

MErCuRIC1: A Phase Ia study of MEK1/2 inhibitor PD-0325901 with cMET inhibitor crizotinib in patients with advanced solid tumours

Wilson RH^{1,2}, Rolfo C³, Elez E⁴, Van Schaeybroeck S^{1,2}, Taieb J⁵, Houlden J⁶, Love S¹², Roberts C¹², André T⁷, Lawler M², Di Nicolantonio F⁸, Grayson M¹, Popovici V⁹, Bardelli A⁸, Laurent-Puig P¹⁰, Salto-Tellez M^{1,2}, Maughan TS¹¹, Tabernero J⁴, Peeters M³, & Middleton M¹¹ on behalf of the MErCuRIC Trial Consortium.

¹*Belfast Health and Social Care Trust, Belfast, UK;*

²*Queen's University Belfast, Belfast, UK;*

³*University Hospital Antwerp, Antwerp, Belgium;*

⁴*Vall d'Hebron Institute of Oncology, Barcelona, Spain,*

⁵*Georges Pompidou European Hospital, Paris, France;*

⁶*Oncology Clinical Trials Office, Oxford, UK;*

⁷*Saint-Antoine Hospital, Paris, France;*

⁸*Department of Oncology, University of Torino, Italy;*

⁹*Masaryk University, Czech Republic;*

¹⁰*University Paris Descartes, Paris, France;*

¹¹*University of Oxford, Department of Oncology, Oxford, UK*

¹²*Centre for Statistics in Medicine, Oxford, UK*

BACKGROUND

RAS activating mutations occur in ~55% of metastatic (m) CRC. RASMT and >50% of RASWT mCRC patients do not benefit from anti-EGFR antibodies. c-MET is overexpressed in ~50-60%, amplified in ~2-3% and mutated in ~1-3% of mCRC. Preclinical data support the clinical evaluation of MEK1/2 and METi, in particular in RASMT tumours and RASWT with aberrant c-MET expression. The primary aim of the phase I study was to establish the maximum tolerated dose (MTD) and assess safety/toxicity profile of PD-0325901 MEKi & crizotinib METi in patients with advanced solid tumours using NCI CTCAE V4.03.

METHODS

A single arm, open-label phase I trial of PD-0325901 with crizotinib was performed in patients with advanced solid tumours, measurable disease, ECOG PS 0-1 and adequate end organ function. Patients received oral PD-0325901 BD (days 1-21 every 28 days) at doses of 2 - 8mg BD with oral crizotinib continuously at 250mg OD or 200mg BD, using a rolling 6 design. Crizotinib started after a 1 week lead-in with PD-0325901. Blood samples for pharmacokinetics, pERK and soluble c-MET levels and skin biopsies for pERK levels were collected.

RESULTS

Between 12/2014 and 11/2015 we enrolled 25 patients; Male (13), Female (12). Median age 63 yrs (range 36-78). MTD was defined at the highest dose; crizotinib: 200mg BD continuously; PD-0325901: 8mg BD days 1-21 every 28 days. 1 of 6 patients exhibited dose-limiting toxicity (fatigue) at this dose level. The 25 patients received a total of 52 cycles. Drug-related adverse events were in keeping with single agent toxicity profiles, including rash, diarrhoea, fatigue, nausea,

hypoalbuminemia and visual disturbances. Best clinical response was stable disease at the end of cycle 2, in 4/25 evaluable patients.

CONCLUSIONS

MEK/METi can be given together at pharmacologically active doses. MTD for the PD-0325901/crizotinib combination was 8mg BD (days 1-21) and 200mg BD continuously in a 28 day cycle. The combination is now being explored further with an alternate MEKi before expansion into *RASMT* and *RASWT* CRC with aberrant c-MET expression. EudraCT registry number: 2014-000463-40.