6569 POSTER

The quantification of plasmatic free DNA is a prognostic factor in advanced non-small cell lung cancer (NSCLC) patients

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Background: Qualitative and quantitative analysis of circulating DNA in blood is a promising non-invasive diagnostic and prognostic tool. Our aim was to study the association between the free amount in plasma of the catalytic subunit of telomerase (hTERT) and several clinical variables in advanced NSCLC patients.
Materials and Methods: We examined 451 NSCLC patients in stage IIIB and IV, treated with cisplatin and docetaxel. Blood samples were collected before chemotherapy, and circulating DNA was extracted from the serum using commercial adsorption columns. The amount of free hTERT in plasma was quantified by using RT-PCR.
Results: Median age was 61 years [35−82] and 84% were males. 99% had performance status 0−1. 84% were in stage IV and 16% in stage IIIB. The histological subtypes were: 32% squamous cell carcinoma, 50% adenocarcinoma, 14% anaplastic large cell, and 4% undifferentiated. 41% of the patients received second line chemotherapy. 1% achieved complete response (CR), 36% partial response (PR), 35% had stable disease (SD) and 28% progressive disease (PD). Median hTERT value was 4856 ng/ml; for patients in IIIB was 48 ng/ml [2–9648] and 48 ng/ml [0.6–43735] in stage IV (p = 0.75). There was not association between hTERT values and response to therapy. hTERT values were not related with the localization of the metastasis. Dividing the cohort in two sets according to hTERT median we found two significantly different groups in terms of Overall Survival (OS) and Time To Progression (TTP). Patients with hTERT 48 ng/ml was 4.1 m [3.5−4.6], (p = 0.0009). OS when hTERT 48 ng/ml was 8.4 m [7.2−9.5], (p = 0.01). In the multivariate analysis, hTERT was an independent predictive variable for TTP (HR 1.39, CI 95% 1.1−1.7, p = 0.002) and OS (HR 1.27, CI 95% 1.1−1.6, p = 0.04).
Conclusions: In advanced NSCLC patients, the quantification of free circulating hTERT in plasma is an affordable and valuable prognostic marker. High plasma hTERT levels are a poor prognostic indicator for TTP and OS.

6570 POSTER

Results for progression-free survival (PFS) from two randomised, double-blind, multicentre phase III studies of bevacizumab in combination with platin-based chemotherapy in patients with advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) are comparable when analysed by similar populations and methodology

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Background: ECOG's phase III open-label trial (E4599) demonstrated that bevacizumab (B) at 15 mg/kg with carboplatin/paclitaxel (CP) improved overall and progression-free survival (OS and PFS) in patients (pts) with advanced NSCLC [Sandler et al. NEJM 2006]. Study BO17704 demonstrated significant improvement in PFS with B at either of two doses, 15 mg/kg (high dose or HD) or 7.5 mg/kg (low dose or LD) added to cisplatin/ gemcitabine (CG) vs CG plus placebo in regions outside of the US.
Methods: Studies E4599 and BO17704 enrolled pts using similar criteria: previously untreated advanced or recurrent non-squamous NSCLC; ECOG PS 0–1; no brain metastases. In BO17704, pts were randomised to LD or HD B, or placebo. The primary endpoint analysis in BO17704 for progression-free survival (PFS) compared the pooled placebo arms vs B-LD or vs B-HD in two pair-wise comparisons for the intent-to-treat (ITT) population. Both studies combined B with chemotherapy for up to 6 cycles then B-alone until disease progression. In order to compare the PFS results of the two studies adequately, analyses were conducted using similar populations; all randomised and BO17704 all treated population (i.e. only patients who received protocol therapy in BO17704; ECOG-eligible population in E4599). Hazard ratios (HR) and confidence intervals (CI 95%) for PFS were calculated using the Cox Proportional Hazards Method.
Results: PFS results for BO17704 are compared to those of E4599 in the table. Results for BO17704 PFS based on dose-specific comparisons to the respective placebo arms will be presented.

	BO17704		E4599
	B-LD:Placebo	B-HD:Placebo	B-15:CP
All randomised[a]	n = 1043		n = 878
HR [CI]	**0.75 [0.62, 0.91]**	**0.82 [0.68, 0.98]**	0.69 [0.60, 0.79]
All treated[b]	n = 986		n = 850
HR [CI]	0.72 [0.60, 0.88]	0.75 [0.62, 0.91]	**0.66 [0.57, 0.77]**

[a]BO17704 Primary Analysis Population.
[b]E4599 Primary Analysis Population; ECOG-eligible (most similar to BO17704 safety population).

Conclusions: Study BO17704 PFS results compared to E4599 appear to vary with the population used for this comparison. Using the safety population for the comparison of these studies, which includes all patients who received protocol therapy, the treatment effect of B in advanced NSCLC observed in both B arms of BO17704 appears to be similar to the effect observed in E4599.

