108 lung cancer patients (stage IIIb-IV) were included. 55/108 had abnormal bone scan and received BPs (Group A)-zoledronic acid, 8 mg i.v. every 21 days- whereas the other 53 patients didn't receive BPs: 30/53 with abnormal bone scan (Group B) and 23/53 patients with normal bone scan (Group C-control group). All patients were treated with a combination chemotherapy consisted of taxan plus carboplatin.

Statistical results are shown in the Table below. Compared to Group C, Group A had a statistically significant longer survival (p=0.015), whereas Group B didn't show any statistical significant difference in survival compared to Group C (p>0.05). A statistically significant positive correlation was found between the number of cycles of therapy with BPs and total patients' survival (p<0.01 Pearson correlation) and time to progression(p<0.01). Pain effect of BPs didn't differ significantly in both groups of patients with abnormal bone scan (p>0.05).

	Median-Std Error for Survival Time
Group A	433 ± 78
Group B	252 ± 78
Group C	255 ± 87
p	0.004

The addition of BPs seems to increase overall survival in lung cancer patients with bone metastases. The longer period of receiving BPs, the better effect on survival and time to progression. Further studies are needed to support the potential usefulness of BPs as a therapeutic agent against lung cancer.

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Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC)

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Background: The multitargeted antifolate and potent TS inhibitor pemetrexed compared favorably (similar efficacy, lower toxicity) to docetaxel in a large, randomized phase III trial of previously treated patients with NSCLC. Preclinical data indicate that overexpression of TS correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. A recent study on chemonaive NSCLC patients indicated higher TS expression in squamous cell carcinoma than in adenocarcinoma. These data suggest that patients with adenocarcinoma may have greater sensitivity to pemetrexed compared to patients with squamous histology. A study to evaluate TS expression in large cell histology is currently being planned.

Methods: This is a retrospective analysis of the large phase III study of pemetrexed (500 mg/m^2 IV with vitamin B12 injections + oral folic acid) vs docetaxel (75 mg/m^2 IV) Q 21 days. A statistical test for treatment-by-histology interaction was performed using a Cox model of overall survival (OS) with main effects for treatment (pemetrexed vs docetaxel) and squamous histology (no vs yes) plus a treatment-by-histology interaction term (non-squamous pemetrexed vs all other). Since a potential for imbalances between arms with respect to prognostic factors within histologic groups existed, the models were cofactor-adjusted by including terms for ECOG performance status (PS 0-1 vs 2), time since prior chemotherapy (≥3 months vs < 3 months), disease stage (IIIB vs IV), and gender (female vs male). Subsequent Cox models of OS provided estimates of cofactor-adjusted treatment hazard ratios (HR) within histologic subgroups. Unadjusted medians within histologic subgroups were calculated using the Kaplan-Meier method.

Results: Treatment-by-histology interaction was statistically significant (p=.001), indicating that the effect of study treatment on survival varied with histology. Medians and hazard ratios by subgroup are presented in the table below. In the squamous cell subgroup, patients treated with docetaxel had statistically better survival than patients treated with pemetrexed (p=.018). However, for each of the non-squamous histologic subgroups the adjusted HRs numerically favored pemetrexed. When combining these into a single non-squamous subgroup, pemetrexed was statistically superior to docetaxel (p=.048).

Histologic Subgroup	N	Median OS, months	Adjusted HR (95% CI)
Squamous Cell:			
pemetrexed	78	6.2	
docetaxel	94	7.4	1.563 (1.079, 2.264)
Adenocarcinoma:			
pemetrexed	158	9.0	
docetaxel	144	9.2	0.915 (0.685, 1.224)
Large Cell:			
pemetrexed	18	12.8	
docetaxel	29	4.5	0.266 (0.112, 0.633)
Other/Indeterminate Histology:			
pemetrexed	29	9.4	
docetaxel	21	7.9	0.570 (0.270, 1.204)
Combined Non-Squamous:			
pemetrexed	205	9.3	
docetaxel	194	8.0	0.778 (0.607, 0.997)

Conclusions: The statistically significant treatment-by-histology interaction indicates that patients with non-squamous histology treated with pemetrexed had significantly higher survival compared to all others on trial. Docetaxel had statistically better survival than pemetrexed in the squamous cell subgroup, while pemetrexed had statistically better survival than docetaxel in the combined non-squamous subgroup. One hypothesis for this observed interaction is that TS overexpression in squamous cell carcinoma leads to reduced sens