ZYTIGA® (abiraterone acetate)
Comparison of ZYTIGA to Cabazitaxel

SUMMARY

- There are limited prospective study data comparing ZYTIGA plus prednisone with cabazitaxel plus prednisone for the treatment of metastatic castration-resistant prostate cancer (mCRPC).
- CARD was a prospective, randomized, multicenter, open-label study that compared the efficacy and safety of ZYTIGA plus prednisone or enzalutamide to cabazitaxel plus prednisone in 255 patients with mCRPC previously treated with docetaxel and had progression ≤12 months while receiving the alternative androgen-signaling–targeted inhibitor. After a median follow-up of 9.2 months, median imaging-based progression-free survival (PFS) was 8 months in the cabazitaxel plus prednisone group and 3.7 months in the androgen-signaling–targeted inhibitor group (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.4-0.73; *P*<0.001). Grade ≥3 adverse events (AEs) were reported in 56.3% of patients in the cabazitaxel plus prednisone group and 52.4% of patients in the androgen-signaling–targeted inhibitor group.[1] Additional pre-specified and post-hoc analyses have been conducted.[2-5]
- The OSTRICh trial (NCT03295565) was a phase 2b, randomized, open-label, multicenter study that compared cabazitaxel to either ZYTIGA plus prednisone or enzalutamide (androgen receptor targeted agent [ARTA] arm) in patients with poor-prognosis mCRPC (N=106). At 12 weeks, the clinical benefit rate (CBR) was 60% (95% CI, 44%-75%) in the cabazitaxel arm vs 51% (95% CI, 35%-68%) in the ARTA arm (*P*=0.50). There was no radiological progression at 12 weeks in 88% and 67% of patients in the cabazitaxel and ARTA arms, respectively (*P*=0.046). Grade ≥3 AEs occurred in 15 (29%) and 8 (15%) patients receiving cabazitaxel and ARTA, respectively.[6]
- A phase 2, randomized, open-label, multicenter study compared cabazitaxel plus prednisone to androgen receptor pathway inhibitor (ARPI) therapy with either ZYTIGA plus prednisone or enzalutamide in ARPI-naïve patients with poor-prognosis mCRPC (N=95). At a median follow-up of 21.9 months, first-line CBR was 80% in the cabazitaxel group and 62% in the ARPI group (*P*=0.039). No differences in overall survival (OS), time to progression, time to PSA progression, or PFS on first-line treatment were observed. The most common first-line treatment-related grade ≥3 AEs were neutropenia (32% vs 0%), diarrhea (9% vs 0%), infection (9% vs 0%), and fatigue (7% vs 5%) for the cabazitaxel vs ARPI groups, respectively.[7]
- An observational study reported efficacy data for 95 patients in a larger study who met CARD trial eligibility and received an androgen receptor (AR) signaling inhibitor (n=35; either ZYTIGA or enzalutamide) or cabazitaxel (n=60). No difference in OS was observed and no safety data were reported. Radiographic PFS was improved in patients who received cabazitaxel compared to AR signaling inhibitors (median 6.0 vs 3.7 months, respectively; *P*=0.03), as was clinical PFS (median 4.4 vs 3.4 months, respectively; *P*=0.01), and PSA50 responses (39% vs 17%, respectively; *P*=0.027).[8]
- CAPRO was a prospective, multicenter, observational study of patients with mCRPC who received second-line treatments (including ZYTIGA plus prednisone [n=100] and cabazitaxel plus prednisone [n=44]) after first-line docetaxel that determined treatment with ZYTIGA plus prednisone was associated with significantly longer clinical/radiographic PFS (HR, 0.57; 95% CI, 0.38-0.85; *P*=0.005) and OS (HR, 0.4; 95% CI, 0.21-0.76; *P*=0.004) compared to cabazitaxel plus prednisone. There were no significant differences between the treatments in biochemical PFS (HR, 0.78; 95% CI, 0.49-1.24). The most frequent AEs in both treatment groups included asthenia, pain, and anemia.[9]
- Additional data available in the published literature include that from a prospectively maintained database of Australian patients with mCRPC as described below.[10]

CLINICAL DATA

Randomized Studies

de Wit et al (2019)[1] investigated the efficacy and safety of third-line cabazitaxel plus prednisone compared to ZYTIGA plus prednisone or enzalutamide in patients with mCRPC who had previously been treated with docetaxel and the alternative androgen-signaling–targeted inhibitor (N=255).

