9116 POSTER

First Report of Upfront Treatment With Gefitinib in Comparison With Chemotherapy in Advanced Non-Small Cell Lung Cancer Patients From South India − Analysis of 120 Patients

R. Louis[1], R. Rajendranath[1], G. Prasanth[1], T.G. Sagar[1], A. Arvind Krishnamurthy[2]. *[1]Cancer Institute (WIA), Department of Medical Oncology, Chennai, [2]Cancer Institute (WIA), Department of Surgical Oncology, Chennai, India*

Background: Lung Cancer is the commonest cause of cancer deaths in males and sixth among females in South India. Lung cancer is being increasingly recognized among non-smokers.
Material and Methods: Stage IIIB and IV advanced non-small cell lung cancer (NSCLC) patients (n = 120) treated from January 2009 to December 2010 were retrospectively analysed. Baseline clinical parameters, treatment protocol, response to therapy and survival were noted. Decision to use upfront Gefitinib was based on parameters like female sex, non-smoking status, adenocarcinoma histology and poor PS as EGFR mutation data was not available in majority. Progression free survival (PFS) and overall survival (OS) were analyzed by the Kaplan Meier method and prognosis by log rank test and Cox regression.
Results: *Baseline parameters:* Median age: 60 years (22−78 years); males sex: 83 (69.2%); Stage IV: 95 (79.2%); Adenocarcinoma: 109 (90.8%); Smokers: 66 (55%); PS 2/3:65(54.2%); *First line therapy*: Gefitinib: 47 (39.2%), chemotherapy: 73(60.8%). Among those progressing after chemotherapy, 17 (23%) received second line Gefitinib. After a median follow up of 7.5 months (1−26 mo), median PFS and OS were 5 months (0−23 mo) and 7.5 months (1−26 mo) respectively. On univariate analysis (Table 1), PFS was significantly improved for non-smokers, females, and upfront treatment with Gefitinib. The only significant factor which affected OS was female sex. No factors were significant on multivariate analysis. Among PS 2/3 patients, PFS was significantly more with Gefitinib (n = 36) than with single agent chemotherapy (n = 29) [median PFS of 10 mo (95% CI 6.4–13.5 mo) versus 4 mo (95% CI 3.4–4.8 mo) (p = 0.017)].
Conclusion: In the largest series on the use of first line Gefitinib from India, we found it to be a useful agent in the treatment of NSCLC especially in females, patients with poor PS and non-smokers, even without EGFR mutation testing. Second line Gefitinib may have negated overall survival differences. However, EGFR mutation studies may help in further individualization of therapy.

Table 1. Univariate analysis of prognostic factors

Parameter	N	PFS (months)	P value (log rank)	OS (months)	P value (log rank)
Age			0.93		0.245
age⩽60 y	71	6		11 mo	
age >60 y	49	5		9 mo	
Sex			**0.024***		**0.042***
Male	83	5		9 mo	
Female	37	7		18 mo	
Histology			0.815		0.77
Adenocarcinoma	109	5		10 mo	
Squamous	11	6		13 mo	
Smoking status			**0.010***		0.110
Smokers	66	4		8 mo	
Non-smokers	54	7		11 mo	
First-line therapy			**0.014***		0.53
Chemotherapy	73	4		10 mo	
Gefitinib	47	10		10 mo	

*Significant p value

9117 POSTER

Randomized Phase II Trial of Zoledronic Acid in Combination With Docetaxel in Previously Treated Non-small Cell Lung Cancer (NSCLC) Patients With Bone Metastases − Result of a West Japan Oncology Group Study

F. Hirai[1], H. Murakami[2], N. Yamamoto[2], T. Yamanaka[3], I. Okamoto[4], T. Sawa[5], T. Hirashima[6], K. Takeda[7], M. Fukuoka[4], K. Nakagawa[4]. *[1]National Kyushu Cancer Center, Department of Thoracic Oncology, Fukuoka, [2]Shizuoka Cancer Center, Division of Thoracic Oncology, Shizuoka, [3]National Kyushu Cancer Center, Laboratory of Cancer Biostatistics Institute for Clinical Research, Fukuoka, [4]Kinki University Faculty of Medicine, Department of Medical Oncology, Osaka, [5]Gifu. Municipal Hospital, Division of Rospiratory Medicine and Medical Oncology, Gifu, [6]Osaka Prefectural Medical Center for Respiratory and Allegic Disease, Department of Thoracic Malignancy, Osaka, [7]Osaka City General Hospital, Department of ClinicalOncology, Osaka, Japan*

