

Characterisation of Phosphorylated Checkpoint Kinase 1 as a Poor Prognostic Biomarker in Serous Ovarian Cancer

K.E. FRANCIS¹; P. MULLEN²; I. UM¹; C. KAY¹; D.J. HARRISON²; S.P. LANGDON¹

¹UNIVERSITY OF EDINBURGH, EDINBURGH, United

Kingdom; ²UNIVERSITY OF ST ANDREWS, ST ANDREWS, United Kingdom

Due to limited studies on the use of biomarkers to overcome ovarian cancer platinum resistance, we set out to characterise checkpoint kinases 1 and 2 (Chk1 and Chk2) in a cohort of ovarian cancers and paired platinum sensitivity serous ovarian cancer cell lines.

Chk1 and Chk2 proteins were measured in a cohort of 128 pre-treatment ovarian cancer lysates using reverse phase protein arrays. A validation cohort of 468 ovarian cancers used automated quantitative immunofluorescence image analysis. Chk1/2 inhibitor AZD7762 and cisplatin treatments of paired serous ovarian cancer cell lines were used to assess Chk1 and Chk2 function in the platinum-induced DNA damage response.

High phosphorylated-Chk1 at Serine 317 (p-Chk1) levels was associated with poor overall survival (corrected P=0.03). In multivariate analysis with other significant factors, high p-Chk1 tumours had a relative risk of 3.0 (95% CI 1.1 -- 8.0, P=0.03). The DNA damage marker p-H2AX (Ser139) was highly expressed in the high p-Chk1 tumour group (P=0.008). In the larger cohort, high cytoplasmic p-Chk1 was associated with poor overall survival (corrected P = 0.02). Within the serous ovarian cancer subgroup, cytoplasmic and nuclear p-Chk1 were associated with poor overall survival (P=0.029 and P=0.043, respectively). In the cell line model, a sublethal AZD7762 concentration sensitised both platinum sensitive and resistant serous ovarian cancer cell lines to cisplatin by inducing apoptosis, inhibiting intra-S phase arrest, and increasing double stranded DNA breaks.

This is the first study to identify p-Chk1 as an independent prognostic ovarian cancer biomarker and supports Chk1 as a therapeutic target in platinum-resistant serous ovarian cancer.