Study Design/Methods

- Randomized, multicenter, open-label study (NCT02485691; CARD Trial)
- Patients were randomized 1:1 to receive either cabazitaxel plus prednisone or an androgen-signaling–targeted inhibitor.
    - Cabazitaxel was administered at a dose of 25 mg/m^2 intravenously (IV) every 3 weeks, along with oral (PO) prednisone 10 mg daily (QD), following premedication with an antihistamine, glucocorticoid, and H2 receptor antagonist; plus primary prophylactic granulocyte-colony stimulating factor was administered during each 3-week cycle.
    - Androgen-signaling–targeted inhibitor group received ZYTIGA 1000 mg PO QD and prednisone 5 mg PO twice daily, or enzalutamide 160 mg PO QD.
- Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), time to disease progression (≤6 months vs >6-12 months), and timing of the prior androgen-signaling–targeted inhibitor (before vs after docetaxel).
- **Primary endpoint:** imaging-based PFS
- **Secondary endpoints:** OS, PFS, prostate-specific antigen (PSA) response (≥50% reduction in PSA level from baseline), tumor and pain responses, the first occurrence of a symptomatic skeletal event in a time-to-event analysis, and safety

Results

Patient Characteristics

- A total of 255 patients were randomized and 250 patients were treated with either an androgen-signaling–targeted inhibitor (n=124; ZYTIGA plus prednisone, n=58; enzalutamide, n=66); or cabazitaxel plus prednisone (n=126).
- Baseline characteristics are noted in Table: Baseline Characteristics.

Baseline Characteristics[1]

Baseline Characteristic	ZYTIGA plus Prednisone or Enzalutamide (n=126)	Cabazitaxel plus Prednisone (n=129)
Select Characteristics		
Median age, years (range)	71 (45-88)	70 (46-85)
ECOG performance status score, n (%)		
0 or 1	119 (94.4)	123 (95.3)
2	7 (5.6)	6 (4.7)
Liver or lung metastases, n (%)	25 (19.8)	21 (16.3)
Median PSA, ng/mL (range)	60.5 (1.5-2868)	62 (1.1-15,000)
Type of progression at study entry, n (%)		
PSA only	10 (7.9)	11 (8.5)
Imaging-based, with or without PSA progression	16 (12.7)	23 (17.8)
Pain, with or without PSA or imaging-based progression	90 (71.4)	86 (66.7)
Missing data	10 (7.9)	9 (7)
Disease History		
M1 disease at diagnosis, n (%)	60 (47.6)	49 (38)

Gleason score 8-10 at diagnosis, n (%)	81 (64.3)	73 (56.6)
First androgen-deprivation therapy		
Median duration, months (range)	12.6 (3-179)	13.7 (2-114)
Duration <12 months, n (%)	57 (45.2)	56 (43.4)
Previous androgen-signalling–targeted inhibitor, n (%)		
ZYTIGA	67 (53.2)	56 (43.4)
Enzalutamide	59 (46.8)	72 (55.8)
Missing data	0	1 (0.8)
Timing of previous androgen-signalling–targeted inhibitor, n (%)		
Before docetaxel	49 (38.9)	50 (38.8)
After docetaxel	77 (61.1)	79 (61.2)
Time from initiation of previous androgen-signalling–targeted inhibitor to progression ≤6 months, n (%)	62 (49.2)	65 (50.4)
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.		

Efficacy

- After a median follow-up of 9.2 months, median treatment was longer in the cabazitaxel plus prednisone group than in the androgen-signaling–targeted inhibitor group (22 vs 12.5 weeks), and the median number of treatment cycles received was higher in the cabazitaxel plus prednisone group than in the androgen-signaling–targeted inhibitor group (7 vs 4 cycles).
    - Treatment discontinuation of cabazitaxel plus prednisone or an androgen-signaling–targeted inhibitor was due to disease progression (in 43.7% and 71.0% of patients, respectively), or an AE (in 19.8% and 8.9% of patients, respectively).
- The median imaging-based PFS was 8 months in the cabazitaxel plus prednisone group and 3.7 months in the androgen-signaling–targeted inhibitor group (HR for imaging-based progression or death, 0.54; 95% CI, 0.4-0.73; *P*<0.001).
- The median OS was 13.6 months in the cabazitaxel plus prednisone group and 11 months in the androgen-signaling–targeted inhibitor group (HR for death, 0.64; 95% CI, 0.46-0.89; *P*=0.008).
- Progression was noted in 111 patients (86%) in the cabazitaxel plus prednisone group and in 115 (91.3%) in the androgen-signaling–targeted inhibitor group.
    - The median PFS was 4.4 months in the cabazitaxel plus prednisone group and 2.7 months in the androgen-signaling–targeted inhibitor group (HR for progression or death, 0.52; 95% CI, 0.4-0.68; *P*<0.001).
- PSA response (reduction of ≥50% from baseline, confirmed by a second value obtained at least 3 weeks later) was observed in 35.7% of 115 evaluable patients in the cabazitaxel plus prednisone group and in 13.5% of 111 evaluable patients in the androgen-signaling–targeted inhibitor group (*P*<0.001).
- Among patients with measurable disease at baseline, tumor response was seen in 37% of 63 evaluable patients in the cabazitaxel plus prednisone group and in 12% of 52 evaluable patients in the androgen-signaling–targeted inhibitor group (*P*=0.004).
- Of the 126 patients who received ZYTIGA plus prednisone or enzalutamide, 42 (33.3%) crossed over to receive cabazitaxel plus prednisone.
- Of the 129 patients who received cabazitaxel plus prednisone in the study, 30 (23.3%) crossed over to receive ZYTIGA plus prednisone or enzalutamide.