Background: The aim of this open-label, multicenter, randomized phase II trial was to evaluate the efficacy and safety of zoledronic acid, nitrogen-containing bisphosphonate, in combination with docetaxel in previously treated NSCLC patients with bone metastases.
Material and Methods: Previously treated NSCLC patients with bone metastases were randomly assigned to receive either docetaxel 60 mg/m^2 with or without zoledronic acid 4 mg on day 1 every 21 days. The study treatment was repeated until disease progression, intolerable toxicity, or discontinuation for another reason. The primary endpoint was progression-free survival (PFS), and secondary endpoints were overall survival (OS), objective response rate (ORR), skeletal-related event (SRE) rate, SRE-free survival, and safety. All patients were followed-up until one year after the last patient enrollment.
Results: From May 2007 to March 2010, 100 patients were enrolled from 15 institutions; 50 patients were randomly assigned to docetaxel plus zoledronic acid (DZ) and 50 to docetaxel alone (D). Patient characteristics were well-balanced. Forty-nine patients in the DZ group received zoledronic acid with a median of three cycles (range 1 to 19). Of 94 patients for efficacy analysis (48 for DZ and 46 for D), the median OS was 10.4 (95% CI, 7.0–15.8) months in the DZ group, as compared with 9.7 (95% CI, 6.1–12.5) months in the D group (stratified log-rank test, p = 0.62). The median PFS in the two groups was 2.7 and 2.6 months, respectively (stratified log-rank test, p = 0.89), with corresponding ORRs of 8% (95% CI, 2−20) and 4% (95% CI, 1−14). The median SRE-free survival in the two groups was 7.2 and 6.0 months, respectively (stratified log-rank test, p = 0.84). The SRE rates at one year were 30% (95% CI, 18−48) for the DZ group and 39% (95% CI, 24−57) for the D group. There were no clinically relevant differences in the frequencies of grade 3 to 4 adverse events between the two groups. No treatment-related death was observed in the DZ group.
Conclusions: The addition of zoledronic acid to docetaxel was well tolerated, but did not improved PFS and OS in unselected NSCLC patients with bone metastases.

9118 POSTER

Prospective Assesment of Combined Pemetrexed and Erlotinib or Gefitinib Therapy After the Relapse to Erlotinib or Gefitinib in Patients With Advanced Non-Small Cell Lung Cancer Having an Active Epidermal Growth Factor Receptor Mutation

K. Okishio[1], N. Yoshimura[2], T. Kimura[2], H. Daga[3], K. Takeda[3], T. Kawaguchi[1], M. Kobayashi[4], T. Hirashima[4], K. Hirata[2], S. Kudoh[2]. *[1]Kinki-Chuo Chest Medical Center, Internal Medicine, Osaka, [2]Graduate School of Medicine Osaka City University, Department of Respiratory Medicine, Osaka, [3]Osaka City General Hospital, Department of Clinical Oncology, Osaka, [4]Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, Department of Thoracic Malignancy, Osaka, Japan*

Background: In patients who develop acquired resistance to erlotinib or gefitinib, some tumour cells may remain sensitive to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI). Gefitinib suppressed the expression of thymidylate synthase in non-small cell lung cancer (NSCLC) cell lines. Low thymidylate synthase expression is a predictive factor for the treatment efficacy of pemetorexed in NSCLC patients. The purpose of this phase II trial was to evaluate the efficacy and toxicity of pemetrexed combined with erlotinib or gefininib after the relapse to erlotinib or gefitinib in patients with advanced NSCLC having an active EGFR mutation.
Methods: Eligibility criteria included histologically or cytologically proven NSCLC with an active EGFR mutation after the relapse to erlotinib or gefitinib, measurable leasions, Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) 0−2, and adequate organ function. Pemetrexed (500 mg/m^2) was administered on day1, and erlotinib or gefininib was sequentially administered on days 2−16. This combination

