SYNOPSIS	
Title of the registry:	Clinical experience with cabazitaxel in patients with metastatic castrate resistant prostate cancer (ECLIPSE)
Design:	A multi-centre, observational, retrospective research study of patients with metastatic castrate resistant prostate cancer (mCRPC) who have received cabazitaxel in England.
Objectives:	**Primary objective** • To describe the anti-cancer treatment pathways for patients who have received cabazitaxel following prior docetaxel treatment **Secondary objective(s)** • To describe the clinical outcomes of patients who have received cabazitaxel following prior docetaxel treatment (according to the treatment sequencing received post-docetaxel) • To describe the characteristics of patients receiving cabazitaxel treatment • To describe side effects associated with cabazitaxel use
Treatment:	No investigational treatment. This was an observational study of patients receiving cabazitaxel and other treatments for prostate cancer as per clinical practice and independent of the study.
Scientific committee and members:	Not applicable
Publications (reference):	Abstract/Poster presentations 1. ESMO European Cancer Conference: [redacted] 2. National Cancer Research Institute (NCRI) Cancer Conference 2015: [redacted] 3. ESMO Asia Cancer Conference 2015 [redacted] 4. British Uro-oncology Group Annual Conference 2015: [redacted] 5. 7th European Multidisciplinary Meeting on Urological Cancers (EMUC) 2015: [redacted] 6. ESMO 2016: [redacted]

	[redacted]
Introduction - Background/ rationale:	Prostate cancer is the most common cancer in men, and the second leading cause of cancer death in men in the UK[1–3]. When the extent of prostate cancer spreads beyond the tissues directly adjacent to the prostate gland, it is called metastatic prostate cancer (PC). Although no longer curative, the aim of treatment of metastatic PC is to control the cancer for several years, relieve any symptoms and improve quality of life. Hormone therapy (androgen deprivation or anti-androgens) or bilateral orchidectomy is the usual primary treatment offered to patients for metastatic PC. However, over time many men experience disease progression despite androgen blockade treatment. This is known as metastatic hormone-resistant prostate cancer (mHRPC) or now more commonly, metastatic castrate-resistant prostate cancer (mCRPC)[4]. Prior to 2011, treatment options for mCRPC were limited, with docetaxel as standard anti-cancer therapy[5] and clinical trials as an alternative. More recently, there has been an emergence of new anti-cancer therapies licensed for treatment of mCRPC, including hormonal therapies (abiraterone and enzalutamide[6,7]) and an antineoplastic agent, cabazitaxel[8]. Cabazitaxel is an anti-cancer chemotherapy developed by Sanofi, Study Sponsor, indicated for the treatment of patients with hormone refractory (castrate-resistant) metastatic prostate cancer previously treated with a docetaxel regimen[9]. These emerging treatment options are funded in the NHS in England following recommendation from the National Institute for Health and Care Excellence (NICE) or via the National Cancer Drugs Fund[5–8,10]. The hormonal therapies abiraterone and enzalutamide both now receive funding to be used before and after docetaxel and prior to cabazitaxel and enzalutamide receives funding for use after cabazitaxel. As a result, the point in the treatment pathway when cabazitaxel is used is thought to vary, with the optimal sequence not known. There is currently limited multi-centre research published describing clinical experience with cabazitaxel in clinical practice in England. This study was designed to describe the clinical experience with cabazitaxel in patients with mCRPC in England. This study describes the anti-cancer treatment sequencing and the profile of patients who have received cabazitaxel. This study also describes the clinical outcomes and side effects associated with cabazitaxel, according to the point at which cabazitaxel was used in the treatment pathway. As clinical experience of cabazitaxel is relatively limited across all specialist centres, the data from the study is providing valuable information for collective learning on how to manage patients with mCRPC more effectively in real world NHS practice. Data from this study are also being combined with data from other real world studies of similar design across Europe looking at clinical experience with cabazitaxel in patients with mCRPC. The study is, therefore, supporting wider on-going evidence generation to determine the optimal treatment sequencing of all life-extending cancer therapies in mCRPC. In particular, to describe the point in which cabazitaxel is used in the patient pathway and the associated patient survival and other clinical outcomes.
Methodology:	**Selection of Sites** Investigator sites were specialist secondary/tertiary hospitals that provide total care of men with mCRPC. Sites were chosen where cabazitaxel chemotherapy was prescribed regularly in standard NHS practice or via the Sanofi cabazitaxel early access programme. **Selection of patients** Patients who met the following eligibility criteria were selected up to a maximum of 150 patients in total: **Inclusion Criteria:** • Male patients diagnosed with mCRPC.

- Patients who have received cabazitaxel at any point following failure of previous docetaxel treatment.
- Patients aged ≥18 years at start of cabazitaxel treatment.
- Patients who first started cabazitaxel treatment at least 1 year before data collection.
- Patients who consent to researcher access to records (unless deceased or in end-stage of terminal illness).

Exclusion Criteria:

- Patients who received cabazitaxel at a point other than following failure of previous docetaxel treatment.
- Patients who decline consent.
- Patients whose records are unavailable for review.

There was variation in number of patients available across centres because of differences in numbers of patients with relapsed mCRPC post docetaxel treatment and also due to different local prescribing habits.

Patients were selected in chronological order according to their date of cabazitaxel initiation (i.e. those prescribed cabazitaxel first were selected first).

As per the Research Ethics Committee approval conditions, all living patients still under the care of the participating centre and eligible to be approached, were invited to consent to allow a researcher access to their medical records for the purpose of data collection for this study. For patients who were no longer under the care of the centre, but not known to have died, the patient's General Practitioner (GP) was contacted to enquire whether the patient was living and could be contacted for consent (i.e. not at end-stage of terminal illness). Consent was only sought from those patients approved by the GP for contact by the clinician-investigator. For deceased patients and those not approved for contact for consent, anonymised data were collected by members of the NHS direct care team to preserve patient confidentiality, so that this important group of patients could be included in the study. Patients who declined consent were not included in the study.

Data collection:

Anonymised data were collected by a member of the NHS direct care team. For patients who consented, a researcher from [redacted] was available for assistance with data collection as required. Data were collected for the study period from the patients' medical records at the investigating sites only. Data were not collected from referring hospitals or the patient's GP. Study data were recorded on paper data collection forms (DCF) in anonymised-coded form. Data were initially collected retrospectively from the medical records (paper and electronic) of all eligible patients at the centres between March 2015 and June 2015. Following a protocol amendment (Protocol Amendment 1: 23rd October 2015) additional data were collected on the same patient cohort and analysis were carried out to enable data to be combined with data from other Sanofi-sponsored studies of similar design across Europe. The additional data were collected between 10th December 2015 and 11th March 2016 from the same patients originally included in this study. In order to limit any unnecessary burden on patients, re-consent for the additional data collection was not carried out as it was not required since (i) the study objectives did not change; (ii) the supplementary data were covered by the original information sheet and consent form; and (iii) the supplementary data were only collected by members of the direct care team.

