Methods: NSCLC pts who received none or only one cytotoxic treatment for advanced disease were screened by FISH for EGFR gene amplification and/or high polysomy. Other eligibility criteria included stage IIIB/IV, PS 0−2, and no prior TKI. Enrolled pts were treated with A (50 mg, daily oral dosing). Pts with available tumour tissue were tested for the common EGFR mutations in exons 19 and 21 by PCR single-strand conformation polymorphism analysis and direct sequencing. The primary endpoint was objective response rate (ORR) per RECIST, with tumour imaging performed every 8 weeks.
Results: Through April 2011, 69 EGFR FISH+ pts have entered the trial and started treatment: 41 pts received A first line and 28 pts second line, 52% were men, and the median age was 67 years. Only 30% of pts were never-smokers. Among 54 evaluable pts, we observed 11 responses to A (1 CR and 10 PRs; confirmed thus far in 7 pts) for an ORR of 20%. Response rate was similar between first- and second-line pts. Regarding EGFR mutation status among responders, 5 of 8 pts have thus far tested negative. Three additional pts had tumour decreases of 29.7%, 29% and 26%. Of the 8 pts with stable disease (SD) for at least 16 wks, 6 of 6 have so far tested negative for EGFR mutations including 1 pt with ongoing SD at 96+ weeks. 36% of all pts had disease control lasting at least 16 weeks. The safety profile of A was similar to that seen previously: diarrhea and rash/acne were the 2 most common adverse events and were effectively managed by supportive care and/or dose reduction.
Conclusions: Afatinib showed encouraging activity and acceptable toxicity in this Phase II trial in EGFR FISH+ pts with advanced NSCLC. Among those tested thus far, EGFR mutation results have been negative for a majority of responders and all pts with SD of at least 16 weeks duration. Further investigations of A in EGFR FISH+ NSCLC is warranted especially as efficacy in non-mutated pts has been observed in this trial.

Oral Presentations (Sun, 25 Sep, 09:00−10:10)
Lung Cancer − Localised/Local Regional

9008 ORAL

Randomized Phase III Trial of Adjuvant Chemotherapy With Gemcitabine Compared With Oral Tegafur-uracil (UFT) in Resected, Stage IB-IIIa Non-small Cell Lung Cancer (WJTOG 0101)

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Background: LACE meta-analysis indicated that adjuvant cisplatin doublet therapy benefits patients with completely resected, stage II-III but not stage I non-small cell lung cancer (NSCLC). On the other hand, milder adjuvant chemotherapy with oral uracil-tegafur (UFT) confers modest but significant benefit in resected NSCLC including stage I as shown by the meta-analysis. Single-agent gemcitabine is considered to be intermediate between platinum doublet and UFT in terms of both tumour response and toxicity in metastatic NSCLC. In this study, we compared adjuvant gemcitabine monotherapy with UFT in an attempt to show superiority of gemcitabine.
Methods: From May 2001 to Dec 2005, 608 patients with completely resected stage IB-IIIA NSCLC were randomized either to receive gemcitabine (GEM) (1000 mg/m^2 day 1 and 8, q3week) X 6 courses or oral UFT 250 mg/m^2 daily for 1 year. Stratification factors included performance status, age, extent of lymph node dissection and institutions. The primary endpoint was overall survival (OS) and the secondary endpoints were disease free survival (DFS) and toxicity.
Results: Patient demographics were well balanced between the arms in terms of sex, age, histologic type or stage. However, pneumonectomy were less frequent in GEM arm (2.7% vs. 8.8%). 61% of patients in GEM arm completed 6 cycles and median administration time of UFT was 289 days. Both treatments were in general well tolerated and there were no treatment related deaths. Final toxicity results are not available as of April, 2011. There was no significant difference in terms of DFS and OS. Median DFS and OS were 87 months and not reached in GEM arm, and 63 months and 108 months in UFT arm, respectively. Hazard ratio was 1.06 (95% confidence interval; 0.813–1.370). Exploratory analyses failed to identify any patient subset that showed difference by the treatment arms. However, there was a weak trend that GEM benefited patients younger than 65.
Conclusion:GEM monotherapy was feasible as adjuvant chemotherapy for completed resected NSCLC, however there was no superiority to oral UFT.