treatment was repeated every 3 weeks until disease progression. Primary endpoint was disease control rate (DCR), and secondary endpoint was toxicities, response rate (RR), progression-free survival (PFS), and overall survival (OS).
Results: Between February 2010 and April 2011, 27 patients were enrolled: male/female 20/7; madian age, 67 years (range, 48−83); PS 0/1/2, 6/20/1; stage IIIB/IV, 0/27; adeno/squamous carcinoma, 26/1. The median number of prior chemotherapy regimen was 2 (range, 0−6). Toxicity and efficacy could be evaluated in 22 patients, and the median treatment cycle number was 6 (range, 1−6). DCR was 86.4% (95% CI 65.1–97.1%), and RR was 31.8% (95% CI 13.9–54.9%). Grade 3/4 toxicities were neutropenia, leucopenia, and anemia in 4 (18%), 3 (14%), 2 (9%) patients, respectively. Grade 3 pulmonary toxicity and infection were noted in 1 (5%) patient each. There was no treatment-related death. Survival was evaluated in 18 patients: median PFS was 6.2 months, and median OS was not reached.
Conclusions: The pemetrexed plus erlotinib or gefitinib combination treatment shows high DCR and acceptable toxicity. Phase III trial for pemetrexed alone versus pemetrexed plus EGFR-TKI after the relapse to EGFR-TKI is warranted.

9119 POSTER

Combination of Pertuzumab and Erlotinib as 2nd-/3rd-Line (2/3L) Treatment for Patients (pts) With Metastatic Non-Small Cell Lung Cancer (NSCLC) − Safety and Anti-Tumour Activity by FDG-PET/CT Imaging Changes

B. Hughes[1], L. Mileshkin[2], P. Townley[3], B. Gitlitz[4], K. Eaton[5], P. Mitchell[6], R. Hicks[2], D. Loecke[7], L. Amler[7], A. Pirzkall[7]. *[1]Royal Brisbane and Women's Hospital, Cancer Care Services, Brisbane, [2]Peter MacCallum Cancer Centre, Division of Haematology and Medical Oncology, Melbourne, Australia; [3]Methodist Estabrook Cancer Center, Nebraska Cancer Specialists, Omaha, [4]University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, [5]University of Washington Medical Center, Department of Internal Medicine, Seattle, USA; [6]Austin Hospital, Ludwig Medical Oncology Department, Melbourne, Australia; [7]Genentech, BioOncology, South San Francisco, USA*

Background: Erlotinib is a small molecule inhibitor of EGFR (HER1). Pertuzumab is an antibody targeting HER2 and inhibiting heterodimerisation with other HER proteins. The combination of erlotinib and pertuzumab may result in a more comprehensive blockade of HER signalling than either agent alone. Clinical studies with either agent alone suggest FDG-PET (PET) provides more robust therapeutic response assessment than CT.
Material and Methods: In this single-arm, open-label Phase II study, pts with relapsed NSCLC received erlotinib (150 mg [n = 35] or 100 mg [n = 6; post-protocol amendment] po qd) and pertuzumab (840 mg loading dose/420 mg maintenance iv q3w) until disease progression or intolerable toxicity. PET/CT was done at baseline (BL) and day (d) 14, 28 and 56. Diagnostic CT was done at BL, d56 and every 42 d thereafter. PET response was determined by central review; partial metabolic response (PMR) was pre-defined as mean decrease of $\geqslant$20% in SUV_{max} across target lesions (max=5). CT response and progression-free survival (PFS) were investigator-assessed. The primary endpoint was the PET response rate (RR) at d56 in all pts and those with EGFR wild-type (wt) tumours. Secondary endpoints included PFS, overall survival (OS) and safety. (NCT00855894; sponsor Genentech).
Results: 41 pts were treated at 5 Australian and 4 US sites. The overall PET RR was 31.7% at d14 and 19.5% at d56 compared with a 12.2% CT RR at d56. Of 5 pts with CT response at d56 (1 complete and 4 partial responses), all (except 1 omitted scan at d14) had PMR or complete metabolic response (CMR) by PET at d14 and d56; all 5 had activating EGFR mutations. Overall, PET CMR or PMR was seen in 13 pts (d14) and 8 pts (d56); 4/11 (d14) and 2/8 (d56) pts were EGFR wt. Both d14 and d56 PET CMR or PMR but not CT partial response were associated with prolonged PFS and OS ($p < 0.05$). CTCAE grade $\geqslant$3 events deemed to be treatment-related were observed in 28 pts (68.3%), including diarrhoea (13; 31.7%), rash (8; 19.5%), fatigue (6; 14.6%), decreased appetite (3; 7.3%), vomiting (3; 7.3%) and pneumatosis intestinalis (3; 7.3%). 30 pts (73.2%) required erlotinib dose modifications, and 9 of 39 pts (23.1%) discontinued treatment due to adverse events.
Conclusions: The combination of pertuzumab and erlotinib shows activity, independent of EGFR mutation status, suggesting benefit from a more comprehensive HER blockade in relapsed NSCLC. However, the tolerability of the combination may limit its clinical use.

