

digital images of various areas of the tumor. Determinations of potential sensitivity or resistance was based on the relative level of comparative IF expression and comparison with an in vitro fluorescent reference standard. The criteria for resistance versus susceptible is established from the internal comparison for the in vitro studies. Within the eight lung cancer cell lines in culture, the comparatively resistant cells require 7-10 fold higher drug concentrations for the same cytotoxicity (IC50) than the comparatively susceptible cells. The expression levels of ERCC-1 and beta-tubulin III correlates well with these requirements of drug concentrations for same cytotoxicity (IC50) with a Pearson coefficient of about 0.9. IF signals exceeding those of the most resistant and overexpressing line were considered resistant. Final characterization of the tumor was based upon both the ERCC1 and BTUBB staining. Specimens sensitive to both agents were characterized as sensitive (S), all others were considered resistant (R). Laboratory personnel were blinded to pt identity and outcomes.

Results: 47 pts were enrolled on the study between 1/2000 and 5/2004. All pts have completed therapy. The median overall survival is 29.6 months and median event free survival is 16.9 months. Specimens from 10 pts have been analyzed. 4 were sensitive and 6 resistant. There was no difference in event free survival between the S and R groups. However, there was a trend (p=.08) towards improved overall survival in the S group.

Conclusions: 1. This IF assesment can be rapidly performed on paraffin blocks and provides a quantitative assessment of ERCC1 and BTUBB III expression that is not observer dependent. 2. These very preliminary data indicate that ERCC1 and BTUBB III may correlate with survival in Stage III NSCLC treated with CMT. Additional data will be available by the time of the meeting.

Supported by a Maryland Industrial Partnerships grant.

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NSCLC: Combined Modality Therapy Posters, Tue, Sept 4

Phase 1/2 trial of ABT-751 in combination with pemetrexed vs pemetrexed alone in subjects with advanced or metastatic non-small-cell lung cancer (NSCLC)

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Background: ABT-751 is an orally bioavailable sulfonamide that binds to the colchicine site on β -tubulin and inhibits polymerization of microtubules. Pemetrexed (Alimta[®]) is an antineoplastic agent that interrupts cell replication. Both compounds have been evaluated individually in advanced NSCLC subjects and in combination in preclinical xenograft models.

Methods: The Phase 1 open-label dose escalation portion of the study was designed to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RPTD) of ABT-751 when administered with pemetrexed. For each cycle, subjects received 500 mg/m² pemetrexed IV on Day 1 and ABT-751 orally QD for 14 consecutive days followed by 7 days off drug. Dose levels of ABT-751 began at 200 mg and escalated in 50 mg increments. Pharmacokinetic sampling was performed on Day 1 of Cycle 1. The Phase 2 portion of the study was designed to determine the effect of ABT-751 plus pemetrexed on progression-free survival.

Results: Nine subjects have been accrued into the Phase 1 portion of the study. The MTD and RPTD were determined to be 200 mg of ABT-751 QD for 14 days. Two of 6 subjects (33%) in the 250 mg cohort experienced a dose-limiting toxicity (DLT) (1 grade 3 [CTCAE version 3.0] neuropathy; 1 grade 5 intestinal infarction, shown by CT scan to be consistent with ischemic infarction). Two additional subjects reported grade 3 treatment-emergent adverse events (fatigue [2], constipation [1], dyspnea [1]), which the investigator considered probably or possibly related to ABT-751. Preliminary pharmacokinetic results for ABT-751 after the concomitant administration of ABT-751 and pemetrexed were comparable to those after the administration of ABT-751 alone in a previous Phase 1 study. Preliminary laboratory data for grade 3/4 hematologic parameters indicate the incidence of neutropenia was 2/8 (25%) and thrombocytopenia and anemia were each 0% for subjects receiving ABT-751 and pemetrexed. The incidences from the pemetrexed label are 5% for neutropenia, 2% for thrombocytopenia, and 8% for anemia. Two subjects had partial responses; 1 confirmed and 1 unconfirmed.

