FIRST-IN-HUMAN EVALUATION OF CO-1686, AN IRREVERSIBLE, SELECTIVE AND POTENT TYROSINE KINASE INHIBITOR OF EGFR T790M

Authors: Lecia V. Sequist, Jean-Charles Soria, Shirish M. Gadgeel, Heather Wakelee, D. Ross Camidge, Andreea Varga, Panagiotis Fidias, Antoinette Wozniak, Joel Neal, Robert C. Doebele, Edward B. Garon, Sarah Jaw-Tsai, Jennifer C. Stern, Andrew Allen, Jonathan Goldman

Background: Efficacy of existing EGFR tyrosine kinase inhibitors (TKIs) in NSCLC is limited by emergence of the T790M mutation in approximately 50% of patients, and significant skin rash and diarrhea, caused by wild-type (WT)-EGFR inhibition, compromises tolerability. CO-1686 is an orally active TKI that targets common activating EGFR mutations and T790M, while sparing WT-EGFR. Animal models suggest maximal efficacy when trough plasma concentrations exceed 200ng/ml.

Methods: This is a first in human phase 1 (3+3) dose-finding study of oral CO-1686, administered continuously in 21-day cycles. To be eligible, patients must have EGFR-mutant NSCLC and prior therapy with an EGFR TKI. Endpoints include safety, pharmacokinetics (PK), and efficacy. All patients undergo a biopsy for genotyping before starting study drug.

Results: As of 18 Jan 2013, 35 patients (18/28 (64%) T790M+; 7 pending) have been treated with CO-1686. Dosing started at 150mg QD and escalated in steps to 900mg QD, 600mg BID and 400mg TID, with a maximum tolerated dose not yet reached. A recommended phase 2 dose is expected to be reached soon. Related AEs of grade 3 or higher were hypoglycaemia (n=1) and hyperglycaemia (n=1). AEs typical of WT-EGFR inhibition (rash, diarrhea) have not been observed.

Dose-proportional PK was observed; plasma half-life was 4-5 hrs and at 900mg QD Cmax=3000ng/ml but trough concentrations were < 200ng/ml. At ≥300mg BID and TID dosing, trough concentrations can exceed 200ng/ml. At 900mg QD, 2 of 3 patients showed clinical benefit after 2 cycles of CO-1686 including one with clinically-relevant tumor shrinkage (18%) and a second with stabilization of a pleural effusion that had previously required repeat thoracenteses at ~10 day intervals. At 300mg BID, one patient (Del(19)/T790M+) with PK trough concentration >200ng/ml exhibited significant tumor shrinkage (29%) after 2 cycles. Further efficacy data from BID/TID cohorts and centrally-confirmed genotypes will be presented at the meeting.

Conclusions:
CO-1686 offers potential for improved activity and better tolerability over current EGFR TKIs, particularly in the treatment of T790M+ disease, an area of high unmet clinical need.

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