Safety

- AEs are noted in Table: Adverse Events (Safety Population).
- At least 1 dose reduction occurred in 29%, 45%, and 21.4% of patients who were assigned to receive ZYTIGA plus prednisone, enzalutamide, and cabazitaxel plus prednisone, respectively.

Adverse Events (Safety Population)[1]

Event	ZYTIGA plus Prednisone or Enzalutamide (n=124)		Cabazitaxel plus Prednisone (n=126)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE, n (%)	117 (94.4)	-	124 (98.4)	-
Any grade ≥3 AE, n (%)	-	65 (52.4)	-	71 (56.3)
Any serious AE, n (%)	48 (38.7)	-	49 (38.9)	-
Any AE leading to permanent treatment discontinuation, n (%)	11 (8.9)	-	25 (19.8)	-
Any AE leading to death, n (%)[a]	14 (11.3)	-	7 (5.6)	-
Common AEs (>20%), n (%)				
Asthenia or fatigue	45 (36.3)	3 (2.4)	67 (53.2)	5 (4)
Diarrhea	8 (6.5)	0	50 (39.7)	4 (3.2)
Infection	25 (20.2)	9 (7.3)	40 (31.7)	10 (7.9)
Musculoskeletal pain/discomfort	49 (39.5)	7 (5.6)	34 (27)	2 (1.6)
Nausea or vomiting	29 (23.4)	2 (1.6)	33 (26.2)	0
Laboratory abnormalities (>20%), n/N (%)				
Anemia	118/124 (95.2)	6/124 (4.8)	124/125 (99.2)	10/125 (8)
Leukopenia	39/124 (31.5)	2/124 (1.6)	93/125 (74.4)	40/125 (32)
Neutropenia	8/124 (6.5)	4/124 (3.2)	81/123 (65.9)	55/123 (44.7)
Thrombocytopenia	20/124 (16.1)	2/124 (1.6)	51/125 (40.8)	4/125 (3.2)
AST increased	35/124 (28.2)	0/124	27/124 (21.8)	4/124 (3.2)

Abbreviations: AE, adverse event; AST, aspartate aminotransferase.
[a]AEs leading to death were assessed during the period from randomization to 30 days after the last treatment administration. ZYTIGA plus prednisone or enzalutamide group: infection (n=2), pulmonary thromboembolism (n=1), cardiac disorder (n=2), cerebral bleeding associated with hyperfibrinolysis (n=1), renal failure (n=2), general health deterioration due to progressive disease (n=6, which in 1 patient was associated with upper gastrointestinal bleeding, hypertensive crisis, and cardiac failure). Cabazitaxel plus prednisone group: infection (n=2), bronchial aspiration (n=1), general health deterioration due to progressive disease (n=2), spinal cord compression (n=1), and head injury (n=1).

van der Zande et al (2021)[6] evaluated cabazitaxel vs ZYTIGA plus prednisone or enzalutamide in patients with poor-prognosis mCRPC (N=106).