Safety data collection:

All Adverse Events (AE) regardless of relationship to cabazitaxel, including those reported in the time spanning from the signature of the informed consent form until the end of the study as defined by the protocol for each patient, were notified to [redacted] who reported to Sanofi immediately (within 24 hours of awareness) for serious AE and within 30 days of awareness for non-serious AEs and were recorded on the corresponding pages of the paper DCF.

Data management, review, validation:

A copy of the completed anonymised DCFs were released to [redacted] for data entry, cleaning and

analysis and reporting, with the original DCFs kept at the site. Data received by [redacted] for data management were checked for patient eligibility, accuracy and completeness using visual and programmed validation checks. Data queries were raised with sites and resolution and any corrections were made by reference to patient medical records by the appropriate healthcare professionals.

Source data verification (SDV) was conducted at each site once approximately 50% of the original data had been collected at the given site. SDV was performed on the whole dataset of a random sample of 10% of records. 'Back to back' SDV (to allow monitoring of data quality while preserving patient confidentiality) was performed by [redacted] SDV was conducted at each site for supplementary data collected after October 2015; this was performed on the whole supplementary dataset of a random sample of at least 10% of records as detailed above.

Statistical considerations:

Analyses were performed by [redacted] and are descriptive in nature. Both distributions and descriptive statistics of both central tendency (arithmetic means) and dispersion (standard deviation [SD]) are presented for quantitative variables. Nominal variables are described with frequencies and percentages, while ordinal variables are presented as medians and interquartile ranges (IQR). Time-to-event variables (progression-free survival [PFS] and overall survival [OS]) were analysed by the Kaplan-Meier method with data presented as survival plots and summarised as median, standard error (SE) and 95% confidence intervals [95% CI], within the follow up period available for each patient (i.e. patients still living at the date of data collection were censored at the date of data collection for analysis of OS and patients still alive and not recorded as progressing at the time of data collection were censored on that date for analysis of PFS).

An interim analysis was performed with available data in April 2015 to support submission of an abstract to ESMO ECC scientific congress and provided to Sanofi for inclusion in a dossier to NICE; a further analysis was performed in October 2015 with all available data as of September 2015 (prior to protocol amendment). This report (updated from the interim report: QSD-005254_Report ECLIPSE_V1 0_18 12 2015 DRAFT) presents the combined results of all data collected according to the original protocol (Version 1.0 5th January 2015) and the supplementary data collected according to the protocol amendment (Protocol Amendment 1: 23rd October 2015).

As the analyses of this study are descriptive in nature, the sample size was not assessed in terms of statistical power, but rather in terms of the precision (95% CI) associated with the pathway outcomes of frequencies or proportions. A sample size of 150 patients in 5-8 centres was chosen to give sufficiently reliable outcomes for the median clinical or radiological PFS and to be representative of patients with mCRPC. The centres varied in both geographic location and size in order to provide a representative sample of patients from across England.

In clinical practice, cabazitaxel may be given at different stages of the patient pathway. Clinical outcome measures, patient characteristics, safety and tolerability of cabazitaxel are presented according to the anti-cancer treatment sequence post-docetaxel for patients with mCRPC.

The evaluation relies on the quality and completeness of the data recorded in the clinical records, as data were sourced retrospectively. Where data were not known or not available from the original medical record, the affected analyses were conducted using only the results of those patients with data available with no imputation.

Throughout this report, all percentages are presented to one decimal place; any inconsistencies in reported total % compared with composite groups within tables and in the accompanying text are due to rounding.

RESULTS

Participants (actual):

This study was conducted in England only.

Investigator	NHS Trust	Number of patients
Dr [redacted]	[redacted]	33
Dr [redacted]	[redacted]	7
Dr [redacted]	[redacted]	23
Dr [redacted]	[redacted]	19
Dr [redacted]	[redacted]	33
Dr [redacted]	[redacted]	0
	Total	115

[a]Did not participate. [redacted]

99 (86.1%) of the patients were deceased at the time of the original data collection.

Participant characteristics and primary analyses:

Patient demographic and clinical characteristics at cabazitaxel initiation

115 male patients with mCRPC from 5 centres in England were evaluated. The mean age of patients at cabazitaxel initiation was 69.4 (SD: 6.7) years (Appendix II [Table 1]). The mean weight of patients was 85.4 (SD: 13.8) kg (Appendix II[Table 2]) and mean body surface area (BSA) was 2.00 (SD: 0.17) m^2 at cabazitaxel initiation (see Appendix II [Table 3]).

No comorbidities were recorded for 54 (47.0%) patients, with 11 (9.6%) patients having at least two recorded comorbidities at cabazitaxel initiation (see Appendix II [Table 4]). The most commonly recorded comorbidity was diabetes mellitus (15/115 [13.0%] patients, see Appendix II [Table 5]).
The most common sites of metastases at cabazitaxel initiation were bone (106/115 [92.2%] patients) and distal lymph nodes (26/115 [22.6%] patients); 15 (13.0%) patients had liver and /or lung metastases (see Appendix II [Table 6]) and 38/115 (33%) of patients had metastases in at least two locations at cabazitaxel initiation (see Appendix II [Table 7]).

Primary evaluation

Treatment Pathway

Following protocol approval, the Chief Investigator and Sanofi agreed that analyses describing the sequences of therapies for mCRPC were to focus on life-extending anti-cancer therapies only, (i.e. abiraterone [A], cabazitaxel [C], docetaxel [D], enzalutamide [E], excluding re-challenge). Due to the numerous sequences of life-extending anti-cancer therapies, when not describing individual sequences, abiraterone and enzalutamide were grouped as androgen receptor targeting agents [ARTA].

The most frequently prescribed first-line androgen deprivation therapy for PC was goserelin (56/115 [48.7%] patients; see Appendix II [Table 8]). Patients received between one and four anti-cancer treatment regimens before cabazitaxel initiation (see Appendix II [Table 9]), between one and four anti-cancer treatment regimens after cabazitaxel initation (see Appendix II [Table 10]) and 7 patients were re-challenged with cabazitaxel (see Appendix II [Table 11]). Patients received a mean of 1.7 (SD: 0.7) anti-cancer regimens pre-cabazitaxel and 1.3 (SD: 0.6) post-cabazitaxel (see Appendix II [Table 12]).

