INTRODUCTION. Relapse during androgen withdrawal therapy is a major cause of prostate cancer morbidity and mortality. Androgen receptor mutations (6-10%) and amplifications (20-30%) may explain relapse in some cases (1,2), however in approximately 70% of cases alternative mechanisms must be invoked (3). Our evidence suggests that type I receptor tyrosine kinases play a role in the development of hormone refractory prostate cancer.

METHODS. Protein expression and activation of type I receptor tyrosine kinases was determined by immunohistochemistry in a cohort of matched tumour pairs (one taken before and one after hormone relapse) from 65 prostate cancer patients. Five antibodies were used, EGFR and EGFR VIII (Zymed), HER2 (DAKO HercepTest™), phosphorylated EGFR (Cell Signalling), phosphorylated HER2 (Neomarkers). Detection and visualisation and was achieved using the LSAB+ kit (DAKO Cytomation) and DAB (Vector Laboratories). Two independent observers using a weighted histoscore method scored each section.

RESULTS. Tumour expression rates for EGFR and phosphorylated EGFR were low in both hormone sensitive (36% and 9%) and hormone refractory tumours (36% and 11% respectively), with no significant increase in expression or activation with the development of hormone refractory prostate cancer. Whilst more tumours expressed HER2, phosphorylated HER2 and EGFR VIII no significant increase in median protein expression was observed with the
development of hormone refractory prostate cancer (48% to 67.3 %, 43% to 42% and 100% to 100%). Intriguingly, those patients whose tumours expressed low levels of phosphorylated HER2 in their primary tumour relapsed significantly earlier than those who expressed high levels of phosphorylated HER2 (0.039).

Using matched tumour pairs we identified patients, for each protein, whose tumours showed an increase, no change and/or a decrease in protein expression with the development of hormone escape. Time to death post hormone relapse, was markedly decreased for patients with an increase in HER2 expression (15.4% of cases, 0.004), and an increase in EGFR expression (7.7%, p=0.0004), but not with phosphorylated HER2 (26.8%), phosphorylated EGFR (6.9%) or EGFR VIII (10.3%). Almost 23.1% of cases showed increased HER2 or EGFR expression at hormone relapse, this was associated with a significant reduction in time to death from hormone relapse (3.00 (1.75-4.25) years versus 1.33 (0.86-1.80) years, p = 0.0002).

CONCLUSION. Increased expression of HER2 or EGFR appears to influence progression to hormone refractory prostate cancer in approximately 1/4 of cases, since a rise in HER2/EGFR expression at hormone relapse is associated with a significant reduction in time to death. These findings support the development of EGFR/HER2 targeted therapies in hormone refractory prostate cancer. We have demonstrated, using a carefully characterized patient cohort, that the EGFR/HER2 pathway may represent one of a number of independent routes to hormone escape in prostate cancer.

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REFERENCES