9004 ORAL

BRCA1 and Astrocyte Elevated Gene-1 (AEG-1) Expression and Outcome of Erlotinib-Treated Non-Small-Cell Lung Cancer (NSCLC) Patients (p) Harboring Epidermal Growth Factor Receptor (EGFR) Mutations

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Background: Progression-free survival (PFS) to erlotinib is 14 months (m) in EGFR-mutant NSCLC p. Aberrant expression of components of DNA repair pathways could shed light on the variability of PFS in these patients.
Material and Methods: We used the NanoString nCounter gene expression system, which captures and counts individual mRNA transcripts, to analyze the expression of 44 selected genes in 55 erlotinib-treated NSCLC p with EGFR mutations. Quantitative PCR was used to validate results in these 55 p and to confirm our findings in 22 additional p. Expression levels were correlated with clinical outcomes in all 77 p.
Results: We generated a two-gene risk model, classifying patients into low-, intermediate-, and high-risk groups, based on expression levels of both BRCA1 and AEG-1. PFS was not reached in the low-risk group, while it was 18 m for the intermediate-risk group and 8 m for the high-risk group ($P = 0.00006$) (HR for high- vs low-risk groups, 6.6; 95% CI, 2−4-18; $P < 0.00001$). MS was not reached in the low-risk group, while it was 31 m for the intermediate-risk group and 18 m for the high-risk group ($P = 0.05$). Complete response was attained in 42.9% of patients in the low-risk group, compared to 3% in the intermediate-risk group and 0% in the high-risk group ($P = 0.02$). In the multivariate analysis for PFS, the only independent prognostic variables were bone metastases (HR, 2.7; 95% CI, 1.1−6.5; $P = 0.03$) and the AEG-1/BRCA1 risk groups (HR for high-risk group, 7.7 (95% CI, 2.8–21.3; $P < 0.00001$).
Conclusions: The BRCA1/AEG-1 model provides robust predictive information, making it a useful tool for therapeutic decision making.

9005 ORAL

Is There a Benefit to Maintenance Therapy After First Line Chemotherapy in Advanced Non-small Cell Lung Cancer − a Systematic Review With Meta-analysis

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Background: Maintenance therapy refers to a treatment of extended duration after frontline induction chemotherapy (CT), for patients with advanced non-small cell lung cancer (NSCLC). Several recent randomized clinical trials (RCTs) showed a survival benefit for maintenance therapy, especially for EGFR tyrosine-kinase inhibitors (TKI), but conflicting results have been published. We performed a meta-analysis of all RCTs, published either as articles or as abstracts.
Patients and Methods: PubMed query using keywords simultaneously: Non Small cell Lung Cancer, Maintenance, Randomized Controlled trials, Survival found 70 references. Abstracts from ASCO and ESMO proceedings were also reviewed. Endpoints were Overall Survival (OS) and Progression Free Survival (PFS). We used a fixed-effect model when heterogeneity was absent and a random-effect model when present. We used EasyMA software.
We included 11 RCTs with IFCT-GFPC trial used twice since it studied 2 maintenance options, chemotherapy and Erlotinib (a TKI). These 11 RCTs included 4281 patients (mean age 61.7 years, 2907 men/1345 women, stage III/IV 1007/3206, adenocarcinoma/ squamous/other histology 2101/998/753, PS0/1/2 1600/2232/241, 2337 received active drugs).
Results: The 5 RCTs assesing a TKI found a statistically significant increase in PFS (HR 0.76; 0.62–0.93, $p = 0.007$) but not in OS (both using random-effect model due to heterogeneity with fixed-effect model). This benefit was higher when pooling only the 3 Erlotinib studies (HR OS 0.85, 0.76–0.95, $p = 0.003$; HR PFS 0.71, 0.64–0.79, $p = 0.001$, fixed-effect models).
Switch maintenance with CT (3 RCTs) significantly improved OS (HR 0.85, 0.75–0.98, $p = 0.02$) and PFS (HR 0.66, 0.57–0.76, $p = 0.001$). Continuation maintenance with CT (4 RCTs) did not improve OS (random-effect model). Side-effects were less precisely assessed by the authors in the RCTs. TKIs induced cutaneous rashes and diarrheas. As expected, all CT increased haematological side-effects.
Conclusions: Maintenance therapy, either TKI (erlotinib) or switch CT, significantly improved both OS and PFS. The benefits/risks balance of these 2 kinds of switch maintenance therapy should be compared.

