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Plasma Analysis for Response Assessment and to Direct the management of Metastatic prostate cancer (PARADIGM)

Anuradha K Jayaram[1,2], Alison Reid[3], Graham Wheeler[4], Constantine Alifrangis[5], Jacqueline O'Dwyer[6], Robert Jones[7], Carmel Pezaro[8], Elias Pintus[9], John Staffurth[10], Simon Crabb[11], Harbir Sidhu[12], Kate Smith[13], Sarah Needleman[13], Susannah Brock[14], Sue Rodwell[15], Anna Wingate[2], Leila Zakka[2], Millenn Chiwewe[16], Marian Duggan[16], Hayley Cartwright[16], Laura White[16], Gerhardt Attard[1,2]

[1]University College London Hospital NHS Trust, UK; [2]UCL Cancer Institute, University College London, UK; [3] The Royal Marsden NHS Trust, London, UK; [4] Imperial Clinical Trials Unit, Imperial College London, UK; [5]Barts Health NHS Trust, London, UK; [6]The Christie NHS Foundation Trust, Manchester, UK; [7]University of Glasgow, Beatson West of Scotland Cancer Centre; [8]Doncaster and Bassetlaw Teaching Hospitals NHS Foundation Trust, UK; [9]Guys' and St Thomas' NHS Foundation Trust, London, UK; [10]Velindre Cancer Centre, Velindre University NHS Trust, Wales, UK; [11]University Hospital Southampton; [12]UCL Centre for Medical Imaging, University College London, UK; [13]Royal Free NHS Foundation Trust, London, UK; [14]Royal Bournemouth Hospital, UK; [15]Aberdeen Royal Infirmary Hospital, Scotland, UK, [16] CRUK and UCL Cancer Trials Centre, University College London

Background

- Long-term androgen deprivation therapy (ADT) alone for patients with newly-diagnosed metastatic prostate cancer is associated with a median time to castration resistance of approximately 13 months[1].
- Recently, the addition of docetaxel or androgen receptor signalling inhibitors (ARSI) at the start of ADT in newly diagnosed metastatic prostate cancer is associated with improved progression-free survival (PFS) and overall survival (OS)[2,3,4,5,6].
- Serum Prostate specific antigen (PSA) levels at 7 months (<0.2, 0.2-0.4, >4ng/dL) has been associated with differential outcomes in patients receiving ADT and docetaxel[7].
- There is a need for a tool to identify patients who will develop early resistance and require alternative or intensified treatments.

Study Design

- PARADIGM is a prospective, observational, biomarker-focused, translational cohort study to determine whether the detection of circulating tumour DNA in plasma (ptDNA) after two or three cycles of standard of care docetaxel (PARADIGM-D) or ARSI (PARADIGM-A) added at the start of ADT is associated with a worse clinical outcome in newly diagnosed poly-metastatic prostate cancer patients (Figure 1).

Key Inclusion Criteria

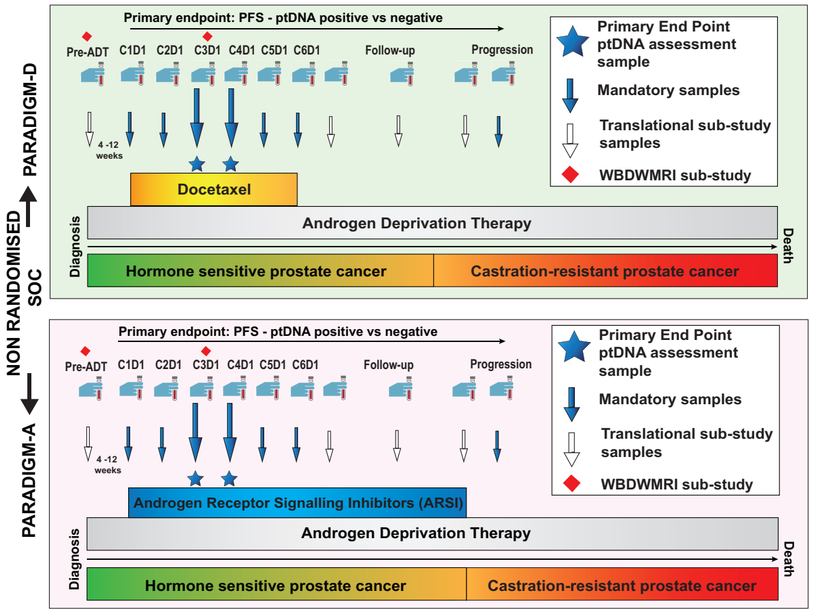
- Poly-metastatic disease defines as one of the following:
  - ≥ 5 bone metastases
  - ≥ 1 unequivocal visceral metastases
- Patients should be either of the following:
  - Planned to start long-term Luteinizing hormone Releasing Hormone (LHRH) suppression, or
  - Started long-term LHRH antagonist within the last 14 weeks, or
  - Started LHRH agonist within the last 16 weeks. When antiandrogens are used in combination with an LHRH agonist, patients have to have started within 18 weeks of starting antiandrogens
- Patients should be planned for addition of docetaxel (PARADIGM-D) or ARSI (PARADIGM-A) within 14 weeks after start of LHRH antagonist (16 weeks if LHRH agonist is started without anti-androgen) or 18 weeks from start of anti-androgen with a target of 6 cycles or continuation until progression respectively.