Docetaxel was followed by cabazitaxel therapy in 58 (50.4%) patients and by abiraterone in 57 (49.6%) patients. The most common sequences prescribed for mCRPC were DAC for 44 (38.3%) patients, DCA for 32 (27.8%) patients and DACE for 9 (7.8%) patients (DC: n=5 [4.3%]; DC[ARTA]: n=49 [42.6%]; D[ARTA]C: n=57 [49.6%]; see Appendix II, Table 13 and Table 14). A total of 39 unique anti-cancer treatment sequences were recorded, as shown in Appendix II (Table 15). Sixteen (13.9%) patients received cabazitaxel as part of a clinical trial (see Appendix II [Table 16]).

The median time from luteinising hormone-releasing hormone analogue (LHRHa) initiation to mCRPC diagnosis was 22.24 (IQR: 11.85 to 42.52) months (see Appendix II [Table 17]). The median time from LHRHa initiation to cabazitaxel initiation was 45.54 (27.29 to 67.17) months and from mCRPC diagnosis to cabazitaxel initiation was 18.00 (IQR: 11.43 to 28.73) months, as shown in Appendix II (Table 18). The median time from docetaxel to cabazitaxel initiation in the overall study population was 12.88 (IQR: 8.30 to 19.53) months (DC: 2.66 [IQR: 1.41 to 3.42] months; DC[ARTA]: 4.60 [2.14 to 9.43] months; D[ARTA]C: 11.93 [6.44 to18.40] months; see Appendix II [Table 18 and Table 19]). The times between the end of each life-extending anti-cancer treatment to the initiation of the next treatment are summarised in Appendix II (between abiraterone and cabazitaxel: Table 20; between enzalutamide and cabazitaxel: Table 21; between docetaxel and abiraterone: Table 22; between docetaxel and enzalutamide: Table 23; between abiraterone and enzalutamide: Table 24).

The mean initial dose of docetaxel was 72.6 (SD: 7.0) mg/m^2 (see Appendix II [Table 25]). The median duration of docetaxel treatment was 3.8 (IQR: 3.4 to 5.9) months (Appendix II [Table 26]), with patients receiving a median of 6 (range: 1 to 12) cycles of docetaxel (Appendix II [Table 27]).

The mean initial dose of cabazitaxel was 23.9 (SD: 2.4) mg/m^2 (see Appendix II [Table 28]). The median duration of cabazitaxel treatment was 3.7 (2.1 to 6.2) months (Appendix II [Table 26], with patients receiving a median of 6 (range: 1 to 15) cycles of cabazitaxel (Appendix II [Table 27]). Cabazitaxel dose reductions were recorded in 28/115 (24.3%) patients (see Appendix II [Table 29]), most commonly due to toxicity (9/28 [32.1%], see Appendix II [Table 30]). Delays in cabazitaxel treatment were recorded in 28/115 (24.3%) patients (Table 29), most commonly due to toxicity (14/28 [50.0%], see Table 30) and 76/115 (66.1%) patients stopped cabazitaxel early (Table 29), most commonly due to toxicity (19/76 [25.0%], see Table 30). Cabazitaxel concomitant medications included prednisolone or prednisone (110 [95.7%] patients), granulocyte-colony stimulating factor (G-CSF; 95 [82.6%] patients) and bisphosphonates (39 [33.9%] patients), as shown in Appendix II (Table 31). The median duration of abiraterone treatment was 4.6 (IQR: 3.2 to 8.3) months and the median duration of enzalutamide treatment was 3.5 (1.8 to 6.0) months (see Appendix II [Table 26]).

Secondary evaluation

Clinical outcome measures

Performance status

World Health Organisation performance status (WHO-PS) score (score ranges from 0 [fully active] to 5 [dead]) was recorded in 40 (34.8%) patients at initiation of cabazitaxel and in 13 patients at disease progression; no patients had a WHO-PS score above 2 at cabazitaxel initiation or progression (see Appendix II [Table 32]). WHO-PS scores were not evaluated according to sequence of life-extending anti-cancer therapy due to small numbers. WHO-PS scores at initiation of docetaxel, abiraterone and enzalutamide and subsequent disease progression were not available for the majority of patients (see Appendix II [Table 33, Table 34, Table 35 and Table 36]).

Biochemical markers of disease progression

Prostate-specific antigen (PSA) progression was the most frequently recorded type of disease progression at the initiation of each life-extending anti-cancer therapy (docetaxel: 101 [46.5%] patients; cabazitaxel: 109 [45.8%]; abiraterone: 84 [48.3%] patients; enzalutamide 22 [39.3%] patients; Appendix II [Table 37]). Pain progression was recorded in 17.8% to 25.0% of patients and radiological progression in 13.2% to 18.0% of patients at initiation of each life-extending anti-cancer therapy (Table 37).

PSA levels were recorded at cabazitaxel initiation for 48/115 (42%) patients.. The median PSA at cabazitaxel initiation was 377.0 (IQR: 124.2 to 967.8) µg/L (DC: 990.0 [IQR: 734.9 to 1265.0] µg/L; DC[ARTA]: 162.5 [IQR: 62.8 to 433.8] µg/L; D[ARTA]C: 578.5 [IQR: 277.5 to 934.3] µg/L; see Appendix II [Table 38 and Table 39]). PSA concentrations were not recorded at the end of cabazitaxel therapy for the majority of patients; in those with data available (n=22) there was a median decrease in PSA of 26.3 (IQR: -273.7 to +177.3) µg/L in the overall patient population, representing a median relative decrease of 9.9% (see Appendix II [Table 40 and Table 41]). In those with data available, a decrease in PSA at the end of cabazitaxel treatment was recorded in 13/22 (59.1%) patients, with a ≥30% reduction observed in 9/22 (40.9%) patients and a ≥50% reduction observed in 8/22 (36.4%) patients (Appendix II [Table 42]). The median PSA nadir from cabazitaxel initiation until initiation of the next anti-cancer treatment was 103.5 (IQR: 28.7 to 316.5) µg/L (DC: 702.5 [IQR: 291.5 to 1165.0] µg/L; DC[ARTA]: 66.1 [IQR: 28.7 to 191.5] µg/L; D[ARTA]C: 164.4 [IQR: 36.0 to 403.0] µg/L; see Appendix II [Table 43]). The median time to PSA nadir was 2.66 (IQR: 1.20 to 5.36) months (DC: 1.38 [IQR: 0.53 to 2.34] months; DC[ARTA]: 3.98 [IQR: 1.36 to 6.25] months; D[ARTA]C: 1.91 [IQR: 1.22 to 4.50] months; see Appendix II [Table 44]).

