A Randomized, Placebo-Controlled, Multicenter, Biomarker-Selected, Phase 2 Study of Apricoxib in Combination with Erlotinib in Patients with Advanced Non–Small-Cell Lung Cancer

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Abstract: Cyclooxygenase-2 (COX-2) overexpression is associated with a poor prognosis in non–small-cell lung cancer (NSCLC) and may promote resistance to epidermal growth factor receptor inhibitors. This randomized phase 2 trial evaluated apricoxib, a novel COX-2 inhibitor, in combination with erlotinib in biomarker-selected patients. Patients with stage IIIB/IV NSCLC previously treated with platinum-based chemotherapy were randomized (2:1) to 400 mg/day apricoxib plus 150 mg/day erlotinib (AP/E) or placebo plus erlotinib (P/E) in 21-day cycles until disease progression or unacceptable toxicity. The primary endpoint was time to progression (TTP). A decrease of 50% or more from baseline urinary prostaglandin E_2 metabolite after a 5-day, open-label, run-in period was used to select eligible patients. One hundred twenty patients (median age 64 years) were randomized (78 to AP/E and 42 to P/E). Overall median TTP was 1.8 months in the AP/E group and 2.1 months in the P/E group, with a 12% objective response rate in both groups (intent-to-treat analysis). A subgroup analysis in patients aged 65 years or younger demonstrated a statistically significant TTP benefit for AP/E (hazard ratio 0.5 [95% confidence interval: not applicable–0.9]; p=0.018) and overall survival advantage at minimum 1-year follow-up (median 12.2 versus 4.0 months; hazard ratio=0.5; p=0.021). The most common adverse events were rash, diarrhea, fatigue, and nausea. Toxicity contributed to early discontinuations in patients aged more than 65 years treated with AP/E. This is the first randomized placebo-controlled study of a COX-2 inhibitor in NSCLC to use a prospective patient-selection strategy. Although AP/E seemed to improve TTP and overall survival in a subset of patients aged 65 years or younger, the primary endpoint of the trial was not met.

Key Words: Non–small-cell lung cancer, Apricoxib, Erlotinib, Cyclooxygenase-2 inhibitor, Prostaglandin E_2 metabolite.

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Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors such as erlotinib and gefitinib have demonstrated clinical activity in NSCLC patients with activating *EGFR* mutations,[1] and after platinum-based chemotherapy in unselected patients.[2]

Preclinical and clinical evidence suggest that hyperactivity of cyclooxygenase-2 (COX-2) may confer resistance to EGFR inhibitors.[3,4] COX-2 is overexpressed in 70% to 80% of patients with NSCLC and is associated with a poor prognosis.[3] To date, however, phase 2 studies combining celecoxib with either erlotinib or gefitinib in unselected patients with previously treated NSCLC have not demonstrated improvements in efficacy over an EGFR inhibitor alone.[5]

Apricoxib is a novel, selective COX-2 inhibitor that has demonstrated potent antitumor effects in animal models. Only those tumors with elevated COX-2 activity, which produced high levels of prostaglandin E_2 (PGE_2), were responsive to the antitumor effects of apricoxib[6,7]; suggesting that a biomarker-driven patient-selection strategy might improve efficacy in the clinic. Intratumoral PGE_2 levels have been shown to correlate with the stable urinary metabolite of PGE_2 (PGE-M).[8] Moreover, an association has been observed between a decrease from baseline in urinary PGE-M and response to celecoxib plus chemotherapy.[8,9] A phase I trial demonstrated that apricoxib at daily doses up to 400 mg was well tolerated in combination with erlotinib (150 mg/day) in patients with advanced NSCLC.[10]

The current, prospective, randomized, double-blind, phase II study was designed to test whether the addition of apricoxib (400 mg/day) to erlotinib would improve time to disease progression (TTP) in biomarker-selected patients with recurrent stage IIIB/IV NSCLC. Selection of patients for this

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study was based on a 50% decrease from baseline urinary PGE-M in response to apricoxib.

PATIENTS AND METHODS

Patient Selection

Adult patients (≥18 years of age) with stage IIIB (pleural effusion; 6th edition of the American Joint Committee on Cancer) or IV NSCLC and measurable disease by Response Evaluation Criteria in Solid Tumors who had failed at least 1 prior platinum-based chemotherapy regimen were enrolled in this study. Eligible patients also had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2 and adequate renal, hepatic, and bone marrow function. By protocol amendment, patients with ECOG PS 2 were subsequently excluded after the Data Safety Monitoring Committee detected increased toxicity in these patients (n=6). Patients with central nervous system metastases were eligible if asymptomatic, and off steroids after radiotherapy for 2 weeks or more. Patients were ineligible if they had received prior treatment with an EGFR tyrosine kinase inhibitor or had a history of significant cardiovascular disease or upper gastrointestinal bleeding.

