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LUNG CANCER

A NEW GENERATION OF EGFR INHIBITION

EGFR inhibitors result in excellent tumour responses and prolonged progression-free survival (PFS) in patients with advanced-stage, *EGFR*-mutant non-small-cell lung cancer (NSCLC); however, acquired resistance is a huge challenge, and might partially explain a paucity of overall survival improvements. Now, two phase I–II trials in patients previously treated with at least one first/second-generation EGFR inhibitor demonstrate that third-generation, mutant-selective, irreversible EGFR inhibitors, AZD9291 and rociletinib, can overcome the most-common EGFR T790M resistance mutation and further prolong survival.

In one of the trials, 253 patients received AZD9291 (20–240 mg daily). The objective response rate (ORR) was 51%; the disease-control rate (DCR) was 84%. Among 222 patients in the dose-escalation cohorts, the median PFS was 8.2 months; specifically in patients with a T790M mutation, the ORR was 61%, the DCR was 95% and the median PFS was 9.6 months, versus 21%, 61% and 2.8 months, respectively, in those lacking this mutation.

The second study reported similar efficacy for rociletinib therapy. Among 47 patients with the T790M mutation and 17 patients without this mutation who were treated with twice-daily rociletinib at 900 mg in its free-base form, or 500–1,000 mg as a HBr salt, the ORR was 59% versus 29%, the DCR was 93% versus 59%, and the estimated median PFS was 13.1 months versus 5.6 months.

Both drugs were well tolerated, adverse events were manageable, and neither study identified a maximum-tolerated dose. Interestingly, hyperglycaemia was the most-common adverse effect of rociletinib (overall frequency of 36%), whereas the syndrome of rash, stomatitis, and paronychia that is associated with inhibition of wild-type EGFR was rare. By contrast, AZD9291 was associated with hyperglycaemia in only six patients (2%); however, rash (40%), paronychia (17%), and stomatitis (12%) were more common, suggesting that the selectivity of this agent for mutant EGFR is compromised at higher doses (160–240 mg).

These data indicate that a new generation of EGFR inhibitors is poised to improve therapy for *EGFR*-mutated NSCLC.

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Original articles Jänne, P. A. *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N. Engl. J. Med.* **372**, 1689–1699 (2015) | Sequist, L. V. *et al.* Rociletinib in *EGFR*-mutated non-small-cell lung cancer. *N. Engl. J. Med.* **372**, 1700–1709 (2015)