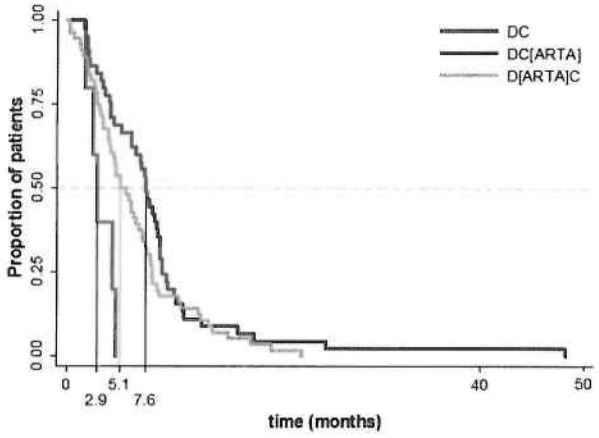
Serum alkaline phosphatase (ALP) levels were recorded at cabazitaxel initiation for 69/115 (60.0%) patients; The median ALP nadir from cabazitaxel initiation until initiation of the next anti-cancer treatment was 108.0 (IQR: 69.0 to 200.0) IU/L (DC: 139.0 [113.5 to 190.3] IU/L; DC[ARTA]: 86.0 [IQR: 66.0 to 164.0] IU/L; D[ARTA]C: 129.0 [IQR: 80.3 to 211.8] IU/L; see Appendix II [Table 47]). The median time to ALP nadir was 3.29 (IQR: 1.31 to 4.73) months (DC: 0.44 [IQR: 0.32 to 1.31] months; DC[ARTA]: 3.45 [IQR: 1.97 to 6.11] months; D[ARTA]C: 2.76 [IQR: 1.31 to 4.11] months; see Appendix II [Table 48]).

Progression-free survival

In the overall patient population, 97 (84.3%) patients progressed within 12 months of cabazitaxel initiation, with a median time to disease progression of 6.21 (IQR: 3.22 to 8.71) months (DC: 2.89 [IQR: 2.53 to 4.40] months; DC[ARTA]: 7.56 [IQR: 4.14 to 9.17] months; D[ARTA]C: 5.09 [IQR: 3.02 to 8.15] months; see Appendix II [Table 49]). In Kaplan-Meier analyses, the median PFS (composite endpoint of PFS or death) from cabazitaxel initiation to disease progression in the overall population was 6.21 (95% CI: 4.67, 7.26) months (DC: 2.89 [95% CI: 1.71 - .] months; DC[ARTA]: 7.56 [95% CI: 6.21, 8.71] months; D[ARTA]C: 5.09 [95% CI: 4.11 - 6.9] months; see Figure 1 and Appendix II [Table 50]).

The median time from initiation of first androgen deprivation therapy to first disease progression was 18.60 (0.23 to 162.43) months (see Appendix II [Table 51]) and was shortest in patients treated with DC (median 8.80 [IQR: 4.57 to 12.22] months; Appendix II [Table 52]).

Figure 1. Progression-free survival from cabazitaxel initiation by treatment sequence (endpoint composite PFS or death)

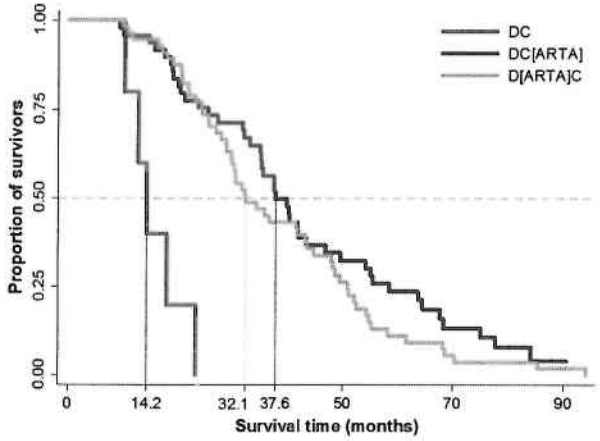


Patient status at data collection:

In the overall patient population, 106/115 (92.2%) patients were deceased at the time of final data collection, with a median time from mCRPC diagnosis to death of 32.49 (IQR: 21.71 to 49.23) months (DC: 14.16 [IQR: 12.68 to 17.71] months, n=5; DC[ARTA]: 37.32 [IQR: 22.24 to 51.83] months, n=43; D[ARTA]C: 32.00 [IQR: 24.03 to 50.20] months, n=55; see Appendix II[Table 53]).

Overall survival from mCRPC diagnosis: In Kaplan-Meier analyses, the median OS from mCRPC diagnosis in the overall population (n=115) was 34.92 (95% CI: 30.36 to 40.25) months (DC: 14.16 [95% CI: 10.12, - .] months [n=5]; DC[ARTA]: 37.59 [95% CI: 32.89, 46.78] months [n=49]; D[ARTA]C: 32.10 [95% CI: 28.68, 43.50] months [n=57]), as shown in Figure 2 and Appendix II (Table 54).

Figure 2. Overall survival from mCRPC diagnosis by treatment sequence

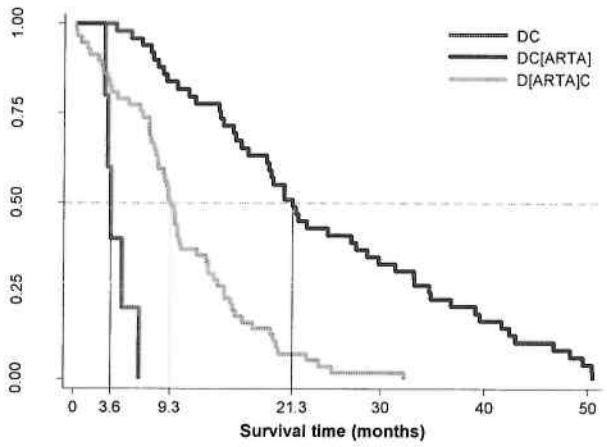


Survival from cabazitaxel initiation

In the overall patient population, the median time to death from cabazitaxel initiation was 11.52 (IQR: 7.29 to 19.84) months (n=106; see Appendix II [Table 55]). Overall, 51/115 (44.3%) patients were alive at 1 year after cabazitaxel initiation (DC: 0/5 (0%); DC[ARTA]: 32/49 [65.3%]; D[ARTA]C: 18/57 [31.6%]) and 19/115 (16.5%) were alive 2 years after cabazitaxel initiation (DC: 0/5 (0%); DC[ARTA]: 17/49 [34.7%]; D[ARTA]C: 2/57 [3.5%]; see Appendix II [Table 56])... At the time of initial data collection, 6/49 (12.2%) patients treated with DC[ARTA] and 2/57 (3.5%) patients treated with D[ARTA]C were still alive (see Appendix II [Table 57]). The cause of death was recorded as PC-related in 62/106 (58.5%) patients (see Appendix II [Table 58]).

