A phase I dose escalation study of the tolerability of the oral VEGFR and EGFR inhibitor vandetanib in combination with the oral MEK1/2 inhibitor selumetinib in solid tumors

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Background: The clinical utility of agents targeting EGFR and VEGFR signalling in Non-Small Cell Lung Cancer (NSCLC) is limited by resistance due to emergent alternative growth stimulatory pathways, particularly that of MEK. Thus, there is strong rationale for developing a strategy to combine EGFR, VEGFR and MEK inhibitors.

Methods: Patients (any solid tumour) received treatment (continuous dosing) as follows: vandetanib (VAN) lead-in, 2-4 days (300mg bd or od) followed by VAN steady state (SDD) (100, 200 or 300mg od), 10-12 days, followed by VAN and selumetinib (SEL), (VAN SDD plus SEL at 25, 50 or 75mg bd or 100, 125mg od). Seven dose levels were explored.

Results: Forty-seven pts received study treatment. GI and skin toxicities were the most prevalent related AEs (GI: 159 AEs in 94% pts; Skin: 90 AEs in 94% pts). Other related AEs included eye disorders in 18 pts (38%) (G1-3) including retinal detachment and retinopathy. QTc prolongation (G1-2) occurred in 10 pts (21%) and 4 pts (9%) experienced other cardiac AEs (G1-3). Evidence of dose dependent skin and eye toxicity was observed. The following AEs (six different dose levels) were assigned DLT status; hypertension, eye toxicity (x3), bradycardia, raised ALP and QTc prolongation. PK data of vandetanib alone and in combination with selumetinib was similar to previously reported for either drug alone.

Conclusions: VAN and SEL have overlapping toxicities with the AE profile consistent with the known monotherapy profiles. Doses of each agent able to be administered safely in combination were larger than anticipated and additional cohorts were included. A higher incidence of reversible eye events was observed in combination than reported with single agent SEL. PK has shown no drug interaction. Based on tolerability, the MTD of both single agent drugs in combination taken forward to the expansion cohort is VAN 200mg od with SEL 50mg bd. This combination is likely to enable adequate inhibition of target proteins based on pre-clinical studies. An expansion cohort in NSCLC, with known EGFR, VEGFR and MEK activation status, is recruiting with anti-tumour efficacy and pharmacodynamic blood and tumour endpoints.

Clinical trial identification: NCT01586624

Legal entity responsible for the study: Cancer Research UK, Centre for Drug Development

Funding: Cancer Research UK, Centre for Drug Development Disclosure: S. Pacey: Research funding from AZ for prostate cancer and ctDNA research. Two grants