Tumor transcriptome-wide expression classifiers predict treatment sensitivity in advanced prostate cancers

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Background

Advanced prostate cancers respond to hormone therapy but outcomes vary and no predictive tests exist for informed upfront treatment selection. To identify novel biomarker-treatment pairings, we examined associations between biological pathways and 14-year survival outcomes of patients randomized in practice-changing Phase 3 trials (testing docetaxel or abiraterone).

Methods

We whole transcriptome profiled prostate tumor index cores using a clinical test (Veracyte), from patients (pts) randomized to the docetaxel (doce) and abiraterone (abi) phase III STAMPEDE trial comparisons. We generated transcriptome-wide expression signatures and immunohistochemistry scores for Ki-67 and PTEN, from 1523 patients (832 metastatic). We followed a pre-defined statistical analysis plan to fit Cox models individually in metastatic (M1) and very high-risk non-metastatic (M0) pts, adjusted for age, WHO PS, pre-ADT PSA, Gleason score, T-stage, N stage (N0, N1), metastatic volume if M1 (CHAARTED definition, high [M1HV] or low [M1LV]). Likelihood ratio tests were used to test the hypotheses that doce effect was larger in Decipher score high vs lower. Primary endpoint was OS. Updated OS (Feb 2024) included record linkage to national datasets. Hazard ratios (HR) provided with 95% confidence intervals.

Results
Tumor androgen receptor signaling associated with longer survival, whilst increased proliferation predicted shorter survival. In a pre-specified analysis, the Decipher score (DS) was both prognostic and predicted survival benefit from doce for metastatic cancers. DS was prognostic: each 0.1 increment increased the hazard of death by 11% (HR = 1.11 [1.06-1.16], p<0.001) for M1, 9% (HR = 1.10 [1.02-1.18], p = 0.012) for M0. DS predicted doce efficacy in M1: high DS, HR = 0.64 [0.48-0.86]; lower DS, HR = 0.96 [0.71-1.30]. This interaction effect was statistically significant (p=0.039). The effect was consistent in M1LV (high DS, HR = 0.53 [0.32-0.88]; lower DS, HR = 0.78 [0.47-1.30]) and M1HV (high DS, HR = 0.72 [0.49-1.07]; lower DS, HR = 1.16 [0.77-1.74]). In M0 there was no evidence of an interaction effect (p=0.302; high DS, HR = 0.75 [0.44-1.28]; lower DS, HR = 1.04 [0.68-1.59]).

Additionally, transcriptome-based classification of PTEN inactivation identified tumors more likely to have PTEN protein loss ($p=4x10^{-37}$). PTEN inactivity associated with shorter OS in pts allocated ADT+abi (HR=1.56, 95%CI: 1.06-2.31) but not in pts allocated ADT+doce (HR=0.93, 95%CI: 0.70-1.24). We found strong evidence (p=0.002) of an interaction between PTEN inactivation and doce sensitivity: PTEN inactive pts benefited from doce (HR=0.57, 95% CI 0.42-0.76) unlike PTEN active pts (HR=1.05, 95% CI 0.77-1.43), this was consistent across M1LV and M1HV. Immunohistochemistry PTEN protein loss was not predictive of doce benefit.

Conclusion
Transcriptome classifiers predict docetaxel benefit and could be clinically-implemented for improved patient management.

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Conflicts of interest and disclosures
Veracyte owns intellectual property and know-how on a number of the transcriptome signatures described herein so could gain commercially from clinical implementation of this study's results and UCL could receive a share of commercial revenue for its contribution to this study, author affiliations to UCL are outlined above. Emily Grist, Yang Liu, James Proudfoot, Elai Davicioni, Peter Dutey-Magni, and Gerhardt Attard have patent applications and/or registrations related to this work.