Decipher mRNA score for prediction of survival benefit from docetaxel at start of androgen deprivation therapy (ADT) for advanced prostate cancer (PC): an ancillary study of the STAMPEDE docetaxel trials

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Background
Docetaxel (Doce) is effective for metastatic (M1) PC but its effect is heterogeneous. Combining Doce with hormone therapy can improve overall survival (OS) but may not be appropriate for all. We hypothesised that the Decipher 22-gene mRNA score (DS) predicts Doce benefit.

Methods
DS were generated from whole transcriptome profiling with a clinical test (Veracyte) on tumor index cores from patients (pts) randomised 1:1 to ADT or ADT + Doce +/- zoledronic acid (ZA) in the STAMPEDE protocol (Oct 2005 - Mar 2013). We followed a pre-defined statistical analysis plan to fit Cox models individually in M1 and very high-risk non-metastatic (M0) pts dichotomised by DS (</= vs > 0.8) 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 DS 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
895 pts (539 M1, 356 M0, 639 [71%] reported to have died) were included and representative of the full trial cohort (N = 2369). DS were significantly lower in M0N0 (adjusted p<0.001) but showed the same distribution across M0N1, M1LV, M1HV. DS were prognostic: each 0.1 increment increased the hazards 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]).

Conclusion
High DS identifies synchronous M1 PC pts who benefit from Doce. DS is the 1st molecular classifier independent of metastatic volume to show a statistically significant interaction with Doce in directly randomised M1 PC pts.

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Conflicts of Interest Disclosure Statement
I am an employee of UCL that through an agreement with Veracyte could benefit commercially from use of their test for the indications discussed in this abstract. The subject matter of this abstract is covered by a pending patent application