Pharmacokinetic parameters of ABT-751 after single oral dose of ABT-751

	200 mg ABT-751 With Pemetrexed	200 mg ABT-751 Alone#	250 mg ABT-751 With Pemetrexed##	250 mg ABT-751 Alone#
N	3	23	5	3
T _{max} (h)	0.8 ± 0.3	2.0 ± 1.3	3.2 ± 1.8	1.3 ± 0.6
C _{max} (µg/mL)	9.9 ± 9.8	9.1 ± 4.5	8.2 ± 4.2	10.9 ± 3.3
AUC ₀₋₈ (µg ^h /mL)	27.2 ± 12.9	33.0 ± 10.1	34.9 ± 15.8	45.5 ± 10.5

#From a previous Phase 1 study M01-303

One subject had unusually low drug plasma levels, which resulted in lower means for C_{max} and AUC₀₋₈ for the 250 mg dose.

Conclusions: Both the MTD and RPTD of the combination of ABT-751 and pemetrexed have been determined. Coadministration of pemetrexed with ABT-751 does not appear to affect the pharmacokinetic profile of ABT-751.

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NSCLC: Combined Modality Therapy Posters, Tue, Sept 4

Randomized phase III Trial comparing three chemotherapy regimens in advanced non-small cell lung cancer (NSCLC)

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Background: Lung cancer is the leading cause of cancer related death worldwide in both males and females. Despite the poor prognosis of patients with advanced NSCLC, treatment with the new generation chemotherapy agents has improved survival, quality of life and decreased toxicity compared to older regimens.

Methods: In this study, patients were randomly assigned to receive either paclitaxel 175mg/m² (day1) or gemcitabine 1,250mg/m² (days 1 and 8) both combined with cisplatin 80mg/m² (day 1) or paclitaxel 175mg/m² (day1) combined with gemcitabine 1,250 mg/m² (days 1 and 8) as first line therapy for stage III b having pleural effusion or supraclavicular lymph node metastasis and stage IV NSCLC. Primary endpoint was comparison of overall survival for the 3 arms. Secondary endpoints included response rate, progression free survival and toxicities.

Results: Sixty two patients (arm A, 19, arm B 23, arm C 20 patients) were enrolled. Major clinical characteristics in arm A/B/C were: Median age 51, 50, and 47 years, stage IV 14 %, 13 %, and 16 %, respectively.

performance status 2 was evident in 26.3 %, 26 %, and 5 % respectively. Among all the patients treated the overall response rate (RR) was 53.2%, 95% confidence interval 40.1-66%. Response rates were 52.6% for arm A, 65.2% for arm B, and 40% for arm C.

The median survival times were as follows: Arm A, 9.8 months, arm B, 12 months, arm C, 9.2 months. Survival did not differ among the 3 arms (p=0.42). The one year survival rate was 26.3 %, 34.7 % and 25% in groups A, B and C respectively. Survival for two years or more was evident in 10.5%, 17.3%, and 5% in group A, B, and C respectively. The median time to progression was 5 months for arm A, 11 months for arm B and 6.3 months for arm C. The median number of cycles was 4 with range 1-6 cycles.

In general, the 3 regimens were well tolerated: Neutropenia (all grades) was encountered in 31.5 %, 47.7 %, and 15 %, thrombocytopenia was encountered in 5.2 %, 26 % and 5 % and anemia occurred in 31.5 %, 34.8 % and 35 % in groups A, B and C respectively. As for non hematological toxicity, arm A and C had more tendency to neuropathy while arm B had tendency to hepatotoxicity but there were no statistical differences.

Conclusion: Our results showed that paclitaxel/cisplatin, gemcitabine/cisplatin, and paclitaxel/gemcitabine combinations provide no significant difference in response, survival or toxicity. Treatment was well tolerated by the patients in the 3 different groups.

