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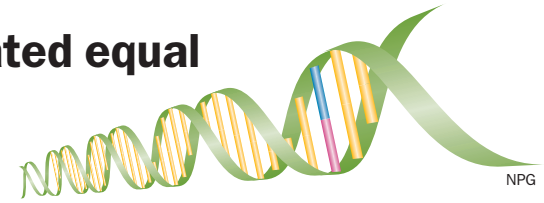
TARGETED THERAPIES

LUX-Lung trials—not all mutations are created equal



Findings from randomized clinical trials have shown that patients with lung adenocarcinomas who harbour *EGFR* mutations and are treated in the first-line setting with EGFR tyrosine kinase inhibitors (TKIs) have improved responses, progression-free survival (PFS) and quality of life. Despite these clinical improvements, a benefit in overall survival remains to be demonstrated, mainly owing to crossover of patients from the standard arm to receive targeted therapies.

Now, a study by James Chih-Hsin Yang and coauthors, has shown for the first time a statistically significant difference in overall survival for patients with lung cancer who have an *EGFR* exon 19 deletion (*EGFR* del19) mutation. Patients with untreated lung cancer and *EGFR*-mutated tumours were randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy with either pemetrexed and cisplatin (LUX-Lung 3) or gemcitabine and cisplatin (LUX-Lung 6). Subset analysis according to *EGFR*-mutation type was pre-planned.

In both studies, patients who had the *EGFR* del19 mutation (50% of all *EGFR* mutations) and received afatinib had a median overall survival duration that was prolonged by 1 year compared with patients who received combination chemotherapy alone. However, in both studies, there was no difference in overall survival in patients with EGFR exon 21 (L858R) point mutations. These results indicate that the *EGFR* del19 mutation is different from *EGFR* L858R mutation, and should be studied separately. Crossover of patients receiving afatinib to chemotherapy and chemotherapy to an EGFR TKI were balanced in approximately 75% of patients in LUX-Lung 3 and 50% of patients in LUX-Lung 6, indicating that the benefit seen in *EGFR* del19 patients was unlikely owing to follow-up treatment.

Yang explains, "this is the first evidence that frontline use of afatinib was not only able to improve PFS, response rate, and quality of life—as noted in previous similar studies—but also overall survival in patients with the *EGFR* del19 mutation." Importantly, Yang highlights that the results of these studies show "that afatinib should be recommended as first-line treatment for patients with *EGFR* mutations, and *EGFR* del19 alterations, and that L858R mutations should be treated differently, and studied differently." In the future, a meta-analysis is planned in similar studies of targeted therapies to investigate whether a difference in overall survival can be detected in patients with *EGFR* del19 versus L858R mutations.

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Original article Yang, J. C.-H. *et al*. Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. doi:10.1016/S1470-2045(14)71173-8