NOVEL TREATMENTS TO OVERCOME TKI RESISTANCE

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TRIAL SUMMARY: Promising early clinical results with CO-1686

BACKGROUND
The efficacy of current TKIs in advanced NSCLC possessing activating mutations in the EGFR is limited by the emergence of treatment resistance. Approximately 60% of cases of TKI resistance are attributable to the emergence of the T790M mutation. CO-1686 is a novel oral, covalent TKI that specifically targets both known activating mutations in EGFR as well as the T790M resistance mutation, while sparing wild-type (WT) EGFR. This phase I/II trial evaluated CO-1686 in a population of patients with EGFR-mutant NSCLC that had progressed on previous EGFR TKI treatment. All patients underwent repeat biopsy to facilitate EGFR genotyping, and endpoints included safety, pharmacokinetics and efficacy.

COMMENTARY: The use of EGFR TKIs has revolutionized the treatment of EGFR-mutant advanced NSCLC. The emergence of TKI resistance in EGFR-mutant NSCLC is unfortunately inevitable in all patients treated with these agents. The most common mechanism of resistance to EGFR TKIs is the emergence of the T790M resistance mutation, which occurs in approximately 60% of patients. The development of novel treatments capable of overcoming TKI resistance represents the crucial next step in the treatment of EGFR-mutant NSCLC.

Forty-five patients were treated on this trial, with 31/42 (74%) found to be T790M-positive and data from 3 patients pending. Median number of previous therapies was 4 with a median of 1 previous TKI. Treatment-related adverse events were primarily mild or moderate and included fatigue (19%), diarrhea (15%), nausea (14%), anemia (10%), arthralgia (7%), muscle spasm (10%), myalgia (7%) and headache (7%). The maximum tolerated dose (MTD) was not yet achieved but 6/9 (66%) of T790M-positive patients at the highest dose level achieved a partial response (PR) and the remaining patient had stable disease (SD).

TRIAL SUMMARY: Promising early clinical results with AZD9291
M. Ranson, S. Ghiorghiu, M. Cantarini, et al. AZD9291: an irreversible, potent and selective tyrosine kinase inhibitor (TKI) of activating (EGFRm+) and resistance (T790M) mutations in advanced NSCLC. WCLC 2013.

AZD9291 is a novel oral irreversible TKI that specifically targets EGFR-activating mutations, as well as the T790M resistance mutation, while sparing WT EGFR. This combined preclinical and phase I clinical trial evaluated AZD 9291. This study examined the efficacy of AZD9291 across several EGFR mutant and wild-type cell lines, as well as mouse xenograft models. The phase I component of the study evaluated AZD9291 in patients with EGFR mutations that had progressed despite at least one previous TKI, had good performance status, had measurable disease and no prior history of interstitial lung disease (ILD). RECIST assessments occurred every 6 weeks and dose escalation occurred after 3 or more patients completed a 21-day cycle of a given dose with no dose-limiting toxicity.

FINDINGS
The authors conclude that CO-1686 demonstrated a favourable toxicity profile with minimal rash and diarrhea, which they attribute to the specificity of this agent for mutant EGFR. They suggest that this agent exhibits a strong dose-response relationship with T790M inhibition and that this early study already shows remarkable efficacy in T790M mutation-positive patients, with minimal toxicity.

The use of the second-generation irreversible EGFR TKI afatinib has been evaluated as a means of overcoming TKI resistance in EGFR-mutant NSCLC. The LUX-LUNG1 trial randomized 585 patients in a 2:1 fashion to either afatinib or placebo. Approximately 68% of these patients possessed EGFR-activating mutations and had progressed on previous TKI therapy. The afatinib treatment arm achieved a very modest response rate (7%) with similarly modest improvement in PFS and no difference in OS. In addition, significant toxicity, including rash and diarrhea,
was associated with treatment. Alternative strategies to overcome resistance, including pulse TKI treatment with afatinib or erlotinib, have met with limited success.

Third-generation EGFR TKIs have been developed to specifically target known EGFR-activating mutations as well as the T790M resistance mutation, while sparing wild-type EGFR. These agents have been designed to treat the most common mechanism of EGFR TKI resistance while avoiding the significant toxicities associated with first- and second-generation EGFR inhibitors. CO-1686 and AZD9291 are 2 such novel oral irreversible third-generation EGFR inhibitors. Their respective abilities to potently inhibit both known EGFR-activating mutations and the T790M resistance mutations at concentrations where WT EGFR is largely spared has been demonstrated in preclinical models.

The data presented in the respective phase I trials discussed above of CO-1686 and AZD9291 are the first to demonstrate the ability of these agents to induce partial responses in TKI-resistant EGFR-mutant advanced NSCLC patients. Response rates in TKI-resistant patients possessing the T790M mutation were 66% (6/9 patients) and 50% (9/18 patients) for CO-1686 and AZD9291, respectively. These are extremely promising in this heavily pretreated study population. The modest toxicity profile of these agents is similarly impressive. Although the goal of these trials is largely to identify an appropriate dose, these early data are already encouraging and will likely spur larger phase II/III trials in the near future.

These trials also highlighted the growing importance of T790M mutation testing. The T790M resistance mutation has previously been demonstrated to have important prognostic implications for patients with TKI-resistant EGFR-mutated NSCLC. However, the early results of these trials demonstrate that T790M also has a role as a predictive biomarker with respect to novel third-generation EGFR TKIs. As the potential efficacy of these third-generation inhibitors is further examined, the importance of routine T790M testing in patients with TKI-resistant disease is likely to increase.

In summary, early data on the toxicity and efficacy of the novel third-generation EGFR TKIs, CO-1686 and AZD9291, are extremely promising. Future phase II/III clinical trials designed to demonstrate the clinical benefit of these agents are likely to proceed in the near future. Depending on the results of these trials, this novel class of agents may become an important treatment option for TKI-resistant EGFR mutant NSCLC. As well, the T790M resistance mutation is likely to evolve from a prognostic to predictive biomarker.

**References**