Overall survival from cabazitaxel initiation:In Kaplan-Meier analyses, the median OS from cabazitaxel initiation in the overall population (n=115) was 13.08 (95% CI: 9.82 to 15.51) months (DC: 3.58 [95% CI: 2.99 - .] months [n=5]; DC[ARTA]: 21.32 [95% CI: 16.95 - 27.6] months [n=49]; D[ARTA]C: 9.33 [95% CI: 7.95 - 10.41] months [n=57]), as shown in Figure 3 and Appendix II (Table 59).

Figure 3. Overall survival from cabazitaxel initiation by treatment sequence



Overall survival from docetaxel initiation

The median time to death from docetaxel initiation (n=106) was 27.86 (IQR 18.36 to 38.16) months, with 45/115 (39.1%) patients surviving for less than 2 years (see Appendix II [Table 60]).

In Kaplan-Meier analyses, the median OS from docetaxel initiation in the overall population (n=115) was 28.48 (95% CI: 23.49 - 31.87) months (DC: 12.22 [95% CI: 7.16 - .] months [n=5]; DC[ARTA]: 34.40 [95% CI: 28.52 - 39.49] months [n=49]; D[ARTA]C: 27.50 [95% CI: 21.32 - 30.72] months [n=57]), as shown in Appendix II (Table 61 and Figure 4).

Reductions in pain and analgesia:

In the overall patient population, 73/115 (63.5%) patients had pain recorded at cabazitaxel initiation, and of these 24/73 (32.9%) patients were recorded as having a reduction in pain (based on clinical opinion) at some point after cabazitaxel initiation and before the next anti-cancer treatment (see Appendix II [Table 62]). A reduction in the quantity and level of analgesia after cabazitaxel initiation was recorded for 18/115 (15.7%) patients (Appendix II [Table 63]) and 5/115 (4.3%) of patients (Appendix II [Table 64]), respectively.

The proportions of patients with pain at the initiation of docetaxel, abiraterone and enzalutamide and those with a reduction in pain and a reduction in the quantity and level of analgesia recorded following initiation of these therapies are presented in Appendix II (Table 65, Table 66, Table 67, Table 68, Table 69, Table 70, Table 71, Table 72 and Table 73).

Additional patient demographic and clinical characteristics

In the overall patient population, the mean age at diagnosis of mCRPC was 67.6 (IQR: 63.4 to 72.6) years and at the initiation of LHRHa treatment was 64.7 (IQR: 61.5 to 69.0) years (see Appendix II [Table 74 and Table 75]).

In the overall patient population, 83 (72.2%) patients had bone metastases and 26 (22.6%) had distal lymph node metastases at docetaxel initiation (Appendix II [Table 76]). At initiation of abiraterone, 61 (60.4%) patients had bone metastases and 16 (15.8%) had distal lymph node metastases (Appendix II [Table 77]). At initiation of enzalutamide, 19 (63.3%) patients had bone metastases and 7 (23.3%) had distal lymph node metastases (Appendix II [Table 78]).

PSA levels at the start of each life-extending therapy:

PSA levels were infrequently recorded at the start of each life-extending therapy. For the 22/115 (19.1%) patients with PSA recorded at docetaxel initiation, the median PSA was 91.9 (IQR: 45.5 to 346.0) µg/L (see Appendix II [Table 79]; no inferences can be made about PSA at docetaxel initiation according to life-extending anti-cancer treatment sequence due to small numbers [Table 80]). For the 42/101 (41.6%) patients with PSA recorded at abiraterone initiation, the median PSA was 76.5 (IQR: 42.8 to 340.5) µg/L (DC[ARTA]: 230.0 [IQR: 59.0 to 496.5] µg/L; D[ARTA]C: 74.0 [IQR: 42.0 to 180.0] µg/L; see Appendix II [Table 81 and Table 82]). For the 12/30 (40.0%) patients with PSA levels recorded at enzalutamide initiation,the median PSA was 201.2 (IQR: 26.8 to 482.5) µg/L (see Appendix II [Table 81]; no inferences can be made about PSA at enzalutamide initiation according to life-extending anti-cancer treatment sequence due to small numbers [Table 82]).

ALP levels at the start of each life-extending therapy:

ALP levels were infrequently recorded at the start of each life-extending therapy. For the 37/115 (32.0%) patients with ALP recorded at docetaxel initiation, the median ALP was 175.0 (IQR: 99.0 to 256.0) IU/L (DC: 129.0 [IQR: 111.0 to 236.5] IU/L; DC[ARTA]: 200.0 [IQR: 127.0 to 410.0] IU/L; D[ARTA]C: 127.0 [IQR: 93.0 to 180.5] IU/L; see Appendix II [Table 85 and Table 86]). For the 56/101 (55.4%) patients with ALP levels recorded at abiraterone initiation, the median ALP was 159.0 (IQR: 91.8 to 291.5) IU/L (DC[ARTA]: 227.0 [IQR: 103.5 to 421.3] IU/L; D[ARTA]C: 159.0 [IQR: 87.0 to 237.5] IU/L; see Appendix II [Table 87 and Table 88]). For the 16/30 (53.3%) patients with ALP levels recorded at enzalutamide initiation,the median ALP was 245.0 (IQR: 149.8 to 502.5) IU/L (see Appendix II [Table 89]; no inferences can be made about ALP at enzalutamide initiation according to life-extending anti-cancer treatment sequence due to small numbers [Table 90]).

Other biochemical and haematological variables at the start of each life-extending therapy:

Testosterone levels were not recorded for the majority (>95%) of patients at the initiation of each life-extending anti-cancer therapy, therefore no analyses were carried out.

Lactate dehydrogenase levels were not recorded for the majority (>95%) of patients at the initiation of each life-extending anti-cancer therapy, therefore no analyses were carried out.

