A PHASE I STUDY OF THE MEK1/2 INHIBITOR SELUMETINIB IN COMBINATION WITH FIRST-LINE CHEMOTHERAPY REGIMENS FOR NSCLC


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Aim: Selumetinib (AZD6244, ARRY-142886) is an orally available MEK1/2 inhibitor with activity in combination with docetaxel in the second-line setting for KRAS mutation-positive advanced NSCLC. This Phase I study assessed the safety, tolerability, recommended Phase II combination dose (RP2D), pharmacokinetics (PK) and preliminary efficacy of selumetinib in combination with first-line chemotherapy regimens in unselected patients (pts) with advanced/metastatic NSCLC.

Methods: This open-label, multicentre study (NCT01809210) enrolled pts into dose-finding cohorts of orally administered selumetinib (50 mg bid [sel50] to 75 mg bid [sel75]) in combination with standard doses of gemcitabine (gem) or pemetrexed (pem) plus cisplatin (cis) or carboplatin (carb). Each dose cohort consisted of at least 3 and up to 6 evaluable pts. On completion of chemotherapy, pts had the option of maintenance selumetinib.

Results: As of 20 April 2014, 17 pts were evaluable (8 female; median age 63; 8 adenocarcinoma, 8 squamous, 1 non-squamous histology) to the following treatment cohorts: gem + cis + sel50, n = 3; gem + cis + sel75, n = 1; gem + carb + sel50, n = 7; pem + carb + sel50, n = 2; pem + carb + sel75, n = 4. Median total selumetinib exposure was 78 days (range 16–224). The majority of adverse events (AEs) were CTCAE Grade 1 or 2. Selumetinib-related AEs of Grade ≥3 were seen in 7 pts: gem + cis + sel50, 0/3; gem + cis + sel75, 0/1; gem + carb + sel50, 6/7; pem + carb + sel50, 1/2; pem + carb + sel75, 0/4. One DLT of thrombocytopenia was observed in the gem + carb + sel50 cohort. Combination therapy did not appear to show any marked effect on the PK profile of selumetinib. Across all cohorts, partial responses were seen in 6/17 (35%) pts evaluable for response, and 4/17 (24%) had stable disease.

Conclusions: The AE profile of selumetinib in combination with these chemotherapy regimens for NSCLC was consistent with the known profiles. Two tolerated dose regimens have been confirmed: gem + cis + sel50 and pem + carb + sel50. The activity of platinum-based regimens seems to be preserved in this unselected population. Dose escalation and expansion is ongoing; updated data including the RP2D and PK will be presented.

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