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Prognostic factors affecting survival on pretreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) – Subgroup analysis in a randomized Ph II study of pemetrexed 500 mg/m^2 and 1000 mg/m^2

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Background: The regimen with pemetrexed 500 mg/m^2 is used for patients with NSCLC in the 2nd or 3rd line settings in worldwide. In a Ph III study comparing pemetrexed with docetaxel in pretreated patients with NSCLC, good PS, early clinical stage, and more than 3 months from the last chemotherapy were identified as longer survival factors in pemetrexed arm. Results from latest randomized Phase II study with 2 dosages of pemetrexed 500 mg/m^2 (Pem 500) and 1000 mg/m^2 (Pem 1000) showed favorable response rates of 18.5% and 14.8%, respectively. We provide the survival outcome and examine the factors affecting longer survival.
Materials and Methods: Pts with PS 0−2, measurable, stage III/IV NSCLC, 1 or 2 previous chemotherapy regimens, were randomized to either Pem 500 or Pem 1000 on day 1 of a 21-day schedule. The planned total sample size was 240 pts. The survival analysis was performed for both arms.
Results: From October 2004 to October 2006, 244 pts were enrolled at 28 centers, 226 pts were randomized and treated, and 216 pts (Pem 500/Pem 1000: 108/108 pts) were evaluable for the survival analysis. Baseline patient characteristics (Pem 500/Pem 1000) were: Male 63%/64%; median age 62/62 years (range: 37−74/26−74); PS 1, 2 61%/67%; Stage IV 81%/80%. One-year survival rates were 59.2%/53.7% and MST were 15.7M/12.6M, respectively. Among the variables examined for the Cox regression analysis (age, gender, histology, time from the last chemotherapy, dosage, with or without a prior platinum regimen, performance status, number of regimen, and clinical stage), factors showed a statistical significance were gender (male/female: HR 2.14), histology (non-adenocarcinoma/adenocarcinoma: HR 2.13), time from the last chemotherapy (⩾3 months/<3 months: HR 0.56), performance status (PS 1, 2/0: HR 2.81), and clinical stage (IV/III: HR 1.81). There is no difference in two dosages.
Conclusions: Female, adenocarcinoma, a longer period from the last chemotherapy, good PS, and early clinical stage were identified as good prognostic factors. High dosage of 1000 mg/m^2 did not prolong survival longer than that of 500 mg/m^2, which supports the use of 500 mg/m^2 of pemetrexed in pretreated patients with NSCLC.

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Gated radiotherapy of lung cancer: interfractional changes in tumor volume and position during the treatment course

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Background: With the purpose of designing intelligent margins for curative radiotherapy, this study investigated the interfraction variations in tumor size and internal displacement with respiratory gating. The variations were also compared for different set up strategies.
Methods and Materials: During the treatment course, the patients underwent 3 respiratory gated CT-scans, equally spaced in time. The tumors were contoured on each CT-scan to evaluate the variation in volume and position. The primary lung tumors and the mediastinal tumors were contoured separately. The positional variations were measured as 3D mobility vectors and related to matching of the scans on the basis of bony landmarks and with skin tattoos.
Results: The median 3D mobility vector for the lung tumors was 0.52 cm for matching performed with bony landmarks and 0.81 cm for matching with skin tattoos. For the mediastinal tumors the corresponding vectors were 0.56 cm and 0.53 cm. The differences between the vectors were significant for the lung tumors. There was a significant reduction in tumor size from the first to the last CT-scan, both for lung (19%) and mediastinal tumors (34%). The interfractional overlap of lung tumors was 80−87% when matched using bony landmarks and 70−76% when matched using skin tattoos. The overlap of the mediastinal tumors were 60−65% and 41−47%, respectively.
Conclusions: The tumors varied considerably, regarding both tumor position and tumor volume. The variations in position were dependent on the set up strategy. Set up using skin tattoos was inferior to set up using bony landmarks.

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First-line treatment with vinorelbine (VNR) plus carboplatin (CBDCA) for patients with advanced non-small-cell lung cancer (NSCLC): MAP4/OP18 mRNA expression as marker predictive of response