9120 POSTER

Linifanib Plus Carboplatin/Paclitaxel (CP) in Japanese Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) − Phase 1 Preliminary Results

F. Ohyanagi[1], T. Horai[1], M. Nishio[1], I. Sekine[2], N. Yamamoto[2], K. Nakagawa[3], I. Okamoto[3], M. Terashima[4], X. Li[5], T. Tamura[2]. *[1]Japanese Foundation for Cancer Research, Thoracic Medical Oncology, Tokyo, [2]National Cancer Center Hospital, Thoracic Oncology, Tokyo, [3]Kinki University, Medical Oncology, Osaka, [4]Nara Hospital Kinki University, Medical Oncology, Ikoma-city, Japan; [5]Abbott Laboratories, Pharmacokinetics, Abbott Park IL, USA*

Background: Linifanib (ABT-869), a potent and selective inhibitor of vascular endothelial growth factor and platelet derived growth factor receptor tyrosine kinases, potentiates the action of CP in preclinical tumour models including NSCLC. This study (Linifanib plus CP in Japanese Subjects with NSCLC; NCT01225302; currently recruiting; sponsor: Abbott Laboratories) assessed safety and tolerability of linifanib plus CP in Japanese NSCLC patients, pharmacokinetics (PK), and preliminary anti-tumour activity.
Material and Methods: Patients $\geqslant$20 years of age with primarily non-squamous histology, ECOG PS score $\leqslant$1, and no prior chemotherapy for NSLCL, received standard CP [C area under the concentration-time curve 6 mg/mL/min; P 200 mg/m^2 on day (d) 1 of every 21-day cycle (c)] and oral linifanib 7.5 mg or 12.5 mg daily starting d3c1 until progressive disease (PD) or unacceptable toxicity. The 12.5 mg cohort was opened at the completion of c1 for patients at 7.5 mg. CT scans were performed every 2 cycles (6 weeks). Evaluations included adverse events (AE, NCI CTCAE v4), efficacy (RECIST 1.1), and PK interactions between CP and linifanib.
Results: Enrollment of patients included 6 at 7.5 mg linifanib and 6 at 12.5 mg. One patient in each cohort experienced a dose-limiting toxicity of grade (G) 4 thrombocytopenia. One patient at 7.5 mg had a serious AE of febrile neutropenia at c2. Seven patients have had partial responses (PR).

Patients	Linifanib dose (mg)		Dose delays/interruptions due to AE		Assessment	
	Initial	Current	Linifanib	CP	End c2	End c4
100101	7.5	7.5	G2 anal mucositis	−	SD	SD
100201	7.5	5.0	G3 febrile neutropenia G3 thrombocytopenia	−	PR	PR
100202	7.5	0	G3 leukopenia G4 thrombocytopenia G4 neutropenia	G3 leukopenia G4 neutropenia	PR	NA
100203	7.5	0	−	−	PR	PD
100301	7.5	5.0	G4 neutropenia	−	PR	PR
100302	7.5	0	G3 thrombocytopenia	−	PR	PD
200101	12.5	12.5	−	−	PR	PR
200102	12.5	12.5	G3 thrombocytopenia	−	SD	NA
200103	12.5	12.5	G3 thrombocytopenia	−	SD	*
200104	12.5	12.5	−	−	*	*
200201	12.5	0	G3 leukopenia G4 thrombocytopenia G4 neutropenia	−	NA	NA
200202	12.5	12.5	G2 thrombocytopenia G3 leukopenia G4 neutropenia	−	PR	*

− No events; *Scheduled after April 15, 2011; NA = not assessed; SD = stable disease.

Other G3/4 AEs (all G3) were lung infection, sensory disturbance, and anemia aggravated. Results from the PK analysis will be presented.
Conclusion: Preliminary findings suggest that CP with daily linifanib is tolerable in Japanese patients with advanced/metastatic NSCLC. PRs have been observed. Updated results of this ongoing study will be presented.