Preoperative gefitinib in clinical stage I NSCLC

Lara-Guerra, Humberto; Leighl, Natasha; Salvarrey, Alexandra; Sakurada, Akira; Paul, Narinder S.; Boerner, Scott; Pond, Greg R.; Shepherd, Frances A.; Tsao, Ming S.; Waddell, Thomas K.

University Health Network, Toronto, ON, Canada

Background: Epidermal Growth Factor Receptor tyrosine kinase Inhibitors (EGFR-TKI) have proven selective efficacy in advanced NSCLC where potential predictors of response have been studied. Their role in early stage NSCLC has not been established.

Purpose: Using pharmacodynamic sampling pre- and post-therapy with gefitinib, 1) to assess the impact of gefitinib on EGFR intracellular signaling pathways; and 2) to assess response and toxicity rates after preoperative gefitinib (Iressa, AstraZeneca)

Methods: Stage I NSCLC patients received gefitinib (Iressa, 250 mg/day) for 28 days followed by mediastinoscopy and surgical resection in a single arm open label study. Tumor response was evaluated by RECIST. Pre-treatment (snap frozen, core needle biopsy) and post-operative (snap frozen and formalin fixed, surgical specimen) tumor samples were obtained. Mutation analysis of EGFR exons 19 and 21 was performed by PCR fragment length analysis and direct sequencing. EGFR, its phospho-isoforms and intracellular signaling pathways were analyzed by immunohistochemistry.

Results: Thirty-four patients have completed treatment. Mean follow-up is 4.7 months (2.3-11.6). Sixty-five percent of cases were active smokers, 38% former smokers and 12% never smoked. No unexpected toxicities during gefitinib treatment were seen. Five patients had serious adverse events within 30 days post-surgery (2 pulmonary infections, 2 prolonged air leaks, 1 pulmonary embolism). Four (12%) patients had exon 19 deletions and two (6%) had exon 21 point mutations. Two pts with exon 19 deletions had a partial response (PR) to treatment, the others stable disease (SD). One pt with exon 21 point mutation had a PR, the other SD. In patients without mutation, 1 had a PR, 22 SD, and 3 PD on therapy. The overall response rate was 11.7% in the sample. No differences in mutations were detected comparing pre- and post-treatment specimens.

Conclusions: Gefitinib can be administered safely preoperatively in early NSCLC. EGFR mutation analysis is feasible on percutaneous biopsies. Short-term EGFR TKI treatment does not result on changes in mutation profile. Comparison of pre- and post-therapy tumor samples may allow additional understanding of EGFR TKI resistance and facilitate patient selection.

Overall, response rates and predictors of response in early stage NSCLC are not different from advanced disease.

PD3-2-5

Molecular Targeted Therapy: EGFR inhibitors, Thu, 12:30 - 14:15

Preoperative gefitinib in clinical stage I NSCLC

Lara-Guerra, Humberto; Leighl, Natasha; Salvarrey, Alexandra; Sakurada, Akira; Paul, Narinder S.; Boerner, Scott; Pond, Greg R.; Shepherd, Frances A.; Tsao, Ming S.; Waddell, Thomas K.

University Health Network, Toronto, ON, Canada

Background: Epidermal Growth Factor Receptor tyrosine kinase Inhibitors (EGFR-TKI) have proven selective efficacy in advanced NSCLC where potential predictors of response have been studied. Their role in early stage NSCLC has not been established.

Purpose: Using pharmacodynamic sampling pre- and post-therapy with gefitinib, 1) to assess the impact of gefitinib on EGFR intracellular signaling pathways; and 2) to assess response and toxicity rates after preoperative gefitinib (Iressa, AstraZeneca)

Methods: Stage I NSCLC patients received gefitinib (Iressa, 250 mg/day) for 28 days followed by mediastinoscopy and surgical resection in a single arm open label study. Tumor response was evaluated by RECIST. Pre-treatment (snap frozen, core needle biopsy) and post-operative (snap frozen and formalin fixed, surgical specimen) tumor samples were obtained. Mutation analysis of EGFR exons 19 and 21 was performed by PCR fragment length analysis and direct sequencing. EGFR, its phospho-isoforms and intracellular signaling pathways were analyzed by immunohistochemistry.

