# End of Trial Report Form

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| **Study Title:** | **Utilising Circulating Tumour Cell (CTC) Counts to Optimize Systemic Therapy of Metastatic Prostate Cancer: CTC-STOP Trial** | | |
| **CCR number:** | **CCR4338** | **REC Reference:** | **16/LO/1502** |
| **CTA No:** | **22138/0022/001-0001** | **EudraCT number:** | **2015-001361-27** |
| **Chief Investigator:** | **Professor Johann de Bono** | | |

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| **List of Principal Investigators and any participating Sites** | C01 Royal Marsden Hospital, Sutton – Professor Johann de Bono<br>C02 Western General Hospital – Dr Jahangeer Malik<br>C03 Velindre Cancer Centre – Dr Satish Kumar<br>C04 UCLH – Dr Ursula McGovern<br>C05 Colchester General Hospital – Dr Dakshinamoorthy Muthukumar<br>C07 Musgrove Park Hospital – Dr Mohini Varughese<br>C08 Derriford Hospital – Dr Peter Sankey<br>C09 St George's Hospital – Dr Mehran Afshar<br>C10 Lister Hospital – Dr Anand Sharma<br>C11 Mount Vernon Cancer Centre – Dr Anand Sharma<br>C12 Royal Lancaster Infirmary – Dr Alison Birtle<br>C13 Royal Shrewsbury Hospital – Dr Narayanan Nair Srihari<br>C14 Belfast City Hospital – Dr Suneil Jain<br>C15 West of Scotland Beatson Cancer Centre – Professor Robert Jones<br>C16 Bristol Haematology and Oncology Centre – Dr Amit Bahl<br>C17 Royal Devon and Exeter Hospital – Dr Denise Sheehan |
| **Study Design** | **Multicentre prospective randomised controlled phase III trial** |
| **Study Start and End Dates** | • Date of favourable ethical opinion: 21 September 2016<br>• First patient randomised: 01 March 2017<br>• Trial closed to recruitment: 02 May 2019<br>• Date end of trial declared: 09 April 2020 |
| **Primary and Secondary Objective(s)** | **Primary Objective:**<br>To determine if the use of serial CTC counts can direct early discontinuation of docetaxel chemotherapy in patients with metastatic castration resistant prostate cancer (mCRPC) without adversely impacting overall survival (OS), when compared with standard approaches to guide treatment switch decisions.<br><br>**Secondary Objectives :**<br>1. To determine clinician and patient acceptance and feasibility of this approach utilising CTC counts to direct treatment (initial feasibility analysis on first 200 patients).<br>2. To determine if the use of serial CTC counts will decrease the administration of cytotoxic chemotherapy in the population.<br>3. To determine if using serial CTC counts result in decreased toxicity burden of systemic therapy.<br>4. To compare quality of life in patients treated with or without CTC monitoring. |

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| | 5. To correlate progression free survival (PFS), radiographic progression free survival (rPFS) and time to symptomatic skeletal related events (SSRE) with CTC progression.<br>6. To correlate treatment related changes in PSA and CTC.<br>7. To establish the rate of response to docetaxel and cabazitaxel in CRPC setting in patients who have previously received docetaxel in the hormone sensitive setting.<br>8. To incorporate CTC count change into a multi-parametric outcome model with previously established prognostic factors.<br>9. To determine the value of "stable" CTC counts relative to Screening (baseline).<br>10. To evaluate the health economic impact and cost-effectiveness in cost per Quality Adjusted Life Year (QALY) of CTC guided treatment switching.<br><br>**Exploratory Objectives**<br>To evaluate patient perception and preferences on therapeutic switch decisions.<br>To evaluate the post-trial treatment options and sequence list study treatments used including amount given, treatment schedules etc |
| **Endpoints/ Outcome Measure(s)** | **Primary Endpoint**<br>Overall survival (OS) will be compared between the two randomised groups. An initial non-inferiority analysis will be conducted and will be followed by a superiority analysis if non-inferiority is demonstrated.<br><br>**Secondary Endpoints**<br>1. Proportion of patients in the intervention group that undergo a chemotherapy switch from docetaxel to cabazitaxel guided by CTC results that fulfil the pre-specified criteria for progression.<br>2. Number of cycles of chemotherapy administered in each of the docetaxel groups.<br>3. Rate of adverse events and toxicity with first and second line chemotherapy.<br>4. Quality of life analysis by evaluation of outcome measures in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) and EuroQoL 5D (EQ-5D) questionnaires.<br>5. Progression Free Survival (PFS)<br>6. Radiographic Progression Free Survival (rPFS)<br>7. Time to First Symptomatic Skeletal Related Event (SSRE)<br>8. Time to CTC progression<br>9. % Change from baseline values of CTC, PSA and pain (assessed by the Brief Pain Inventory (BPI) during first and second line therapy<br>10. Rate of pain response, PSA declines and CTC response to first and second-line chemotherapy.<br>11. Proportion of patients with a stable CTC count by 12-weeks (or earlier if 1st line treatment discontinued).<br>12. Health economic assessments.<br><br>**Exploratory Endpoints**<br>**1.** Patient perception and preferences on therapeutic switch decisions.<br>**2.** Proportion of patients receiving post-trial treatment. |
| **Statistical Methods** | The objective of this trial is to find out if CTC-guided earlier treatment discontinuation will decrease the administration of ineffective and potentially toxic docetaxel chemotherapy while not adversely impacting overall survival |