Haemoglobin (Hb) levels were recorded infrequently at the start of each life-extending therapy. In the 80/115 (69.6%) patients with Hb recorded at cabazitaxel initiation,the mean Hb was 11.68 (SD: 1.35) g/dL (DC: 12.50 [SD: 0.50] g/dL; DC[ARTA]: 11.73 [SD: 1.35] g/dL; D[ARTA]C: 11.51 [SD: 1.36] g/dL; see Appendix II [Table 91 and Table 92]). An abnormally low Hb at cabazitaxel initiation (based on clinical

	judgement) was recorded for 47/115 (40.9%) of patients (DC: 0/5 patients; DC[ARTA]: 25/49 [51.0%]; D[ARTA]C: 21/57 [36.8%]; see Appendix II [Table 93 and Table 94]). In the 37/115 (32.2%) patients with Hb levels recorded at docetaxel initiation the mean Hb was 12.2 (SD: 1.7) g/dL (DC: 11.3 [SD: 1.2] g/dL; DC[ARTA]: 12.3 [SD: 1.8] g/dL; D[ARTA]C: 12.4 [SD: 1.6] g/dL; see Appendix II [Table 95 and Table 96]). In the 47/101 (46.5%) patients with Hb levels recorded at abiraterone initiation,the mean Hb was 11.8 (SD: 1.9) g/dL (DC[ARTA]: 11.1 [SD: 2.0] g/dL; D[ARTA]C: 12.2 [SD: 1.7] g/dL; see Appendix II [Table 97 and Table 98]). In the 17/30 (56.7%) patients with Hb levels recorded at enzalutamide initiation, the mean Hb was 11.0 (SD: 1.6) g/dL (see Appendix II [Table 99]; no inferences can be made about ALP at enzalutamide initiation according to life-extending anti-cancer treatment sequence due to small numbers [Table 100]). In the 79/115 (68.7%) patients with neutrophil counts recorded at cabazitaxel initiation, the mean neutrophil count was 5.34 (SD: 2.66) x10^9/L (DC: 5.79 [SD: 2.19] x10^9/L; DC[ARTA]: 5.12 [SD: 3.06] x10^9/L; D[ARTA]C: 5.67 [SD: 2.26] x10^9/L; see Appendix II [Table 101 and Table 102]). In the 63/115 (54.8%) patients with lymphocyte counts recorded at cabazitaxel initiation, the mean lymphocyte count was 1.49 (SD: 0.72) x10^9/L (DC: 1.10 [SD: 0.80] x10^9/L; DC[ARTA]: 1.58 [SD: 0.64] x10^9/L; D[ARTA]C: 1.48 [SD: 0.78] x10^9/L; see Appendix II [Table 103 and Table 104]). In the 67/115 (58.2%) patients with albumin levels recorded at cabazitaxel initiation,the mean albumin was 36.4 (SD: 5.0) g/L (DC: 33.8 [SD: 4.3] g/L; DC[ARTA]: 37.4 [SD: 4.5] g/L; D[ARTA]C: 35.9 [SD: 5.1] g/L; see Appendix II [Table 105 and Table 106]). In the 62/115 (53.9%) patients with calcium levels recorded at cabazitaxel initiation,the mean calcium was 2.28 (SD: 0.20) mmol/L (DC: 2.47 [SD: 0.09] mmol /L; DC[ARTA]: 2.34 [SD: 0.13] mmol /L; D[ARTA]C: 2.22 [SD: 0.23] mmol /L; see Appendix II [Table 107 and Table 108]). ***Risk scores:*** Total Gleason scores (biopsy scores 2-6: well differentiated cells; 7: moderately differentiated cells; 8-10: poorly differentiated cells) were recorded for 78/115 (67.8%) patients at the time of PC diagnosis. Of the patients with available data, 54/78 (69.2%) patients had a Gleason score of ≥8 (DC: 3/4 [75.0%]; DC[ARTA]: 29/38 [76.3%]; D[ARTA]C: 21/57 [61.8%]; see Appendix II [Table 109 and Table 110]). Clinical tumour stage for the primary tumour (T) was recorded for 71/115 (61.7%) patients at diagnosis of PC, with stage T3 (tumour broken through the prostate gland capsule[11]) or T4 (tumour spread to nearby organs[11]) recorded in 50/115 (43.5%) patients (see Appendix II [Table 111]; see Table 112 for T stage according to life-extending anti-cancer therapy]). Lymph node stage (N) was recorded for 69/115 (60.0%) patients at diagnosis of prostate cancer, with stage N1 or N2 (cancer cells present in the lymph nodes[11]) recorded in 25/115 (21.7%) patients (see Appendix II [Table 113]; see Table 114 for N stage according to life-extending anti-cancer therapy]). Metastases stage (M) was recorded for 73/115 (63.4%) patients at diagnosis of prostate cancer, with stage M1 (cancer spread outside the pelvis[11]) recorded in 43/115 (37.4%) patients (see Appendix II [Table 115]; see Table 116 for M stage according to life-extending anti-cancer therapy]). ***Other variables:*** Diagnosis of CRPC was made >12 months following first androgen deprivation therapy in 83/115 (72.2%) patients (see Appendix II [Table 117; see Table 118 for time to CRPC diagnosis according to life-extending anti-cancer therapy]). In the overall patient population, 87/115 (71.3%) patients did not undergo curative therapy; the most common curative therapy was radiation therapy (24/115 [20.8%] patients; see Appendix II [Table 119; see Table 120 for curative therapy according to life-extending anti-cancer therapy]).

	Adverse events Adverse events were reported in 85/115 (73.9%) patients, with Grade ≥3 diarrhoea reported in 7 (6.1%) patients, other gastrointestinal (GI) disorders reported in 34 (29.6%) patients and neutropenic infection reported in 14 (12.2%) patients (see Appendix II [Table 121]).