6571 POSTER

Open-label study of pemetrexed (P) alone or in combination with a platinum in patients (pts) with peritoneal mesothelioma (PM): results from the international expanded access program (EAP)

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Background: Few large studies have examined pts with PM; rather, treatment of this rare disease has typically followed advances demonstrated for pleural disease. The superior efficacy of P+cisplatin (Cis) versus Cis observed in the phase III trial of pleural mesothelioma led to the development of an EAP. Data from 3275 EAP participants were available. Here we report the results of P alone or with a platinum for the 109 EAP pts with PM (3.3% of the total).

	P	P+Cis	P+Cb
Baseline characteristics and Gr 3/4 toxicity (N = 109)	n = 38	n = 37	n = 34
Median age, yrs (range)	62 (43−79)	56 (24−74)	58.5 (33−76)
Male, % of pts	60.5	67.6	70.6
Karnofsky performance status ⩾80, % of pts[a]	83.3	85.3	90.6
Prior chemotherapy, % of pts[b]	78.4	35.1	48.4
Leukopenia, % of pts	31.4	13.5	25.0
Neutropenia, % of pts	40.0	27.0	37.5
Thrombocytopenia, % of pts	8.6	10.8	15.6
Anemia, % of pts	11.4	2.7	21.9
Efficacy[c] (N = 91)	n = 32	n = 30	n = 29
Response (CR+PR) rate, % of pts (95% CI)	12.5 (3.5, 29.0)	20.0 (7.7, 38.6)	24.1 (10.3, 43.5)
Disease control rate (responders +SD), % of pts, (95% CI)	50.0 (31.9, 68.1)	80.0 (61.4, 92.3)	75.9 (56.5, 89.7)
One-year survival rate, % (95% CI)	41.5 (4.6, 78.4)	57.4 (10.3, 100)	NE

[a]>90% of pts in each treatment arm were assessed for performance status.
[b]Pre-treatment status of 1 pt on the P arm and 1 pt on the P+Cb arm was not recorded.
[c]Time to progressive disease is not reported because it was not estimable (NE) for two arms.

Methods: Eligible pts had histologic or cytologic diagnosis of PM not amenable to curative surgery. P 500 mg/m^2 alone or in combination with either Cis 75 mg/m^2 or carboplatin (Cb) AUC 5 was given on day 1 of each 21-day cycle, with vitamin B_{12}, folic acid, and dexamethasone. Investigator-determined best response and survival data (with censoring) were recorded at the end of study participation. Myelosuppression data (NCI CTC, version 2.0) were also collected.
Results: In this nonrandomized, open-label study 109 pts received $\geqslant$1 dose of P, P+Cis, or P+Cb and were evaluable for safety; 91 pts were evaluable for efficacy. Baseline characteristics, efficacy, and safety data are summarized in the table. A higher percentage of pts on the P arm received prior therapy, which generally corresponded to greater toxicity.
Conclusions: The results of this large, nonrandomized study confirm that P and P+platinum are efficacious in the treatment of pts with PM. The response results are comparable to those previously reported for the EAP in pts with pleural mesothelioma.

6572 POSTER

Stereotactic body radiotherapy (SBRT) for lung cancer: Clinical experience for medically inoperable lung tumours with excellent local control

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Background: To report clinical results from ours first patients with resecable lung tumours, but clinically inoperable patients, treated with stereotactic body radiotherapy (SBRT) employing hypofractionated high dose fraction schedule.
Material and Methods: Between July 2002 and February 2007, 21 lung tumours patients have been treated using SBRT, all of them resecable, 20 medically inoperable, one operable but with 1 brain metastasis treated with radiosurgery. After immobilization with Stereotactic Body Frame (ELEKTA) we have made 3 CT simulation studies in 1 week and measured the variations in CTV and organs and calculated the position statistical variability to determine the PTV for each patient. All patients have been treated with 6 to 12 coplanar or no coplanar conformed beams (average 8.2 beams), 3 fractions in 1 week, the dose was prescribed to cover PTV with no more margin, T1 with 16 Gy each fraction and total dose of 48 Gy and T2−3 with 14 Gy/fraction and total dose of 42 Gy. Dose calculation included heterogeneity corrections. Follow-up was at 4−6 weeks and then every 3 months.
Results: For 21 patients, median age was 73 years (range 55−84). There were 19 males and 15 (83.3%) smokers. The mean follow-up was 15.8 months (range 1.5−56). All have pathology diagnosis: 8 SCC, 6 ADC, 1 SCLC and 6 non-specifics NSCLC. Pretreatment PET was made in 15 (71.4%) patients. Tumor stages were 10 T1, 9 T2, 1 T3, 1 metastasis, 1 local relapse. Four patients (19%) received previous cisplatin-based chemotherapy. All lesions were resecable, but 20 patients (95.2%) were medically inoperable. All SBRT was completed without interruptions. GTV mean volume was 16.2 ml (95% CI: 8.8−23.6), PTV mean volume was 52.2 ml (95% CI: 30.5−73.9). There was no acute esophagitis, one patient develops acute pneumonitis and no delayed lung toxicities were found. At the moment, only 10 patients were evaluated for response: 7 (70%) complete responses, 2 (20%) partial responses and 1 (10%) stable disease. No patient failed locally and only 2 patients (9.5%) developed distant metastasis.
Median survival was 30 month (95% CI: 9.2−50.8). Overall survival at 12 and 18 months were 83.9% (95% CI: 83.7−84.1) and 67.1% (95% CI: 66.8−67.4), respectively.
Conclusions: SBRT for lung cancer demonstrates a high response rate and excellent local control and survival. There are minimal toxicities and no treatment related deaths.