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| | (OS) from mCRPC in a randomised trial. This trial is therefore a "non-inferiority" trial. Patients will be allocated 1:1 to either group (CTC-guided therapeutic decisions versus standard of care). If non-inferiority is demonstrated, a further statistical analysis will evaluate whether the CTC treatment group has superior overall survival.<br><br>The primary end-point of this trial is OS. **The median OS in the control group (standard of care) is assumed to be 15 months.** This figure has been inferred following published results from clinical trials, where median OS time for three-weekly docetaxel is 18.9 months in the TAX327 study; 15.1 months from start of cabazitaxel after docetaxel failure in the TROPIC study. On the other hand, there is some evidence that in the post-abiraterone/enzalutamide setting, chemotherapy may not be as efficacious: median OS in these retrospective studies was found to be around 12 months. The CTC-STOP trial will recruit patients following progression with abiraterone/enzalutamide, but all patients will receive docetaxel and cabazitaxel, so potentially they could do better than the patients reported in these retrospective studies. A 15 months' median OS has been chosen as a compromise from the available evidence.<br><br>The trial will be powered to exclude a 20% increase in mortality (i.e. hazard ratio (HR) not worse than 1.20) in patients whose treatment management has been based on CTC values. This corresponds to a median OS in the intervention group of no less than 12.5 months (i.e. the median survival cannot be reduced by more than 2.5 months).<br><br>For the sample size calculation, a recruitment period of 24 months has been assumed, with staggered accrual rate (30% 1st year, 70% 2nd year); all patients will be followed for a minimum of 24 months.<br><br>In order to show non-inferiority with HR=1.20 with a 5% one-sided alpha and a 15% beta (i.e. power = 85%), a total sample size required is 1122 patients and a total of 868 events are required for analysis. Assuming a potential 5% loss-to-follow up, 1178 patients will be recruited during a period of 2 years, with an additional follow-up after recruitment of 2 years.<br><br>In order to randomize 1178 patients with a CTC count ≥5, approximately 2356 patients may need to be screened.<br><br>Given the uncertainty around the assumed median OS in the control group, we have computed the power achieved with the above sample size, should the median OS be different from 15 months:<br>a. If the median OS in the control group (standard of care) is 12 months instead of 15 months, as preliminary evidence suggests, a sample size of 1122 patients will allow the rejection of a similar 20% increase in mortality (from 12 to 10 months of median survival) with 87.6% power, with 5% one-sided alpha.<br>b. If the median OS in the control group (standard of care) is 18 months instead of 15 months, in line with published results from clinical trials, a sample size of 1122 patients will allow the rejection of a similar 20% increase in mortality (from 18 to 15 months of median survival) with 82.3% power, with 5% one-sided alpha. |
| **No. of Patients (planned and analysed)** | The study planned to recruit 1178 patients. Due to low level of recruitment, the study was closed to recruitment prematurely. 12 patients were randomised and analysed. |