Study Design and Treatment

This was a multi-institutional phase II trial. Patients entered an open-label run-in period where they received single-agent apricoxib (400 mg/day) for 5 consecutive days. Urinary PGE-M was measured on the first and last day of the run-in period. Patients with at least a 50% decrease from baseline were randomized 2:1 to apricoxib (400 mg/day) plus erlotinib (150 mg/day) or placebo plus erlotinib on 21-day cycles. The primary efficacy endpoint was TTP. Secondary endpoints included overall response, progression-free survival (PFS), overall survival (OS), safety, and biomarker analysis (COX-2 expression and urinary PGE-M).

Patients were evaluated at baseline, on day 1 of every even-numbered cycle, for tumor response according to Response Evaluation Criteria in Solid Tumors version 1.0.[11] Safety was assessed using National Cancer Institute Common Toxicity Criteria version 3.0. Urinary PGE-M was assessed at baseline and on day 1 of cycles 2 and 3.

The sample size was determined to achieve 80% power to detect a 40% improvement in TTP corresponding to a Cox proportional hazard ratio (HR) of 1.4 by one-sided log-rank test with an α error of 0.20. The original sample size was 115, and this was increased to 122 by amendment excluding enrollment of patients with an ECOG PS of 2.

RESULTS

Patients

A total of 176 patients were enrolled into the 5-day open-label run-in period (Fig. 1). Of these, 120 patients

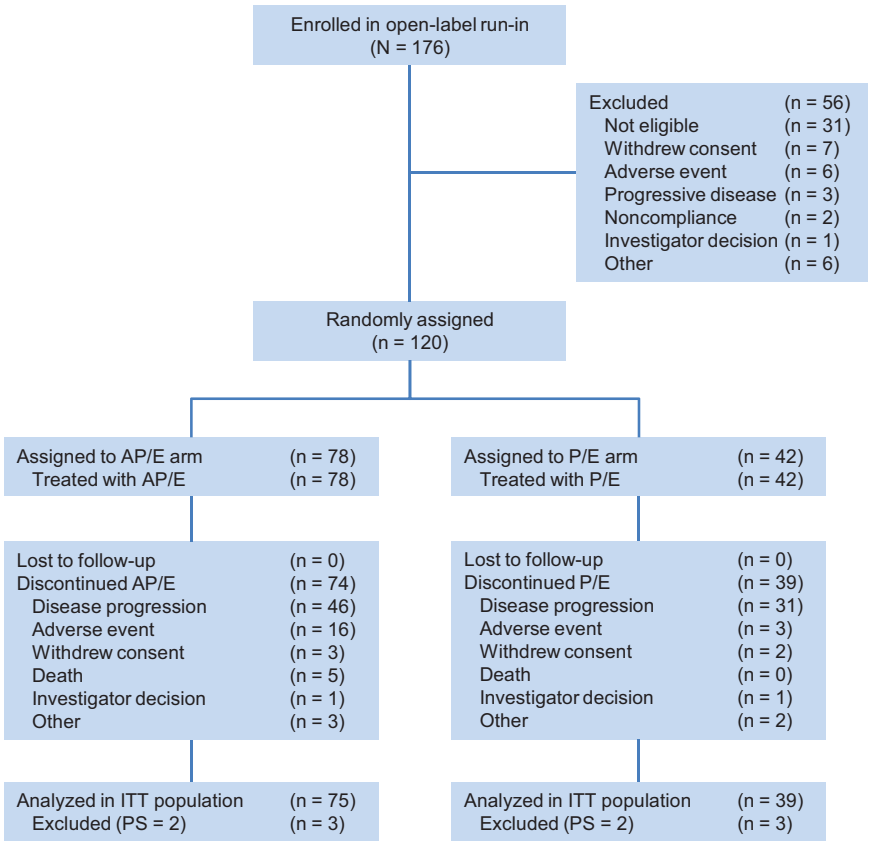

FIGURE 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. P/E, placebo plus erlotinib; AP/E, apricoxib plus 150 mg/day erlotinib; ITT, intent-to-treat; PS, performance status.