Results: Thirty-four patients have completed treatment. Mean follow-up is 4.7 months (2.3-11.6). Sixty-five percent of cases were active smokers, 38% former smokers and 12% never smoked. No unexpected toxicities during gefitinib treatment were seen. Five patients had serious adverse events within 30 days post-surgery (2 pulmonary infections, 2 prolonged air leaks, 1 pulmonary embolism). Four (12%) patients had exon 19 deletions and two (6%) had exon 21 point mutations. Two pts with exon 19 deletions had a partial response (PR) to treatment, the others stable disease (SD). One pt with exon 21 point mutation had a PR, the other SD. In patients without mutation, 1 had a PR, 22 SD, and 3 PD on therapy. The overall response rate was 11.7% in the sample. No differences in mutations were detected comparing pre- and post-treatment specimens.

Conclusions: Gefitinib can be administered safely preoperatively in early NSCLC. EGFR mutation analysis is feasible on percutaneous biopsies. Short-term EGFR TKI treatment does not result on changes in mutation profile. Comparison of pre- and post-therapy tumor samples may allow additional understanding of EGFR TKI resistance and facilitate patient selection.

Overall, response rates and predictors of response in early stage NSCLC are not different from advanced disease.

PD3-2-6

Molecular Targeted Therapy: EGFR inhibitors, Thu, 12:30 - 14:15

Interim safety results from the East/South East (E/SE) Asian subgroup of the open-label TRUST (TaRceva Iung cancer Survival Treatment) study of erlotinib for advanced non-small-cell lung cancer (NSCLC)

Park, Keunchil1 Lee, Jong-Seok2 Wu, Yi-Long3 Zhang, Li3 Cheng, Ashley4 Siu-Kie-Au, Joseph5 Voravud, Narin6 Muthalib, Abdul8 Wahid, Mohd Ibrahim A.9 Yang, Chih-Hsin9

1 Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea 2 Seoul National University Bundang Hospital, Sungnam, Korea 3 Guangdong Provincial People’s Hospital, Guangzhou, China 4 Sun Yat-Sen University Cancer Center, Guangzhou, China 5 Princess Margaret Hospital, Kwai Chung, China 6 Queen Elizabeth Hospital, Kowloon, China 7 King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand 8 MMC Hospital, Jakarta, Indonesia 9 Pantai Medical Centre, Kuala Lumpur, Malaysia 10 National Taiwan University Hospital, Taipei, Taiwan

Background: The phase III Randomised BR.21 study demonstrated that in patients with relapsed advanced NSCLC, erlotinib (Tarceva®) improved survival and prolonged time to symptom deterioration compared with placebo (Shepherd et al. NEJM 2005;353:123-132). Erlotinib was well tolerated, with rash and diarrhoea the most common adverse events (AEs), both being generally mild to moderate in severity. The global, open-label TRUST study was initiated to provide erlotinib access to patients with advanced NSCLC. Data are reported here for the E/SE subgroup.

Methods: Eligible patients with stage IIB/IV NSCLC had failed previous chemotherapy for advanced disease (≤2 prior regimens) or were unsuitable for chemotherapy. Erlotinib was administered orally 150mg/
day until disease progression or unacceptable toxicity. Dose reductions (50mg increments) were allowed as required. The NCI-CTC v3.0 was used to assess toxicities, including: incidence and grade of erlotinib-related rash; serious AEs (SAEs) and treatment-related SAEs; and AEs leading to treatment withdrawal. Other treatment-related AEs were reported if they were not included on a list of 15 pre-specified AEs in the study protocol (rash; pruritis; dry skin; diarrhea; nausea; vomiting; stomatitis; abdominal pain; fatigue; dyspnoea; cough; anorexia; infection; conjunctivitis; and keratoconjunctivitis sicca).