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Background: Non-small-cell lung cancer (NSCLC) patients (pts) with locally advanced or metastatic disease at the time of diagnosis show marginal response to chemotherapy in terms of tumor shrinkage, time to progression and median survival. MAP4 and stathmin have been previously reported as potential markers of resistance to treatment based on microtubule-destabilizing agents.
Materials: 51 chemonaive pts with stage IIIB (with pleural effusion)-IV NSCLC and ECOG PS 0−1 were accrued at 7 sites between October 2003 and June 2006. Treatment consisted of CBDCA AUC5 IV day 1 plus VNR 25 mg/m^2 IV, days 1, 8 every 21 days. In this study, we have used quantitative PCR to analyze the expression of MAP4, stathmin, beta-tubulin III, BRCA1 and ERCC1 using mRNA isolated from peripheral blood samples.
Results: Median age 59 years (range 42−75); males 91%/females 9%; smokers: 72%; adenocarcinoma, 54%/squamous 33%; stage IIIB: 26%, IV: 74%. Median cycles: 3 (1−6). Hematological toxicities (%pts): grade 3/4 neutropenia, 18%/8%; grade 3/4 thrombocytopenia, 16%/6%; grade 3 anemia, 11%. Febrile neutropenia appeared in 2 pts (4%). Non-hematological toxicities (%pts): nausea/vomiting grade 3/4, 18%. Efficacy in evaluable population (n = 33): CR, 0%; PR, 39%; ORR, 66% (95% CI 47−73%); SD, 33%. With a median follow up of 7.2 months, median survival for the whole population was 7.75 (95% CI 6.98−8.51) months (mo), progression free survival 5.8 (95% CI 3.7−8.2) mo, 1-year survival 28.5%. In a preliminary set, 46 patients with stage IIIB and IV were analyzed. Lower levels of MAP4/OP18 mRNA expression are statistically associated with a response to vinorelbine-based treatment ($p = 0.029$). This significant relationship is maintained in a second analysis after 3rd cycle of treatment ($p = 0.032$). Higher levels of MAP4/OP18 were associated with a lower TTP ($p = 0.05$).
Conclusions: These preliminary results suggest that the ratio MAP4/OP18 may be a good predictor of response for NSCLC patients treated with vinorelbine-based chemotherapy.

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High-dose 130-nanometer albumin-bound paclitaxel in combination with carboplatin as first-line therapy in advanced non-small cell lung cancer

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Background: Carboplatin AUC of 6 mg/min·ml (C6) plus solvent-based (SB) paclitaxel (Taxol®) is a commonly used regimen in first line patients (pts) with advanced NSCLC resulting in response rates of 17–32%, median progression-free survivals (PFS) and survivals of 4–5 and 8–10 months, respectively. In these trials a median of 4 cycles were typically given and the rates of Grade (gr) 3 and 4 neutropenia and sensory neuropathy ranged between 35–63% and 3–15% respectively. We previously reported the results of solvent-free nab-paclitaxel (Abraxane®) 225–340 mg/m^2 and C6 both administered on day 1 every 3 weeks (q3w) in first line pts with NSCLC

[Hawkins et al., ASCO, 2006] At the time of that analysis, the objective response rate (ORR) in 25 patients in the highest dose group of nab-paclitaxel (340 mg/m^2) was 28% with median progression-free (PFS) and overall survivals of 4.6 and >7.0 months, respectively. Gr 3/4 neutropenia and sensory neuropathy (SN) were 32/16% and 24/0%, respectively. The aim of the current study was to obtain further clinical experience with nab-paclitaxel 340 mg/m^2 in combination with C6 in 76 additional pts with NSCLC.
Methods: Pts with previously untreated, stage IIIB or IV NSCLC with measurable disease and a life expectancy of over 12 weeks received nab-paclitaxel 340 mg/m^2 followed by carboplatin AUC 6 q3w.
Results: Patients Characteristics: 101 pts (99% Caucasian, 1% Hispanic; 80% male; median age, 59; performance status score: 0 [22%], 1 [78%]; stage IIIB [20%], IV [80%]). The median number of cycles was 6 and the median cumulative nab-paclitaxel dose was 1800 mg/m^2. The primary efficacy endpoints are provided in the table. Gr 3/4 hematologic toxicities were: neutropenia, 30%/20%; thrombocytopenia, 23%/4%; leukopenia, 22%/2%; anemia, 9%/5%. The most common non-hematologic toxicities (any grade) were SN, 87%; alopecia, 50%, fatigue, 38%; myalgia, 45%; arthralgia, 44%; nausea, 40%; and vomiting, 28%. Gr 2/3 SN were 22%/29%. Gr 3 SN improved by at least 1 gr in a median of 21 days.
Conclusions: The combination of nab-paclitaxel 340 mg/m^2 + C6 is very active with an ORR 33% in patients with advanced NSCLC. Preliminary PFS and survival data are encouraging. Hematologic toxicity was comparable to that reported with SB-paclitaxel and C6. The higher incidence of grade 3 SN was consistent with the increased dose of paclitaxel in our study, and was reversible. Mature PFS and survival data will be presented.

	nab-Paclitaxel 340 mg/m^2 + C6
ORR	33%
95% Confidence Interval (CI)	24–42
Disease Control[a]	48%
95% CI	38–57
Median PFS (months)	6.2 (62% of events)
95% CI	4.9–7.7
Median Survival (months)	13.1 (32% of events)
95% CI	11–17

[a]SD $\geqslant$16 weeks or Confirmed Response.

