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650TiP PARADIGM: Plasma analysis for response assessment and to direct the management of metastatic prostate cancer (mPCa)

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Background: Adding docetaxel or androgen receptor signalling inhibitor (ARSI) at start of androgen deprivation therapy (ADT) for mPCa improves progression-free survival (PFS) and overall survival (OS). Duration of benefit is variable; although serum PSA at 7 months (mth) associates with differential outcome, physicians still lack the tools to identify who will develop early resistance and require alternative or intensified treatments.

Trial design: This is a prospective, observational, biomarker-focused, translational, cohort study to determine whether detection of circulating tumor DNA in plasma (ptDNA) after 2 or 3 cycles of standard-of-care docetaxel (PARADIGM-D) or ARSI (PARADIGM-A) added at start of ADT is associated with a worse clinical outcome in newly diagnosed polymetastatic prostate cancer(PCa). The primary endpoint is PFS. PFS will be reported separately for PARADIGM-D and PARADIGM-A cohorts. PARADIGM-D assumes a 12 mth PFS rate of of 50% in ptDNA positive (+) and 80% in ptDNA negative (-) patients (pts), giving a HR of 0.322; to achieve at least 95% power, 40 events (12 in ptDNA (+) and 28 in ptDNA (-) pts) need to be observed in 65 pts. For PARADIGM-A, we assume a 12 mth PFS rate of 60% in ptDNA (+) and 85% in ptDNA (-) pts, giving a HR of 0.322; to achieve at least 90% power, 33 events (11 in ptDNA (+) and 22 in ptDNA (-) pts) need to be observed in 65 pts. PARADIGM-A will report pts on any ARSI. Descriptive statistics will report the distribution of pts and events by different ARSI. For both cohorts, a two-sided log-rank test with a type I error of 10% is assumed with an expected dropout rate of 5% per year for both ptDNA (+) and ptDNA (-) pts. Secondary endpoints include PCa specific survival and OS. Pts will have plasma collected at cycle (C) 3 day (D) 1 and/or C4D1 of their allocated treatment for classification as ptDNA (+) or ptDNA (-). Additional samples will be collected at pre-ADT, C1D1, C2D1 C5D1, C6D1, every 3 months, and at progression/initiation of next line of treatment. Translational endpoints include circulating tumour cell dynamics, interrogation of the peripheral immune system and whole body MRI to assess imaging biomarkers as potential surrogates for response. The study opened in September 2019 and recruitment is ongoing.

Clinical trial identification: NCT04067713.

Legal entity responsible for the study: University College London CRUK Clinical Trials Unit.

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