NB: Patients randomised to any of the following experimental drugs; PARPi, PD-1/PD-L1, AKTi, PSMA-lutetium, if given in combination with ADT + docetaxel or ARSI, or to the placebo arm in an open-label clinical trial may be recruited

Key Exclusion Criteria

- Concurrent or planned for (i.e. prior to development of castration resistance), treatment with oestrogens, radiotherapy or surgery to the primary tumour.
- Prior systemic therapy for prostate cancer other than for LHRHa with or without anti-androgen started within the time limits defined in inclusion criteria.
- Any surgery or radiotherapy planned prior to Cycle 4 day 1

Figure 1. Study Design (NCT04067713)



SOC=standard of care; pre-ADT= prior to start of androgen deprivation therapy; ptDNA=plasma tumour DNA, C=cycle, D=Day, WBDWMRI= whole body diffusion weight magnetic resonance imaging

Primary Endpoint

- PFS defined as the interval from start of docetaxel or ARSI to disease failure determined by either radiological disease progression, PSA progression, symptomatic progression or prostate cancer specific death.

Secondary Endpoints

- Prostate Cancer Specific Survival (PCSS) defined as time from start docetaxel or ARSI with ADT to death from prostate cancer.
- OS defined as time from start of ARSI or docetaxel with ADT to death from any cause.

Translational Research

- Comparison of ptDNA dynamics and PSA kinetics and correlation with PFS and OS.
- ptDNA fraction pre-ADT and association with PFS and OS.
- ptDNA detection on ADT and association with PFS and OS.
- Circulating tumour cell (CTC) dynamics pre and post ADT and association with PFS and OS.
- Utility of WBDWMRI derived imaging biomarkers as a surrogate of response.
- Interrogation of peripheral immune changes and correlation with PFS and OS for docetaxel or ARSI.

Statistical Analysis Plan

- PFS will be reported separately for PARADIGM-D and PARADIGM-A.
- PARADIGM-D:
  - Assumes a 12 month PFS rate of 50% in ptDNA positive (+) and 80% in ptDNA negative (-) patients, giving a HR of 0.322.
  - To achieve at least 95% power, 40 events (12 in ptDNA (+) and 28 in ptDNA (-)) need to be observed in 65 patients.
- PARADIGM-A:
  - Assume a 12 month PFS rate of 60% in ptDNA (+) and 85% in ptDNA (-) patients, giving a HR of 0.322.
  - To achieve at least 90% power, 33 events (11 in ptDNA (+) and 22 in ptDNA (-)) need to be observed in 65 patients.
- PARADIGM-A will report patients on any 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 (-) patients.

Conclusions

- The study is currently opened in 17 hospital sites across the United Kingdom.
- The first patient was consented in September 2019
- Recruitment is currently ongoing.

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Disclosures: AKJ has no financial disclosures or conflicts of interest.

The PARADIGM study (Clinicaltrials.gov: NCT04067713) is funded by Prostate Cancer UK and managed by the CR UK & UCL Cancer Trials Centre. The study is sponsored by UCL.

Contact details: Presenting author: Anuradha Jayaram – a.jayaram@ucl.ac.uk, Chief Investigator: Gert Attard - g.attard@ucl.ac.uk, PARADIGM Trial Coordinator - ctc.paradigm@ucl.ac.uk