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**FAILURE PATTERNS TO CRIZOTINIB AND SURVIVAL BENEFIT IN ADVANCED ALK-POSITIVE LUNG ADENOCARCINOMA**

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Aim: Lung adenocarcinoma harboring gene fusion of EML4 and anaplastic lymphoma kinase (ALK) was proved responsive to crizotinib, but acquired failure inevitably developed after a median of 7.7 months. The failure patterns and their correlation with survival benefit remain unclear.

Methods: Patients with fluorescent in situ hybridization assay (FISH)-proven ALK fusion and with failure to crizotinib treatment were enrolled into the study. Demographic and clinicopathologic factors were reviewed. Failure patterns were defined as dramatic, gradual, and local progression according to the published criteria. Survival benefit in different patterns was analyzed.

Results: Totally 61 patients with lung adenocarcinoma, including 60 trial patients and one routine patient were enrolled. Fifty-four percent of the cohort was female, and 77% of patients were non-smokers. Brain metastasis occurred in 21% of the group. Six patients had concurrent EGFR gene mutations and ALK fusion. Twelve patients received first-line crizotinib, and ninety-five percent (41/43) of patients were switched to crizotinib after failure to prior chemotherapy. Sixty-eight percent (36/53) of patients were radiologically assessed as failure to crizotinib treatment. Seventy-five percent (27/36) of patients manifested dramatic progression on failure to crizotinib. One patient was with gradual progression, and 8 patients (22%) had local progression. The subgroup of dramatic progression had an inferior progression-free survival (PFS1) than other patients (3.5 vs 10.5 months, P < 0.001). In seven patients with local progression, continuation of crizotinib plus local intervention produced a median 3-month survival prolongation (PFS2). Patients experiencing dramatic progression showed shorter overall survival when compared with other patients (14.0 vs 45.5 months, P = 0.002).

Conclusions: Dramatic progression was prevalent in ALK-positive lung adenocarcinoma when failure to crizotinib occurred, and predicted poor overall survival.

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