study will provide useful data on the efficacy and safety of everolimus in combination with erlotinib in patients with advanced NSCLC who have received prior chemotherapy; there is an urgent need to improve treatment options for these patients.
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9175 POSTER

The effectiveness of erlotinib (Tarceva®) treatment in KRAS negative lung adenocarcinomas – preliminary results of an observational cohort study

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Background: In the BR.21 pivotal study, adenocarcinoma histology was significantly associated with responsiveness to erlotinib treatment. KRAS mutations are found in 25−35% of lung adenocarcinomas, and these mutations may be predictive of resistance to treatment with erlotinib. Recent publications have provided support for the hypothesis that KRAS mutational status could be utilized as a diagnostic marker for predicting response to erlotinib-treatment in NSCLC. However, survival data for the KRAS negative cohort are inconclusive.
Materials and Methods: This observational study is conducted in 37 Hungarian sites. Eligible patients have histologically or cytologically verified, advanced, KRAS (codon-12, codon-13) negative lung adenocarcinoma, refractory to at least one prior chemotherapy. Primary endpoint is progression-free survival. Secondary endpoints include tumor response according to RECIST, overall survival, safety and quality of life. KRAS gene mutational status is assessed using real-time PCR. KRAS positive cases are confirmed by DNA sequencing. Planned accrual is 260 patients.
Results: One hundred and sixteen patients were enrolled between February and November 2008. Baseline characteristics: median age: 61 (42−103) years; stage: III/B: 21%, IV: 79%; smoking status: non-smoker: 40%, ex- or current smoker: 60%; prior chemotherapy: erlotinib in the 2nd line: 57%, erlotinib in the 3rd line: 43%. Treatment was discontinued in 33 cases. Treatment length before discontinuation: 80 (8−116) days. Cause of discontinuation: disease progression (15 pts), death of any reason (13 pts), patient decision (1 pt), no reason specified (4 pts).
Conclusions: KRAS mutation screening may influence the clinical practice for erlotinib-treatment of NSCLC. Our study evaluates the effectiveness of erlotinib in a preselected cohort of KRAS negative lung adenocarcinoma patients in the routine clinical practice. Updated survival data will be presented at the meeting.

9176 POSTER

Biomarker analyses from SATURN, a phase III placebo-controlled study of erlotinib as first-line maintenance therapy for advanced NSCLC

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Background: Erlotinib has proven clinical benefit in second-line advanced NSCLC (Shepherd et al, 2005). SATURN (BO18192, Roche, complete) investigated erlotinib maintenance therapy in patients (pts) with advanced NSCLC who did not progress during first-line chemotherapy. To date, no molecular marker to predict outcomes has been identified. This randomised, global, phase III study was the first to include prospective molecular marker analyses for erlotinib, with mandatory sample collection.
Materials and Methods: The following tests were performed in order of priority (tissue was limited; not all analyses could be performed for all samples): EGFR expression (by IHC), EGFR gene copy number (by FISH), and EGFR and KRAS mutation status (by DNA sequencing). EGFR intron 1 CA-repeat polymorphism genotyping was performed using baseline blood samples. Pts were stratified by EGFR IHC status. Co-primary endpoints were PFS in all pts and PFS in EGFR IHC+ pts.
Results: Baseline characteristics, including biomarker status, were similar in both arms. Erlotinib significantly prolonged PFS in all pts (HR 0.71, p = 0.000003), and EGFR IHC+ pts (HR 0.69, p = 0.00002). Molecular subgroup analyses are shown in the table. All biomarker subgroups showed a PFS benefit with erlotinib, including pts whose tumours had wild-type (wt) EGFR. EGFR mut+ status (exon 19 deletions and/or L858R) was associated with a marked improvement in PFS with erlotinib therapy. KRAS mutation status was a prognostic factor but did not affect the clinical benefit seen with erlotinib.
Conclusions: In the SATURN study, although EGFR FISH+ or mut+ pts had longer PFS than those with FISH− or wt tumours, PFS improvement was observed in all patient subgroups, irrespective of biomarker status. In particular, pts receiving erlotinib obtained similar PFS benefit regardless of KRAS mutation status. EGFR mutations appear to be a strong positive predictor of PFS benefit with erlotinib.

Biomarker status	n (% per biomarker)	HR for PFS	interaction p value
EGFR IHC+[a]	618 (84)	0.69	0.6312
EGFR IHC−	121 (16)	0.77	
EGFR FISH+[b]	231 (48)	0.68	0.3515
EGFR FISH−	255 (52)	0.81	
EGFR mut+[c]	49 (11)	0.10	0.0004
EGFR wt	388 (89)	0.78	
KRAS mut+[d]	90 (18)	0.77	0.9480
KRAS wt	403 (82)	0.70	
Long *EGFR* CA-repeat[e]	396 (51)	0.75	0.6104
Short *EGFR* CA-repeat	385 (49)	0.68	

[a]EGFR IHC+: ⩾10% any membranous staining; [b]scoring according to Cappuzzo et al, 2005; [c]L858R and/or exon 19 deletions; [d]codons 12, 13 and/or 61; [e]sum of alleles >35 for Caucasian patients and >37 for Asian patients

9177 POSTER

Lipocalin-2 is an important predictor of susceptibility to therapy with pemetrexed in non-small cell lung cancers

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Background: The pemetrexed disodium (Alimta ®), LY231514 is the first antifolate which is able to inhibit both the synthesis of purines and pyrimidines at the same time. Pemetrexed has been approved for second and first-line treatment in non-small cell lung cancer (NSCLC) patients. However, there is still lacking of clinical biomarkers for predicting the therapeutic response of Alimta. The aim of this study is to establish the correlation between the changing of new biomarker levels and the clinical outcomes.
Material and Methods: Human NSCLC cell lines, with variable expression of the known molecular determinants of Alimta sensitivity, were exposed to Alimta. Antitumor effect was measured by growth inhibition by MTT assay, cell cycle distribution by flow cytometry, and expression of cell cycle mediators by immunoblots. Using Superarray cancer pathway gene array, a total of 482 genes was screened in A549 cell after Alimta treatment.
Results: Significant higher expressions of many genes, especially lipocalin-2 (LCN-2)proteins, were noted in Alimta-sensitive cells (A549) than in resistant cells (H1355) and were confirmed by Western blot and RT-PCR analysis. RNA interference (RNAi)-mediated LCN-2 down-regulation generated susceptibility to Alimta in A549 cells.
Conclusions: From the results in this study, it indicated that LCN-2 could play an important role in resistance to Alimta and LCN-2 could be a potential new drug target.