Other analyses:	**Analyses for Abstract to ESMO ECC 2015** For the purposes of the ESMO ECC abstract, the number of life-extending therapies was summarised (see Appendix II [Table 122]). Overall survival was presented from mCRPC diagnosis (rather than cabazitaxel initiation as specified in the original protocol analysis plan) following discussion with the Chief Investigator and Sanofi Medical team. A copy of the original abstract submitted to ESMO ECC 2015 is presented in Appendix IV. The ensuing poster included an analysis of the full dataset from the original data collection. However, it became apparent during the collection of the additional data that there were some inconsistencies in dates recorded for mCRPC diagnosis during the original data collection which impacted on the classification of treatment sequences in a small number of patients and OS from mCRPC diagnosis. Consequently the analyses have been updated for consistency with the main data analysis. The results of the original OS analyses reported in the poster are summarised in Appendix II (Figure 5, Figure 6 and Figure 7). The updated analyses and analysis of OS from docetaxel initiation according to the same treatment sequences, have been included in an abstract being prepared for submission to ASCO-GU 2017, and are summarised below. The median OS from mCRPC diagnosis varied according to different sequences of life-extending therapies as shown in Appendix II (Figure 8, Figure 9, Figure 10, Table 123, Table 124 and Table 125). Median OS from mCRPC diagnosis was longer in patients receiving ≥3 life-extending therapies including two taxanes than those receiving only two life-extending therapies ($p<0.001$), see Appendix II (Figure 8). Median OS was similar in patients treated with cabazitaxel either as the 2nd or 3rd line life-extending therapy after docetaxel (Appendix II [Figure 10]; DCA vs. DAC). OS was evaluated according to presence of lung/liver metastases and according to DAC and DCA treatment sequences in patients with lung and/or liver metastases as additional analyses for information only (see Appendix II [Figure 11 and Table 126]). **Analyses for NICE cabazitaxel dossier** The additional analyses carried out and provided for the NICE cabazitaxel dossier are presented in Appendix II (Table 127, Table 128, Table 129, Table 130, Table 131, Table 132, Table 133, Table 134, Table 135 and Table 136). These data have also been updated as a result of the update to the data collected and are presented in Appendix II (Table 137, Table 138, Table 139, Table 140, Table 141, Table 142, Table 143, Table 144, Table 145 and Table 146 and Table 147).
Discussions:	**Sites and patients** 115 patients with mCRPC from 5 centres in England were evaluated, which was lower than the required sample size of 150 patients. The numbers of patients confirmed eligible following local study approvals were less than anticipated based on the pre-study feasibility assessment. This was primarily due to patients being excluded because of unavailability of the required pathway data. To include more patients, an additional centre was recruited (Dr [redacted] However, Dr [redacted] did not participate. Sanofi decided to continue with the remaining 5 centres. The 115 patients evaluated represented all eligible patients receiving cabazitaxel at the participating centres,

which were chosen specifically as they were known regular prescribers of cabazitaxel chemotherapy that provide total care of men with mCRPC.

Patient demographic and clinical characteristics

The age of patients and proportion of patients with visceral metastases at cabazitaxel initiation were similar to those seen in the Sanofi sponsored Phase III TROPIC clinical trial[12], which looked at prednisone plus cabazitaxel or mitoxantrone for patients with mCRPC progressing after docetaxel treatment, and patients included in a UK cabazitaxel early access programme(EAP)[13] and a German cabazitaxel compassionate use programme (CUP)[14].

Although the proportion of patients with bone metastases in the present study was similar to those reported in previous observational studies[13,14], the proportion of patients with bone metastases in this study was slightly higher than in the TROPIC trial (80%)[12]. This may reflect the fact that patients in the TROPIC trial received cabazitaxel as 2nd-line therapy after docetaxel, whereas in ECLIPSE, the UK EAP and the German CUP patients may have received one or more additional life-extending anti-cancer therapies prior to receiving cabazitaxel[13,14] leading to inclusion of patients at a more advanced disease stage than in the original TROPIC trial.

Treatment Pathway

Numerous anti-cancer treatment sequences were used to treat men with mCRPC in real world clinical practice. The majority of patients received ≥3 different life-extending therapies, with cabazitaxel most commonly given as the 2nd- or 3rd-line life-extending anti-cancer therapy. The 5 patients treated with DC had all had progressed on docetaxel; the median time to cabazitaxel initiation was less than 3 months suggesting their prognosis was poor. Overall, docetaxel was followed by cabazitaxel or an ARTA in similar proportions, with DAC in about two fifths of patients (38.3%) followed by DCA in just over one quarter (27.8%). Just over one third of patients took part in a mCRPC clinical trial and almost 1 in 7 patients received cabazitaxel as part of a clinical trial. The median time from mCRPC diagnosis to cabazitaxel initiation was 18 months and ranged from approximately 2 weeks to over 6 years, reflecting the different points at which patients were treated with cabazitaxel during the treatment pathway and highlighting early use in some patients who may have had aggressive disease not responding to docetaxel. The initial dose of cabazitaxel was in line with the posology specified in the Jevtana® Summary of Product Characteristics[9], with the majority of patients being initiated on 25 mg/m^2 cabazitaxel. Patients received a median of 6 cycles of cabazitaxel, similar to other observational studies[13,14] and the TROPIC clinical trial[9]; notably, almost one third of patients received 10 or more cycles of cabazitaxel consistent with previous studies[12,13], suggestive of the positive tolerability of cabazitaxel.

Secondary evaluation

Clinical outcome measures

Performance status and biochemical markers of disease progression

Performance status, PSA and ALP were were infrequently recorded in the medical record limiting our ability to interpret the data relating to these outcomes. Fewer than 40% of patients had WHO-PS recorded at cabazitaxel initiation and fewer than 80% had WHO-PS recorded at initiation of the other life-extending therapies, therefore no inference about patients' performance status in relation to life-extending therapies can be made. A ≥50% reduction in PSA was observed at the end of cabazitaxel treatment for 36.4% of those with available data, which is similar to the 39.2% of patients with a ≥50% reduction in PSA in the TROPIC trial[12]. The median times to PSA nadir and ALP nadir were approximately 3 months which may suggest an early response to treatment, however, caution is required in interpretation due to the lack of data recorded at cabazitaxel initiation. In addition, testosterone and lactate dehydrogenase were recorded for fewer than 5% of patients at initiation of each life-extending therapy.

Survival

The median PFS from cabazitaxel initiation was 6.2 months, which was longer than the TROPIC trial[12] (2.8

months) and German CUP (3.8 months)[14]. However, the median PFS of patients treated with DC (2.9 months) was similar to TROPIC, with longer PFS in patients treated with DC[ARTA] (7.6 months) and D[ARTA]C (5.1 months). These data suggest that sequential treatment with life-extending anti-cancer therapies provides additional benefits in terms of disease-free status, with no clear advantage in terms of sequencing order of cabazitaxel and ARTA therapies.

