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A phase III study of erlotinib as maintenance therapy in NSCLC to delay progression following first-line chemotherapy (SATURN)

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Background: Erlotinib (Tarceva®), a small molecule tyrosine-kinase inhibitor of the epidermal growth factor receptor (EGFR), has proven efficacy in second-line advanced non-small-cell lung cancer (NSCLC; Shepherd et al, 2005). The phase III SATURN study (BO18192, Roche, complete) was initiated to determine the efficacy and tolerability of erlotinib as first-line maintenance immediately following non-progression with chemotherapy (CT).
Materials and Methods: Patients (pts) who received 4 cycles of CT without unacceptable toxicity and/or progressive disease were randomised to receive either erlotinib 150 mg/day or placebo until progression or unacceptable toxicity. Co-primary endpoints were progression-free survival (PFS) in all pts and PFS in pts with EGFR immunohistochemistry-positive (IHC+) disease.
Results: Of the 1,949 pts who were enrolled and received initial CT, 889 were subsequently randomised to erlotinib (n = 438; median age 60yrs) or placebo (n = 451; median age 60yrs). Baseline characteristics were similar in both arms; 14% of patients were Asian. EGFR IHC status (% +/−/unavailable) was 70/14/16 for erlotinib and 69/13/18 for placebo. Co-primary endpoints were met, with significantly prolonged PFS (as determined by investigator assessment) seen with erlotinib versus placebo in all pts (hazard ratio (HR) 0.71 [95% CI 0.62−0.82]; p = 0.000003) and in pts with EGFR IHC+ disease (HR 0.69 [95% CI 0.58−0.82]; p = 0.00002). Pre-planned subgroup analyses found that erlotinib maintenance provided a PFS benefit in all pts regardless of histology, smoking status, gender, ECOG PS, EGFR expression or ethnicity. Overall survival data will be presented. Quality of life (FACT-L questionnaire) was similar in both arms. Erlotinib significantly extended time to pain (HR 0.61; p = 0.008) and time to analgesic use (HR 0.66; p = 0.0199). Rash and diarrhoea were the most common treatment-related toxicities (TRTs); most cases were grade 1/2. Serious TRTs occurred in 10 pts (2.3%) in the erlotinib arm and one (0.2%) in the placebo arm, and 14 pts withdrew from the study due to a TRT (12 of whom received erlotinib).
Conclusions: Erlotinib is effective in significantly prolonging PFS as maintenance therapy following first-line CT. This approach allows us to maintain and improve the benefits of first-line therapy in advanced NSCLC without negatively impacting quality of life.

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Influence of aromatase and epidermal growth factor receptor inhibitors in non-small cell lung cancer

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Background: Estrogen and epidermal growth factor receptor (EGFR) pathways are important in the progression of non-small cell lung cancer (NSCLC). Aromatase is an enzyme complex that catalyses the final step in estrogen synthesis and is present in several tissues, including the lung. Deregulation of EGFR signaling may induce cell proliferation and metastasis. The aim of this study is to investigate whether the dual inhibition of aromatase and EGFR may improve the antitumor effect of each target alone.
Material and Methods: In the current study we used exemestane, an irreversible steroidal aromatase inactivator, and erlotinib, an EGFR tyrosine kinase inhibitor. *In vitro* experiments were performed using H23 and A549, two NSCLC cell lines with low and high levels of aromatase, respectively. Cell proliferation was measured by MTT assay. Zymography was used to detect metalloproteinase (MMP) levels and boyden chamber assay was used to determine cell migration. Immunofluorescense assay was performed to detect EGFR protein location.
Results: Exemestane and erlotinib inhibited H23 and A549 cell proliferation either alone or in combination, 48h after their application. However, the combination of exemestane and erlotinib had a synergistic effect on H23 cell proliferation. Additionally, exemestane decreased MMP-2 and MMP-9 levels in H23 cells while erlotinib did not affect the MMPs levels. The combination of both agents caused the same result as exemestane alone. The effect in cell migration was in line with the results in MMP levels. No change was found in MMP levels or cell migration in A549 cells. Moreover, we found that exemestane altered the location of EGFR protein in H23 cells without affecting EGFR protein location in A549 cells.
Conclusions: Although each agent alone exerted an antitumor effect on the proliferation of both cell lines, the combination had a synergistic effect in H23 cells. The sensitivity of cells with low levels of aromatase in the combination of exemestane and erlotinib might have an additive effect of exemestane on EGFR protein levels. Erlotinib did not enhance the effect of exemestane on MMPs secretion and migration in the same cells.

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Molecular and clinical biomarkers of outcome with cetuximab: Data from the phase III FLEX study in non-small cell lung cancer (NSCLC)

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Background: The phase III FLEX study showed that adding cetuximab to a standard 1st-line platinum-based chemotherapy (CT) increases overall survival time (OS) compared to CT alone in patients (pts) with advanced NSCLC. This analysis investigated the potential of molecular and clinical markers to predict cetuximab efficacy.
Materials and Methods: KRAS mutations (codons 12/13) and EGFR kinase domain mutations (KDMs) were detected in genomic DNA derived from formalin-fixed paraffin-embedded tumor tissue using an LNA-mediated qPCR clamping assay and a mutation-specific real-time PCR assay, respectively. EGFR gene copy number status was determined by FISH, and PTEN expression by IHC. OS was estimated by the Kaplan–Meier method. All pts treated with CT + cetuximab and alive at 21 days were included in an analysis assessing the association between 1st-cycle rash (developing $\leqslant$21 days from treatment initiation) and OS.
Results: Of 395 pts for whom KRAS mutation status was evaluable, 75 (19%) had KRAS mutant (mt) tumors. No significant differences in OS were observed between pts with KRAS wild-type (wt) or mt tumors in either treatment arm. Of 293 pts for whom EGFR mutation status was evaluable, 49 (17%) had tumors with EGFR KDMs. OS was longer in pts with EGFR mt tumors compared with wt tumors in both treatment arms, indicating that EGFR KDMs are prognostic rather than predictive biomarkers for cetuximab in NSCLC. Of 279 pts for whom EGFR gene copy number status was evaluable, 102 (37%) had FISH+ tumors. No significant differences in OS were detected between pts with FISH+ or FISH− tumors in either treatment arm. Of 303 pts for whom PTEN expression was evaluable, 196 (65%) had PTEN-expressing tumors. OS was higher (but not significantly) in pts with PTEN-expressing tumors in both treatment arms, indicating potential prognostic rather than predictive value. Of 518 pts included in the landmark analysis (CT + cetuximab arm), 290 (56%) developed 1st-cycle rash (grade 1−3). Median OS was significantly longer for pts who developed 1st-cycle rash (15.0 mo) than those who did not (8.8 mo).
Conclusions: Adding cetuximab to a standard 1st-line platinum-based CT significantly increases OS. The biomarker analysis suggests that KRAS and EGFR mutations, EGFR gene copy number status, and PTEN expression are not predictive for outcome with cetuximab when added to CT. However, 1st-cycle rash is associated with improved outcome for pts receiving cetuximab added to CT.