**Results:** 885 patients were included in the analysis at the data cut-off (20/11/06) from Taiwan (n=297), mainland China (n=248), Hong Kong (n=160), South Korea (n=146), Thailand (n=30), Indonesia (n=2) and Malaysia (n=2). The median age was 61 years (range 22-95). Patient characteristics included: male 55%, female 45%; stage IIB 20%, stage IV 79% (no data 1%); ECOG PS 0 15%, PS 1 67%, PS 2 14%, PS 3 4%; non-smoker 52%, ever-smoker 47% (no data <1%); adenocarcinoma 68%, squamous-cell carcinoma 19%, other 13%; erlotinib 1st line 11%, 2nd line 55%, 3rd line 33%, other <1%. Data on the occurrence of rash were available for 882 patients, 83% of whom experienced rash, mostly grade 1/2 (88% of those with rash). Adverse event (AE) safety data were available for 598 patients, 54% of whom experienced at least one AE. 19 patients (3%) had treatment-related SAEs, most commonly gastrointestinal (GI) disorders (1%), including abdominal pain (n=2), diarrhea (n=5) and gastric ulcer haemorrhage (n=1). 17% of patients had at least one other treatment-related AE that was not pre-specified (3% had at least one grade 3/4 event); mucosal inflammation occurred in 3% of patients (<1% grade 3/4), but no other single event occurred in more than 2% of patients. Treatment-related interstitial lung disease (ILD; grade 2) was suspected in one patient, but this event was not reported as an SAE and did not lead to treatment withdrawal; the patient continued on erlotinib until disease progression. 18 patients (3%) had at least one treatment-related AE leading to withdrawal of erlotinib; the most common such events were rash (4 patients), diarrhea (3 patients) and pneumonitis (3 patients). Among 589 patients with available data, 76 (13%) required dose reduction due to a treatment-related event, mainly rash (n=57). Efficacy data will be presented.

**Conclusions:** Safety data for the E/S Asian patient population in TRUST support the safety profile of erlotinib seen in clinical trials. The incidence of ILD and ILD-like events is <1%, which is in-keeping with what has been seen with erlotinib universally. In the ‘real-life’ clinical setting, erlotinib is well tolerated, with full therapeutic doses administered to the majority of patients.

**PD3-2-8** Molecular Targeted Therapy: EGFR inhibitors, Thu, 12:30 - 14:15

Phase II Trial of Cetuximab (C225) in Combination with Monthly Carboplatin (Cb) and Weekly Paclitaxel (Pac) in Patients with Advanced NSCLC: Promising Early Results

Langer, Corey J.1 Ruth, Karen2 Borghaei, Hossein1 Treat, Joseph A.1 Shafer, Danielle1 Millenson, Michael1 Tuttle, Holly1 Rovito, Marc4 Mintzer, David5

1 Fox Chase Cancer Center, Philadelphia, PA, USA 2 Fox Chase Cancer Center Statistics Division, Philadelphia, PA, USA 3 Oncology Physicians Network, Philadelphia, PA, USA 4 Delaware County, Philadelphia, PA, USA 5 Pennsylvania Hospital, Philadelphia, PA, USA

**Background:** C225 is a unique monoclonal antibody targeting epidermal growth factor receptor. Weekly C225 in combination with standard q 3 week PacCb yielded a median survival of nearly 11 months in a large phase II trial of SWOG (Kelly, ASCO 2006), and is currently being tested in combination with bevacizumab and PacCb. We mounted a phase II trial of this agent in combination with monthly Cb and weekly Pac, in an effort to capitalize on potential synergy between taxane and C225, and to mitigate taxane-induced neuropathy and myalgia/arthralgias.