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| **Main inclusion/exclusion criteria** | **Inclusion Criteria**<br>1. Written informed consent.<br>2. Age ≥18 years<br>3. Histologically confirmed diagnosis of adenocarcinoma of the prostate with availability of archival tumour tissue for molecular analyses (small cell prostate cancer is an exclusion); if no histological diagnosis has ever been acquired a fresh bone marrow trephine tumour biopsy confirming the presence of CRPC must be pursued.<br>o *Tumour tissue blocks will be requested for processing. Sections will be cut with the blocks then returned to the referring hospital. If the block is not available, at least ten tumour tissue sections (formalin-fixed paraffin-embedded) at 5 microns each will be requested.*<br>4. Metastatic castration-resistant disease with only bone metastases, confirmed by bone scan (within 4 weeks) or CT (within 6 weeks), of starting this trial (Cycle 1 Day 1). Patients with local recurrence, and bone metastases with an associated soft tissue component, will be allowed into the trial. Pelvic lymphadenopathy <1.5cm in short axis is not an exclusion.<br>5. Systemic chemotherapy indicated for disease progression, defined as:<br>o Bone Scan Progression: Two or more new documented bone lesions over previous 6 months.<br>AND/OR<br>o Increasing serum PSA level: Two consecutive increases in PSA levels documented over a previous reference value obtained at least one week apart are required. If the third PSA value is less than the second, an additional fourth test to confirm the rising PSA is required.<br>6. Baseline laboratory values as stated below:<br>o Creatinine ≤1.5 x upper limit of normal (ULN)<br>o Bilirubin ≤1.0 x ULN<br>o SGOT (AST) and SGPT (ALT) ≤2.5x ULN<br>o Castrate serum testosterone level (<50 ng/dL-or-<1.7 nmol/L)<br>o ANC ≥1.5 x $10^9$cells/L<br>o Platelet count ≥100 x $10^9$/L<br>o PSA ≥ 5ng/mL<br>7. CTC levels ≥ 5 cells / 7.5 mL<br>8. Prior treatment with abiraterone and/or enzalutamide, discontinued due to disease progression.<br>9. Patient willing to continue primary androgen suppression with gonadotropin-releasing hormone (GnRH) analogues (either agonists or antagonists) throughout the study, unless treated with bilateral orchiectomy.<br>10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see Appendix A2).<br><br>**Exclusion Criteria**<br>1. Received any prior cytotoxic chemotherapy as treatment for castration-resistant prostate cancer. Patients that have received chemotherapy for hormone-sensitive metastatic prostate cancer will be allowed onto the trial, if the patient merits retreatment with docetaxel and at least 12 months has elapsed since the patient has completed that previous docetaxel therapy. |

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| | 2. Measurable soft tissue or lymph node metastases or any metastatic disease outside the bone that is RECIST measurable will be an exclusion (unless it is pelvic nodal disease <1.5cm in short axis). Bone metastases with associated soft tissue components will also not be an exclusion.<br>3. Received any cycling, intermittent or continuous hormonal treatment 28 days prior to randomisation with the exception of the continuous LHRH analogues.<br>4. History of or current documented brain metastasis or carcinomatous meningitis, treated or untreated. Brain imaging for asymptomatic patients is not required.<br>5. Current symptomatic cord compression requiring surgery or radiation therapy. (Once the patient is successfully treated the patient will be considered eligible for the study).<br>6. Active second malignancy (except non-melanoma skin or superficial bladder cancer) defined as requiring anticancer therapy or within the previous two years.<br>7. Serious medical conditions such as heart failure, myocardial infarction, pulmonary thromboembolism within 12 months; stroke or treatment of a major active infection within 3 months of randomisation, as well as any significant medical illness that in the opinion of the Investigator would preclude protocol therapy. |
| **Investigational Medicinal Product(s)** | • Docetaxel<br>• Cabazitaxel |
| **Duration of Treatment** | Patients would receive up to ten 3-week courses of docetaxel and may receive up to ten 3-week cycles of cabazitaxel, so the maximum overall duration of study treatment will be 60 weeks. In routine practice a median number of 6-8 courses of docetaxel and 4-6 courses of cabazitaxel are generally administered. |
| **Did the study achieve its objectives?** | No. The CTC-STOP trial experienced a low recruitment rate since the trial opened in January 2017, and this remained a major challenge while the trial was open to recruitment. A threshold of 50 patients to be recruited by 31 March 2019 was set by the Trial Steering Committee (TSC) at the end of 2018. Progress against this target was reviewed by the TSC members at their meeting on 18 April 2019 (12 patients randomised), and it was agreed that, despite the efforts of all involved and the consensus on the importance and relevance of the research question, recruitment to the trial had not increased significantly enough to demonstrate viability. The TSC members therefore recommended the trial close to recruitment immediately, and this decision was also subsequently endorsed by the CTC-STOP Trial Management Group.<br><br>In light of these decisions, the study team suspended recruitment to the trial on 02 May 2019. |
| **Conclusions** | • Between 06 February 2017 and 01 May 2019, 36 patients with mCRPC and predominant bone disease were registered into the trial. 12 out of these 36 patients went on to randomisation (6 in the control group. 6 into the intervention group). The most frequent reason for registered patients not proceeding to randomisation was ineligibility due to CTCs<5 (14 patients).<br>• Baseline features of the 12 patients randomised into CTC-STOP:<br>o white British (100%); |

