Conclusions: In this randomized Phase II trial of 1st-line advanced NSCLC, vandetanib + CP met the primary endpoint of prolonging PFS vs CP but did not provide a detectable survival advantage. Treatment options with vandetanib in 1st-line NSCLC continue to be explored, and Phase III evaluation of vandetanib in advanced, previously treated NSCLC is ongoing.

C1-03 Molecular Targeted Therapy: Beyong EGFR, Wed, 10:30 - 12:15

A phase III randomised, double blind, placebo controlled trial of gemcitabine/carboplatin with or without thalidomide in advanced non-small cell lung cancer (NSCLC)

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Background: We hypothesised that thalidomide, an oral anti-angiogenic agent with tumour vasculature stabilising, anti-cachexic and immuno-modulatory properties, when combined with chemotherapy and as maintenance treatment would improve survival in patients with stage IIIb or IV NSCLC. Thalidomide has already been shown to be effective in treating myeloma. Here, we present the preliminary findings of the largest phase III trial of thalidomide conducted in NSCLC to date.

Methods: Chemo-naive patients with pathologically proven NSCLC, Stage IIIb or IV disease and ECOG performance status (PS) 0-2 were entered into a double-blind placebo-controlled trial from 66 centres in the UK. Patients had adequate renal and haematologic function for platinum based treatment and an estimated life expectancy of greater than 8 weeks. All patients received up to 4 cycles of Gemcitabine 1200 mg/m^2 IV (days 1 & 8 of 21 day cycle) and Carboplatin AUC 5 (day 1). Patients were randomised to receive placebo or thalidomide taken orally from the start of chemotherapy and then daily for up to 2 years. The thalidomide/placebo dose began at 100mg/day during chemotherapy. If the patient was able to tolerate this dose, it was increased to 150mg/day after the last chemotherapy cycle for one month, then to 200mg/day for the rest of the trial. Strict guidelines were given regarding pregnancy testing and contraceptive measures. The study end-points were overall survival, time to disease progression, response rates, toxicity and quality of life. The trial had 80% power to show a difference in the overall survival rate at 2 years of 7% (from 12 to 19%).

Results: Between 2003 and 2006, 722 patients were randomized (placebo n=350; thalidomide n =372). The median age was 63 yrs (range 33-84); 64% were male; main histological subtypes were adenocarcinoma (36%) and squamous cell carcinoma (32%); 44% had stage IIIB and 56% had stage IV disease; and majority had good performance status (ECOG score of 0 and 1 were 31%, 59% respectively). Baseline patient characteristics were well balanced between the arms. The proportions of patients completing all 4 intended chemotherapy cycles were 67% (placebo) and 65% (thalidomide), and the proportions of patients who had their chemotherapy dose delayed or reduced were similar between the trial arms. At the time of this analysis the median follow-up in all patients was 18 months and 620 had died (295 placebo and 325 thalidomide), of which 90% were reported to have died from lung cancer. There was no evidence of a difference in overall survival. The median survival was 8.9 months (placebo) and 8.4 months (thalidomide). The hazard ratio was 1.13 (95% CI 0.96 to 1.32), p=0.14 from a logrank test. The 2-year survival rate was 14% and 10% in the placebo and thalidomide arms respectively. Subgroup analyses based on gender, age, performance status, tumour stage and cell type did not provide any evidence of a beneficial effect of thalidomide for any of these factors. The results on progression-free survival were consistent with those on overall survival, and again showed no survival effect of using thalidomide. The main adverse effect associated with thalidomide was a thrombotic event and this was easily treated with anti-coagulants. 117 patients experienced at least one such event (mainly pulmonary embolus and deep vein thrombosis) with 20% in the thalidomide arm compared to 12% on placebo - relative risk of 1.68 (95% CI 1.19 to 2.38). There was no statistically significant difference in haematological toxicities, 40% (placebo) vs 43% (thalidomide), or non-haematological toxicities (excluding thrombotic events), 16% (placebo) vs 19% (thalidomide).

Conclusions - Preliminary analyses demonstrated that thalidomide in combination with gemcitabine and carboplatin and as maintenance treatment in chemotherapy-naive NSCLC patients did not improve survival and progression-free survival over gemcitabine and carboplatin alone and was associated with increased thrombotic events. The final analyses, including those on quality of life and response rates, will be presented for both treatment groups.

C1-04 Molecular Targeted Therapy: Beyong EGFR, Wed, 10:30 - 12:15

A phase II study of RAD001 (everolimus) monotherapy in patients with advanced non-small cell lung cancer (NSCLC) failing prior platinum-based chemotherapy (C) or prior C and EGFR inhibitors (EGFR-I)

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Background: RAD001®, an oral inhibitor of the mammalian target of rapamycin (mTOR) that has shown anti-tumor activity both as single-agent and in combination with other anticancer agents in *in vitro* and *in vivo* NSCLC models. In a phase I study, 4 disease stabilizations (SD) and 1 partial response (PR) as per RECIST were reported from 14 NSCLC pts treated with R monotherapy.

Methods: Advanced NSCLC pts with adequate organ function, performance status ≤ 2, failing either ≤ 2 C (arm 1) or ≤ 2 C and an EGFR-I (arm 2) were treated with R at 10 mg qd if tolerable until progression (PD). The study applied a Simon-2-stage design with primary endpoint of objective tumor response rate (RR) according to RECIST. CT scans were performed every 28 days until month 4 and then every 2 months thereafter. Adverse events (AE) were assessed using NCI CTC v.3.0. Biomarker analysis was performed on tumor tissues.

Results: This analysis is based on data acquired up to 20Sep2006. 85 pts were enrolled between Aug 2005 and May 2006. Demographics and patient disposition were (arm 1/arm 2): 42/43 (7 pts ongoing), female 38.1%/51.2%, never smoker 14.3%/44.2%, adenoca. 57.1%/62.8%,