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PROSTATE CANCER

An abiraterone ultraresponsive phenotype

> These data could be useful in determining which patients will respond to abiraterone

Researchers have identified a molecular signature in castration-resistant prostate cancer (CRPC) patient-derived xenografts (PDX) that is associated with a tumour phenotype ultraresponsive to abiraterone.

Abiraterone is a CYP17A1 inhibitor that blocks biosynthesis of androgens, and has been shown to improve survival in CRPC. However, some patients respond only slightly, and many develop resistance. A biomarker by which responders and nonresponders can be identified could be valuable in order to determine who would benefit from abiraterone treatment.

Lam *et al.* used PDX SCID mouse models carrying four different tumour types: LuCaP 136CR, LuCaP 77CR, LuCaP 96CR, and LuCaP 35CR. Once PDXs had reached >100 mm^3 in volume, 0.5 mmol/kg abiraterone treatment was administered using oral gavage.

Treatment with abiraterone improved survival in three of the four tumour PDX models used — LuCaP 136CR saw a 221% improvement in survival, and was deemed an ultraresponder. More modest, though still significant, survival gains were seen in the LuCap 77CR and LuCaP 96CR models, whereas no improvement was seen in the LuCap 35CR mice. The three models that responded also displayed significantly delayed tumour and PSA progression. Transcriptome analysis of the PDX lines identified 531 differentially expressed genes between the ultraresponder and the intermediate and minimal responder, 68 of which were secreted proteins. The team selected the 10 most highly upregulated and downregulated genes and compared them between the different responders, creating and validating a highly consistent eight-gene signature that was upregulated in abiraterone ultraresponders. This signature correlated with the survival gain noted, demonstrating its potential for prediction of abiraterone responsiveness. Further characterization of the ultraresponsive phenotype revealed reduced androgen receptor (AR) signalling and low nuclear glucocorticoid receptor (GR) localization, as well as alterations in steroid metabolism and epithelial–mesenchymal transition enrichment, as possible mechanisms for the effect.

By revealing a spectrum of response phenotypes and a means to identify them, these data could be useful in determining which patients will respond to abiraterone and those for whom further inhibition along the AR–GR pathway might be an effective therapeutic option.

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ORIGINAL ARTICLE Lam, H.-M. *et al.* Characterization of an abiraterone ultraresponsive phenotype in castration-resistant prostate cancer patient-derived xenografts. *Clin. Cancer Res.* http://dx.doi.org/10.1158/1078-0432.CCR-16-2054 (2016)