), B 7.5 mg/kg (n = 345) or B 15 mg/kg (n = 351) every 3 wks. B was to be administered until disease progression. Data for HTN was recorded at baseline; pts were followed until resolution or stabilisation. HTN was defined by the need for anti-HTN therapy.
Results: There was an increased incidence of HTN of all grades observed in the 7.5 mg/kg (24%) and 15 mg/kg (33%) B arms compared with placebo (11%). Hypertensive crisis occurred in 2 pts in the 7.5 mg/kg B arm and 1 in the 15 mg/kg B arm. A high proportion of pts received anti-HTN therapy, including calcium channel blockers (32.7%) and ACE-inhibitors (27.6%). Few pts discontinued therapy due to HTN.
Conclusions: The incidence of severe HTN observed in this trial is consistent with that observed in the previous phase III trial in NSCLC. The incidence of worsening HTN in pts with pre-existing HTN versus the incidence of de novo HTN appeared similar with B treatment. Very few clinically relevant severe events occurred. Hypertension should be controlled to levels suggested by public health guidelines.

	CG + placebo n (%)	CG + 7.5 mg/kg B n (%)	CG + 5 mg/kg B n (%)
HTN at baseline	91/327 (27.8)	96/330 (29.1)	88/329 (26.7)
Increased baseline HTN	14/91 (15.4)	24/96 (25.0)	28/88 (31.8)
De novo HTN	18/236 (7.6)	52/234 (22.2)	74/241 (30.7)
Discontinuation due to HTN	3/32 (9.4)	6/76 (7.9)	8/102 (7.8)
Grade 3−4 HTN	6 (2)	21 (6)	29 (9)

6510 ORAL

Erlotinib in patients with advanced non-small-cell lung cancer (NSCLC): interim results from the European subpopulation of the open-label TRUST study

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Background: Erlotinib (Tarceva®) is a well tolerated oral agent that significantly improved survival, delayed symptom deterioration and improved QoL in the BR.21 study in patients (pts) with previously-treated advanced NSCLC. TRUST is a global open-label study that provides erlotinib access for pts with stage IIIb/IV advanced NSCLC. We present here interim data from European sites.
Methods: Pts are eligible for TRUST if they have failed on/are unsuitable for chemotherapy and are ineligible for other erlotinib trials. Oral erlotinib (150 mg/day) is given until progression or unacceptable toxicity. Safety parameters include: incidence/severity of erlotinib-related rash; treatment-related adverse events (AEs) leading to withdrawal; serious AEs (SAEs) and treatment-related SAEs. Other treatment-related AEs are reported if not included on a list of 15 pre-specified events. Dose reductions are permitted in 50 mg decrements, if required.
Results: At data cut-off (1/3/07), 3663 pts from 27 countries had received $\geqslant$1 dose of erlotinib and were included in the database. Median age was 63 years (range 19−91); males 64%, females 36%; stage IIIB 22%, stage IV 78%; ECOG PS 0/1 75%, PS 2/3 25%; non-smoker 21%, ever smoker 79%; adenocarcinoma 49%, squamous cell 29%, other 22%; erlotinib 1st line 13%, 2nd line 46%, 3rd line 40%, other 1%. 55% of 3615 pts experienced grade (gr) 1/2 rash; 12% gr 3/4. 54% of 3448 pts experienced $\geqslant$1 AE, and 4% had a treatment-related SAE, most commonly gastrointestinal (GI) disorders (<1% gr 1, 2% $\geqslant$ gr 3). 8% of pts had an AE that was not pre-specified in the protocol. Erlotinib was discontinued in 6% of pts due to a treatment-related AE, mainly GI disorders (1% gr 1/2, 2% gr 3/4) and rash (1% gr 1/2, 1% gr 3/4). 13% of 3446 pts required dose reduction due to a treatment-related event, mostly rash (n = 324) or diarrhoea (n = 55). The disease control rate (CR, PR + SD) was 66% at the time of interim analysis (73% in 1st line, 64.5% in 2nd/3rd line) and median time to progression (TTP) was 11.3 wks (95% CI 10.6–12.0) across all treatment lines and 15.1 wks (12.7–16.1) in 1st-line pts. TTP was also longer in pts with good PS (15.1, 11.9, 8.6 and 6.1 wks for PS 0, 1, 2 and 3). Overall survival data is not yet mature.
Conclusions: These interim data from the TRUST European subpopulation confirm the favourable safety profile of erlotinib observed in previous clinical trials and its effectiveness when used in the wider clinical setting.