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| | o a mean (SD) age of 74 years (8.3)<br>o a median (IQR) of 3.5 years (2.6-9.4) from initial diagnosis;<br>o a median (IQR) of 1.6 years (1.2-2.1) from diagnosis of mCRPC;<br>o 7 (58.3%) patients had metastatic disease at diagnosis, all of these 7 patients had bone metastasis;<br>o 4 patients (33.3%) had a Gleason score ≤7 at diagnosis;<br>o the majority of patients (9 patients, 75%) had documented PSA and bone progression at trial entry;<br>o 2 patients (16.7) had lymph nodes metastasis (<2cm) at trial entry;<br>o a median (IQR) PSA of 43.1 ng/ml (16.8-226.5) at diagnosis.<br>• The median overall follow up, calculated to date last seen is 20.2 months (Q1 6.2 months to Q3 25.3 months).<br>• No formal statistical analysis was performed due to the small number of randomised patients. Outcomes for all randomised patients are summarised descriptively below.<br>• Results<br>o *Primary endpoint - Overall Survival*<br>Overall, 7 patients (58.3%) remained alive at the end of the study, 3 in the intervention group, and 4 in the control group.<br>o *Secondary endpoint – Treatment switch as recommended*<br>In the intervention group, 3 patients (50%) were recommended to undergo a chemotherapy switch from docetaxel to cabazitaxel, guided by CTC results that fulfil the pre-specified criteria for progression. Of these 3 patients, only 1 patient switched to cabazitaxel.<br>o *Secondary endpoint - Number of cycles of chemotherapy administered*<br>Median (IQR) number of docetaxel cycles was 6 (4-9) in the intervention group, 4 (3-6) in the control group. 7 patients received cabazitaxel, with median (IQR) number of cycles of 5 (2-5) in the intervention group, 3.5 (2.7) in the control group.<br>o *Secondary endpoint - Progression of disease*<br>9 patients (75%) progressed on trial, 8 (66.7%) of whom had clinical progression, 7 (58.3%) bone progression, 4 (33.3%) progressed on RECIST, and 8 (66.7%) on PSA<br>o *Secondary endpoint - Number of CTC progressions*<br>A total of 7 patients (58.3%) had CTC progression.<br>• A total of 13 serious adverse events (SAEs) were reported in 7 patients, 9 of which were serious adverse reactions (SARs). 5 of the 9 SARs were related to docetaxel, and 4 to cabazitaxel. The most common SAR was neutropenia, a total of 6 events were reported in 5 patients, including febrile and non-febrile neutropenia, across grade 2 to 4. |
| **List of Publications (or planned publications)** | Lorente D, Olmos D, Mateo J, Bianchini D, Seed G, Fleischer M, Danila D, Flohr P, Crespo M, Figueiredo I, Miranda S, Baeten K, Molina A, Kheoh T, McCormack R, Terstappen L.W.M.M, Scher H.I, DeBono J (2016). Decline in |

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| | Circulating Tumor Cell Count and Treatment Outcome in Advanced Prostate Cancer. Eur Urol 2016 Dec;70(6):985-992.<br>DOI: https://doi.org/10.1016/j.eururo.2016.05.023<br><br>Lorente D, Ravi P, Mehra N, Pezaro C, Omlin A, Gilman A, Miranda M, Rescigno P, Kolinsky M, Porta N, Bianchini D, Tunariu N, Perez Lopez R, Mateo J, Payne H, Terstappen LW, Ijzerman M, HALL E, DeBono J (2018). Interrogating metastatic prostate cancer treatment switch decisions: A Multi-institutional Survey. Eur Urol Focus 2018 Mar;4(2):235-244<br>DOI: http://dx.doi.org/10.1016/j.euf.2016.09.005<br><br>Degeling K, Schivo S, Mehra N, Koffijberg H, Langerak R, De Bono JS, Ijzerman MJ. Comparison of Timed Automata with Discrete Event Simulation for Modeling of Biomarker Based Treatment Decisions: An Illustration for Metastatic Castration-Resistant Prostate Cancer. Value Health. 2017 Dec;20(10):1411-1419.<br>DOI: http://dx.doi.org/10.1016/j.jval.2017.05.024 |
| **Will the results of this research be communicated to the Participants?** | No. The study was closed prematurely and no formal analysis will be performed. 6/12 participants are now deceased. Patients were informed about the early closure of the trial in August 2019. |

***Chief Investigator/Principal Investigators Signature:*** 

***Print name:*** ***Professor Johann de Bono***

***Date:*** ***2 March 2021***