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A multicenter phase II study of carboplatin plus gemcitabine followed by concomitant chemoradiation in patients with non-resectable stage III non-small-cell-lung cancer: preliminary report of the Cher@Nos trial

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Background: Combined chemoradiotherapy is now considered the standard of care in patients with unresectable stage III NSCLC. Despite the therapeutic advances that have been made during the last decennium, there remains a need for better local and distal control of disease in patients with locally advanced NSCLC. At present it is not clear which combined modality approach provides optimal results (both in terms of survival and toxicity).

In the present study we wanted to evaluate whether by combining a carboplatin-gemcitabine based induction chemotherapy with weekly cisplatin during standard thoracic radiotherapy, it is possible to obtain good efficacy with minimal toxicity

Methods: Patients (PS 0-1) with unresectable stage III NSCLC were treated with 3 cycles of induction chemotherapy followed by chemo-radiotherapy. The induction chemotherapy consisted of carboplatin (AUC 5 on day 1) with gemcitabine (1200 mg/m² on day 1 and 8) every 3 weeks for 3 cycles. The chemo-radiotherapy consisted of cisplatin (30 mg/m² weekly) concomitant with conventional radiotherapy (2.0 Gy/fraction, 5 fractions a week, up to a total dose of 60 Gy). The primary endpoint of this phase II trial was a survival rate at 2 years of >35%.

Results: Between February 2003 and November 2005, 45 patients were enrolled: The demographics were as follows: 34/11 male/female, 14/30 stage IIIA/IIIB, median age 62 y (range 41-81 y), 42% squamous cell and 33% adenocarcinoma. All patients received at least one cycle of induction chemotherapy: 7% only 1 cycle, 7% 2 cycles and 87% all 3 cycles. Chemoradiotherapy was started in 36 patients. Median total radiation dose and duration was 60 Gy and 43 days.

Grade 3/4 toxicities during chemotherapy were: neutropenia (36%), thrombocytopenia (18%), febrile neutropenia (1%), rash (1%), elevation of transaminases (1%) and constipation (1%). The effect of the treatment on the pulmonary function is summarized in the following table:

	Baseline	Post-chemo	Post-chemoradio	Follow-up at 6 months	Follow-up at 12 months
Mean FEV1 (L)	2.26	2.42	2.48	2.33	2.27
Mean FVC (L)	3.19	3.41	3.14	3.32	3.05
Mean DLCO (%)	67.7	60.4	60.7	64.2	65.4

The overall response rate was 31% (2% CR, 29% PR) following induction chemotherapy, and 58% (2% CR, 56% PR) at the end of treatment. With a median follow-up of 14.4 months (range 1-35 months), the median progression-free survival is 10.6 months. The overall 1- and 2-year survivals are 61% and 39%.

Conclusions: The preliminary results from this phase II trial showed that induction chemotherapy with carboplatin and gemcitabine followed by thoracic radiotherapy with concurrent weekly cisplatin is a well tolerated combined modality approach with promising overall survival in patients with unresectable stage III NSCLC.

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NSCLC: Combined Modality Therapy Posters, Tue, Sept 4

Mediastinal-based treatment decision tree in stage IIIA-N2 non-small cell lung cancer

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Involvement of N2 lymphatic structures, i.e. ipsilateral mediastinal lymph nodes in non-small cell cancer of the lung represents a very inhomogeneous disease, according to size, number, location, extension, and biologic features. Despite recent advances, the therapeutic strategy for stage IIIA subcategory remains unclear, particularly regarding the role of surgical resection. Controversial recent data suggest a potential impact of post-induction surgery specifically limited to patients who respond at the mediastinal level. Others make differences in approaches according to the location of mediastinal N2 involvement. Authors propose a simple decision-making algorithm based upon last advances in imaging, clinical trials, mediastinal status, response after induction, staging and re-staging new techniques, and current burning remaining questions.