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Frontline cytotoxic chemotherapy (CTx) for newly diagnosed non-small cell lung cancer (NSCLC) patients presenting with brain metastasis compared to whole brain radiotherapy (WBRT): result of a randomized pilot study

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Background: WBRT followed by CTx is commonly used for NSCLC patients (pts) with brain metastasis. However, when neurologic symptoms or signs are absent or controlled by supportive care, CTx could be a choice of treatment. We conducted a randomized trial of frontline CTx compared with WBRT in this clinical setting whether frontline CTx was feasible and its efficacy and toxicity profile as well as quality of life and survival outcome was affected by the time of WBRT.
Materials and Methods: The eligibility criteria are as follows: pathologic confirmed NSCLC, stage IV with brain metastasis at first diagnosis, age 18−75, ECOG PS 0−2, and adequate organ functions. After stratified according to PS (ECOG 0−1 vs 2), the number of intracranial metastases (<3 vs 3$\leqslant$) and presence of extrathoracic extracranial metastasis, eligible pts were randomized to the two arms; Arm A, CTx followed by WBRT; Arm B, WBRT followed by CTx. CTx consisted of gemcitabine 900 mg/m^2 and vinorelbine 25 mg/m^2 on D1 & 8 q 3 wk, up to 6 cycles. WBRT consisted of 30 Gy/10fx/12d. We assessed tumor response, toxicity profile and quality of life according to WHO response criteria, NCICTC and EORTC C-30/LC-13 questionnaire, respectively.
Results: Between 2002 Aug and 2005 Nov, 48 pts were enrolled. All of 25 pts in Arm A received CTx and WBRT, while 4 (17%) of 23 pts in Arm B could not receive CTx due to deterioration of PS or death during or immediately after WBRT. Intracranial tumor responses to CTx in Arm A were closely correlated with extracranial responses (k=0.82). There were no statistically significant differences in overall response rate (28% vs. 43%), time-to-progression (3.6 mo vs 4.4 mo) and survival (9.1 mo vs 9.9 mo). However, grade 3/4 neutropenia occurred more frequently in Arm B (79% vs 40%, p = 0.014). Cognitive function deteriorated during frontline CTx, while it already deteriorated after WBRT but did not further deteriorate during chemotherapy.
Conclusions: Frontline chemotherapy can be an appropriate treatment when neurologic symptoms or signs are absent or controlled by supportive care. The timing and the real need for WBRT should be defined in further trials.

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Is relapsed small-cell lung cancer (SCLC) under treated?

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Background: Second line treatment of small cell lung cancer (SCLC) has long been a nihilistic area as patients with a short treatment free interval (TFI) are expected not to derive benefit. However a recent study (O'Brien et al, JCO, December 2006) reported that oral topotecan was associated with a prolongation of median survival and symptomatic benefit compared to best supportive care in patients with relapsed SCLC.
Methods: A retrospective analysis of 49 patients receiving second line chemotherapy between 2001–2006 for SCLC [26 with sensitive (>90 days TFI) and 23 with resistant (<90 days TFI) disease] was performed at the Royal Marsden Hospital, UK. We wished to determine if a subgroup of SCLC patients had significantly better outcomes following re-treatment with chemotherapy.
Results: The median age of patients was 61 (range 40−81 years) and 62 (range 34−85 years) with sensitive and resistant disease respectively. The majority of patients (76%) received carboplatin and etoposide first-line. The median TFI after first-line therapy was 303 days (sensitive disease, 95% CI 273 –365 days) and 49 days (resistant disease, 95% CI 21−77 days). At first disease relapse 33% of our patients had limited and 67% had extensive stage disease and the majority (53%) received an anthracycline-based regimen 2nd line.
Median overall survival was 26 weeks (95% CI 20−32 weeks) and median time to progression after 2nd line chemotherapy was 22 weeks (95% CI 13−30 weeks). Factors such as gender and age of patients or the presence of liver metastases had no significant effect on survival.

Table 1. Factors influencing survival after 2nd line chemotherapy (CT).

Variable	Group	MS (weeks)	95% CI	Significance
Gender	Male	24.7	19.5−30.3	0.733
	Female	36.8	15.6−58.0	
Age	<65 years	26.9	21.2−32.9	0.410
	>65 years	23.4	18.2−29.0	
Sensitivity to 1st line CT	Resistant	26	22.9−29.5	0.238
	Sensitive	23.8	6.9−40.3	
PS	1	45.5	25.6−65.4	**0.019**
	2	24.7	18.2−31.6	
	3	5.2		
Liver metastases	No	26.9	9.1−45.1	0.087
	Yes	25.1	15.6−34.7	

Performance status (PS) at the start of 2nd line chemotherapy had a significant impact on median survival: PS 1 (10.5 months) compared to PS 2 (5.7 months) and PS 3 (1.2) months (p = 0.019). Interestingly median survival was similar in patients with resistant disease (6 months) compared to sensitive (5.5 months) disease (p = 0.238).
Conclusions: These data suggest that contrary to current guidelines even patients with resistant disease can have good median survivals and chemotherapy should be considered in this group, particularly in those of good performance status.