Overall, 53.0% of patients were still alive at one year and 20.0% were still alive at two years after cabazitaxel initiation (similar to the 15.9% of patients in TROPIC who survived ≥2 years[15]), although this varied according to treatment sequencing. Fewer than 5% of patients treated with D[ARTA]C survived for two years, whereas more than one-third of patients treated with DC[ARTA] were still alive two years after cabazitaxel initiation. No patients treated with DC survived for 12 months following cabazitaxel initiation, suggesting their prognosis was poor at the time they were initiaited on cabazitaxel. At the time of final data collection 92.2% of patients were deceased. Median OS from cabazitaxel initiation in the present study (13.1 months) was similar to the median OS from cabazitaxel initiation in the original TROPIC clinical trial[12] (15.1 months) and that of the German CUP (13.9 months)[14]. The OS in the present study was shortest in patients treated with DC (3.6 months), longest in patients treated with DC[ARTA] (21.3 months) and intermediate in patients treated with D[ARTA]C (9.3 months), reflecting the different points in the treatment pathway at which cabazitaxel was initiated. In order to account for the impact of treatment sequencing, time to death was also evaluated from mCRPC diagnosis and from docetaxel initation. The median OS from mCRPC diagnosis was shortest for patients treated with DC (14.2 months), longest for those treated with DC[ARTA] (37.6 months) and intermediate in those treated with D[ARTA]C (32.1 months). Similarly, median OS from docetaxel initiation was shortest in patients treated with DC (12.2 months), longest in patients treated with DC[ARTA] (34.4 months) and intermediate in patients treated with D[ARTA]C (27.5 months). It is noteworthy that the median OS from mCRPC diagnosis and from docetaxel initiation were at least 5 months longer in patients treated with DC[ARTA] compared with those treated with D[ARTA]C. The slightly longer OS from docetaxel initiation in patients treated with DC[ARTA] is consistent with the results of a recent systematic review and meta-analysis[16] comparing treatment sequencing for mCRPC after docetaxel (group 1:DAE/DEA = D[ARTA][ARTA]; group 2: DAC/DEC = D[ARTA]C; group 3: DCA/DCE = DC[ARTA]) that demonstrated the cumulative 12-month survival rate was highest for DC[ARTA] (76.4%), intermediate for D[ARTA]C (61.3%) and lowest for D[ARTA][ARTA] (28.5%). In the meta-analysis the data were not suggestive of any benefit of abiraterone over enzalutamide but suggested treatment with cabazitaxel was beneficial compared to no cabazitaxel therapy[16]. Taken together, these data suggest a potential survival benefit in patients treated with DC[ARTA] compared with D[ARTA]C. However, these results should be interpreted with caution due to the possibility of patient treatment selection bias since many treatment-related and patient-related factors can influence treatment decisions following docetaxel failure, including toxicity profile, performance status, disease staging, duration of response to docetaxel and which may also impact on survival. Due to the retrospective nature of this study there was a considerable amount of missing data for Gleason scores, WHO-PS and other biochemical variables previously shown to be predictive of poor outcome; it is therefore difficult to speculate further on the disease status of patients at initiation of cabazitaxel in the different treatment sequencing groups that may have influenced outomes. A prospective observational study would be required to more fully evaluate the impact of different life-extending treatment sequencing strategies on OS.

Reductions in pain and analgesia

Pain is a major symptom in mCRPC, largely due to the presence of bone metastases, and cabazitaxel has been shown to have a similar pain response rate to mitoxantrone[12]. In the present study 63.5% of patients had pain at initiation of cabazitaxel and a reduction in pain was recorded in 32.9% after cabazitaxel initiation, however, it should be acknowledged that pain reduction data were not available or were missing for the majority of patients. The beneficial effect of cabazitaxel on pain is supported by data from the UK EAP that reported between 31% and 57% of patients reported no pain during therapy, with a higher proportion of patients being pain-free during the later cycles of therapy[13].

Adverse Events

Cabazitaxel was stopped early due to toxicity in this real world study in 25.0% of patients, which was a

	slightly higher proportion than the TROPIC study[9] (18%), possibly reflective of patients' attitudes to therapy adherence during clinical trial participation and the limited availability of alternative therapies. AEs were common, reported in 73.9% of patients; however, very few AEs were reported at grade ≥3, with neutropenic infection reported in 12.2% patients (data on febrile neutropenia were not collected separately), consistent with the results of the UK EAP[13]. The most frequently observed AEs were GI disorders, with grade ≥3 diarrhoea reported in 6.1% of patients (consistent with TROPIC[12]), other GI disorders (predominantly diarrhoea grade <3, nausea and vomiting) reported in 29.6% of patients and fatigue reported in 7.8% of patients. In contrast to the TROPIC trial[12], neutropenia, thrombocytopenia and leukopenia were uncommon AEs in the present study despite the higher proportion of patients with bone metastases at cabazitaxel initiation, consistent with the UK EAP[13]. This is likely to reflect the fact that prophylactic G-CSF was not permitted in TROPIC[12] except after first occurrence of neutropenia, whereas 82.6% of patients in the present study and 79.5% of patients in the UK EAP[13] received G-CSF. Diarrhoea, nausea, vomiting and fatigue were also less common in the present study than in the TROPIC trial[12] and the UK EAP[13], which may suggest more favourable tolerability in unselected patients treated in a real world setting or may reflect more stringent patient assessment and AE reporting in clinical trial patients and those included in the EAP. **Limitations of the study** • All data were sourced retrospectively from patient medical records and therefore the interpretation of the results is reliant on the availability and quality of the data recorded. • A considerable number of patients had missing data for Gleason scores, WHO-PS, pain and other biochemical variables previously shown to be predictive of poor outcome making it difficult to interpret these data in relation to treatment sequencing. **Generalizability of the study results** Given the similarity in healthcare across the UK NHS and the fact that this study collected recent data from hospitals across England experienced in the treatment of patients with mCRPC with life-extending anti-cancer therapies, the results of this study can be considered to be generalizable to the wider UK population of adult patients with mCRPC treated with cabazitaxel in normal clinical practice.
Conclusions:	This study has demonstrated there is a variety of treatment sequences used to treat men with mCRPC in real-world clinical practice, with the majority of patients receiving ≥3 different life-extending therapies. It is noteworthy that the longest median OS from mCRPC diagnosis, from docetaxel initiation and from cabazitaxel was observed for patients treated with DC[ARTA], and were at least 5 months longer in patients treated with DC[ARTA] compared with those treated with D[ARTA]C. OS was also observed to be longer in those receiving ≥3 different life-extending therapies than those receiving two therapies.Cabazitaxel was generally well tolerated and showed relatively low toxicity. Due to the limitations of retrospective observational studies, a prospective observational study would be required to more fully evaluate the factors influencing OS in patients with mCRPC treated with different sequences of life-extending anti-cancer therapies.
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