9009 ORAL

Immunohistochemical Analysis of a Panel of DNA Repair Proteins in NSCLC Predict for Cisplatin Benefit in Resected Squamous-cell Carcinoma but Not in Adenocarcinoma

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Background: Cisplatin acts through DNA adduct formation and subsequent induction of cell death. Most NSCLC patients receive cisplatin-based chemotherapy even though clinical response is restricted to a subset of patients. DNA repair protein levels are possible surrogates for adduct repair efficiency and thus may serve as molecular determinants of therapeutic efficacy. The IALT-bio study previously suggested ERCC1 and MSH2 levels as predictive of cisplatin-based therapeutic benefit.
Materials and Methods: DNA repair protein expression was assessed by immunohistochemistry (IHC) on TMAs of a large subset of patients (N = 550–716 depending on the marker) from the IALT lung trial. Slides were digitally scanned and signal quantified by user defined macros. Statistical analyses used binary cut-offs on median H-score against 5 yr-DFS and 5 yr-OS, both with and without adjustments on selected clinical variables.
Results: IHC expression levels of XPF, BRCA1, ERCC1, MSH2, p53, PARP1, and ATM were examined. By stratifying patient groups based on SCC and adenocarcinoma, several markers displayed statistically significant p-values including ATM, p53, PARP1 and confirmed previous results with ERCC1 and MSH2 (Table 1). All significant p-values for predictive response were seen in SCC, not in adenocarcinoma.
Conclusions: The predictive utility of a panel of DNA repair enzymes co-segregates exclusively with SCC histology, limiting the utility of evaluation of DNA repair enzyme levels to this histological subclass of NSCLC. Distinct mechanistic pathways of response or resistance to chemotherapy might exist in different histologies in solid tumour malignancies.

Table 1. Prognostic and predictive value of DNA repair proteins (adjusted or not on classical clinical variables)

Protein	5-Year DFS				5-Year OS			
	no var		adj var		no var		adj var	
	Prog	Pred	Prog	Pred	Prog	Pred	Prog	Pred
ERCC1								
SCC	**0.010**	**0.006**	**0.031**	**0.010**	0.073	0.052	0.152	0.063
Adeno	0.865	0.612	0.774	0.326	0.322	0.930	0.548	0.236
ATM								
SCC	0.167	**0.011**	0.214	**0.005**	0.458	**0.049**	0.504	**0.027**
Adeno	0.633	0.269	0.200	0.131	0.744	0.269	0.387	0.230
PARP1								
SCC	0.054	**0.023**	0.056	**0.035**	0.095	**0.048**	0.097	0.069
Adeno	0.632	0.790	0.688	0.505	0.327	0.913	0.361	0.180
p53								
SCC	0.080	**0.026**	0.076	**0.039**	**0.032**	**0.011**	**0.049**	**0.027**
Adeno	0.234	0.720	0.117	0.190	0.653	0.729	0.462	0.169
MSH2								
SCC	**0.028**	**0.011**	0.142	**0.037**	0.181	0.118	0.516	0.236
Adeno	0.331	0.220	0.916	0.951	0.133	0.246	0.542	0.733
BRCA1								
SCC	0.756	0.718	0.922	0.776	0.975	0.747	0.968	0.816
Adeno	0.997	0.256	0.628	0.678	0.944	0.478	0.694	0.746
XPF								
SCC	0.295	0.152	0.417	0.241	0.482	0.301	0.660	0.436
Adeno	0.449	0.195	0.297	0.311	0.882	0.730	0.892	0.771