6573 POSTER

Clinical evidence for the radiosensitivity of mesothelioma following postoperative image-guided radiotherapy

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Background: The increasing incidence of mesothelioma presents a serious problem around the world with no standard therapy and no treatment proven to offer durable benefit. The high mortality rate has not significantly improved with radical surgery or new systemic therapies, but there is growing evidence that a trimodality approach using postoperative radiotherapy may be curative in selected patients. Mesothelioma is characterized by relentless locoregional growth that spreads beyond the scope of surgery, and it is timely to evaluate newer techniques of image-guided radiotherapy (IGRT) in this disease.
Objective: To document locoregional control from high dose postoperative radiotherapy in pleural mesothelioma patients who have PET scans accurately reflecting disease distribution.
Materials and Methods: Thirteen consecutive patients were treated with postoperative radiotherapy to regions of residual disease with doses of 45 to 60 Gy, after pleurectomy/decortications from 2003 to 2006. 3D-conformal or intensity-modulated radiotherapy techniques were used with PET/CT fusion IGRT. All had pre-treatment PET scans showing ^{18}FDG-avid disease, and post-treatment imaging including followup PET or PET/CT scans in 10 cases. All but one received intraoperative phototherapy. Ten had epithelioid and 3 had biphasic mesothelioma.
Results: There were no in-field relapses within the planning target volume (PTV) confirmed with PET scan co-registration, resulting in a local control rate of 100% at a median followup of 10 months post-radiotherapy. Relapses outside the PTV were found in 11 cases, all in multiple sites. Many were in areas deemed at moderate risk but not included in the PTV due to strict dose constraint criteria required to minimize the risk of major radiation toxicities.
No patient died as a consequence of radiotherapy. Radiation morbidity was seen in two cases, with transient grade 2 pneumonitis and liver injury, both patients remaining well and disease-free 30 months after surgery. Six received palliative chemotherapy for distant relapse and only 1 had neoadjuvant chemotherapy. Additional palliative radiotherapy was given in 2 cases.
Conclusions: Mesothelioma appears to be a radiosensitive disease that can be locally controlled by radiation doses of 50 Gy in conjunction with debulking surgery. Using modern technological advances in planning and delivery, radiotherapy can be administered safely and accurately without significantly damaging surrounding tissues.

6574 POSTER

A phase I/II study on stereotactic body radiotherapy for stage I non-small cell lung cancer

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Background: The outcome of stage I non-small cell lung cancer (NSCLC) patients treated with conventional radiotherapy is inferior to that of the patients treated with surgery. The aim of this study is to evaluate the clinical outcome of stereotactic body radiotherapy (SBRT) in the treatment of stage I NSCLC.
Materials and Methods: We performed SBRT on 31 patients with stage I NSCLC. Of the 31 patients, 20 were medically inoperable, and 11 refused surgery. Nineteen tumors were T1 stage masses and 12 tumors were T2. The median tumor size was 25 mm. SBRT was delivered at 45 Gy/3 fractions except in cases in which the tumor was close to an organ at risk, in which case we used 60 Gy/8 fractions. The radiation target was the primary tumor, and photon energy was 6 MV in all cases.
Results: The median duration of observation for all patients was 32 months (range 4−87 months). The 5-year overall and cause-specific survival rates were 48.9% and 62.6%, respectively. In 9 of the 31 cases, there was evidence of local recurrence. The local control rate of T1 tumors was 84.2% (16/19 cases) and of T2 tumors, 50.0% (6/12 cases). Five patients developed acute pulmonary toxicity greater than grade 2, although the symptoms improved with medical treatment.
Conclusions: SBRT was shown to be an effective treatment for stage I NSCLC patients, although the local control rate for T2 tumors was low. A more intensive treatment regimen should be considered for T2 tumors because no severe toxicity occurred.

6575 POSTER

Is there still a place for surgery in the treatment of locally-advanced non-small cell lung cancer (IIIA, N2)?

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Background: Surgical resection for patients with stage IIIA (N2) non-small cell lung cancer (NSCLC) results in disappointing 5-year survival