9006 ORAL

Results of a Phase 2 Study of Gemcitabine/Cisplatin/Iniparib (GCI) Versus Gemcitabine/cisplatin (GC) in Patients With Advanced NSCLC

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Background: Iniparib (BSI-201) is a novel agent being studied in combination with chemotherapeutic agents in a range of solid tumours. At high μM concentrations, iniparib binds to PARP1; however, the mechanism of action is not fully understood and is under investigation. Iniparib combined with gemcitabine/carboplatin (GCI) improved efficacy outcomes in a Phase 2 study in patients (pts) with metastatic triple-negative breast cancer with no increase in toxicity; however, an OS benefit was not confirmed in the Phase 3 setting. The present randomised, open label Phase 2 study will be the first completed efficacy trial in NSCLC of iniparib in combination with GC as first-line therapy (Clinicaltrials.gov number NCT01086254).
Methods: Eligible pts ($n = 119$) had histologically confirmed stage IV NSCLC, without prior chemotherapy for stage IV disease. Pts were randomised (2:1) to receive G (1250 mg/m^2, IV; d 1, 8), and C (75 mg/m^2, IV; d 1) (GC), ± iniparib (5.6 mg/kg, IV; d 1, 4, 8, 11; GCI) every 21 days for a maximum of 6 cycles. The primary objective was investigator assessed overall response rate. Secondary objectives were to assess OS, PFS, safety and biomarker utility. Randomisation was stratified by tumour histology (squamous/non-squamous) and smoking status.
Results: Pts received GCI (77 treated) or GC (39 treated). Median age was 59 years (29–73); 76% male; 12% of pts had squamous cell carcinoma and 70% adenocarcinoma; 13 (11%) were never-smokers. ECOG PS 0 vs.1 was 49 vs. 51% and 61 vs. 39% in the GC/GCI arms, respectively. As of December 2010, >60% of pts were still receiving treatment. Dose reductions, dose intensity, number of cycles (median 3), and discontinuations due to tumour progression or adverse events were similar in both arms. The safety profile was similar in both arms; however, more pts in the GC arm required dose reductions due to neutropenia (23.1 vs. 10.4%). Febrile neutropenia was only reported in the GC arm ($n = 2$). Rates of thrombocytopenia were similar in the GC/GCI arms (10.3 vs. 9.1%, all grades); asthenia was more frequent in the GC vs. GCI arm (66.7 vs. 46.8%, all grades; 15.4 vs. 4.9%, Grade 3/4). Neurotoxicity (all grades) was more frequent in the GC arm, with no Grade 3/4 events.
Conclusions: In pts with metastatic NSCLC, combination therapy with GCI had a similar safety profile to that seen with standard doses of GC, with no additional toxicities. Final efficacy and safety data will be presented.

9007 ORAL

Phase II Study of Afatinib (BIBW 2992), an Irreversible ErbB Family Blocker, in Patients With EGFR FISH-positive Advanced NSCLC

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Background: Afatinib (A), a potent irreversible tyrosine kinase inhibitor (TKI) of the erbB family of receptors, has previously shown high activity in NSCLC patients (pts) harboring EGFR mutations (Yang et al., ESMO 2010, Abstract 367PD). However, it is not known if this activity extends to those pts with increased EGFR gene copy number (GCN). We conducted a multicenter Phase II study to evaluate efficacy of A in pts with advanced NSCLC and increased EGFR GCN identified by FISH testing.

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