Study Design/Methods

- Phase 2b, randomized, open-label, multicenter study (NCT03295565)
- Patients were randomized 1:1 to receive cabazitaxel 25 mg/m^2 IV every 3 weeks or ARTA (ZYTIGA 1000 mg PO daily plus prednisone 5 mg PO twice daily or enzalutamide 160 mg PO daily).
- **Select inclusion criteria:** patients with poor-prognosis mCRPC (visceral metastases and/or <12 months responsive to androgen deprivation and/or progressing during or within 6 months after docetaxel therapy)
- **Select exclusion criteria:** treatment with life prolonging therapy between docetaxel completion and study randomization
- **Primary endpoint:** establish the CBR (no radiotherapy, no ECOG performance status increase ≥2, no change of therapy, and no radiological progression) at 12 weeks
- **Secondary endpoint:** formal comparison of CBR
- **Additional endpoints:** serum PSA decrease ≥50% from baseline, radiological progression free survival (rPFS), and OS

Results

Patient Characteristics

- Median age: 70 years (interquartile range [IQR], 67-75 years)
- Median PSA: 79.4 ng/mL (IQR, 29.0-160 ng/mL)

- ECOG performance status score: 99 (93%) patients had a score of 0-1 and 7 (7%) patients had a score of 2
- Thirty-six (34%) patients were previously treated with docetaxel and 41 (39%) patients previously received ARTA

Efficacy

- Efficacy results for the cabazitaxel and ARTA treatment arms are reported in Table: Efficacy Results of Cabazitaxel and ARTA in Patients with Poor-Prognosis mCRPC.

Efficacy Results of Cabazitaxel and ARTA in Patients with Poor-Prognosis mCRPC[6]

Endpoint	Cabazitaxel (N=53)	ARTA (N=53)	*P*-value
CBR at 12 weeks, n/N (%) 95% CI	26/43 (60%) 44%-75%	20/39 (51%) 35%-68%	0.50
No Radiological Progression at 12 weeks, n/N (%) 95% CI	30/34 (88%) 73%-97%	24/36 (67%) 49%-81%	0.046
Serum PSA decrease ≥50% from baseline[a], n (%) 95% CI	12 (23%) 12%-36%	26 (49%) 35%-63%	0.008
Median rPFS, months (95% CI)	6.0 (4.11-14.5)	5.8 (5.22-10.2)	0.5
Median OS, months (95% CI)	15.3 (9.49-22.4)	13.8 (11.7-16.4)	0.8

Abbreviations: ARTA, androgen receptor targeted agent; CBR, clinical benefit rate; CI, confidence interval; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiological progression-free survival.
[a]After a median follow-up of 16.4 months.

Safety

- Grade ≥3 AEs occurred in 15 (29%) and 8 (15%) patients treated with cabazitaxel and ARTA, respectively.

Annala et al (2021)[7] evaluated cabazitaxel plus prednisone vs ZYTIGA plus prednisone or enzalutamide in ARPI-naïve patients with poor-prognosis mCRPC (N=95).

Study Design/Methods

- Phase 2, randomized, open-label, multicenter study (NCT02254785)
- Patients were randomized 1:1 to group A (cabazitaxel 25 mg/m^2 IV every 3 weeks plus prednisone 5 mg PO twice daily [n=45]) or group B (investigator's choice of an ARPI: either ZYTIGA 1000 mg PO daily plus prednisone 5 mg PO twice daily [n=27] or enzalutamide 160 mg PO daily [n=23]).
- Treatment continued until disease progression (clinical progression [≥2 level increase in ECOG performance status or a change in anticancer therapy for worsening cancer-related symptoms]; PSA progression [PSA increase ≥25% and ≥2 ng/mL above the baseline in patients without a PSA decline, or PSA increase ≥25% and ≥2 ng/mL above the nadir in patients with a PSA decline, confirmed by a second value ≥3 weeks later after 12 weeks of trial treatment as per PCWG2 criteria]; and/or radiographic progression [RECIST version 1.1 for measurable disease, or appearance of ≥2 new bone lesions on bone scan confirmed on a subsequent scan with ≥1 additional new bone lesions]), unacceptable toxicity, or withdrawal of consent. Crossover to the opposite treatment was permitted if patients continued to meet eligibility criteria upon progression.
- **Select inclusion criteria:** patients with poor-prognosis mCRPC (presence of liver metastases, development of castration resistance within 12 months of surgical or chemical castration for metastatic disease, or the presence of at least 4 of the following poor-prognosis features: lactate dehydrogenase (LDH)>upper limit of normal (ULN), ECOG performance status 2, visceral metastatic disease, serum albumin ≤4 g/dL, ALP>ULN, or <36 months since start of initial ADT)

- **Select exclusion criteria:** prior chemotherapy (1 course of docetaxel was allowed), next-generation anti-androgen or CYP17 inhibitors[11]
- **Primary endpoint:** investigator-assessed CBR, defined as PSA decline ≥50% from baseline, measurable radiographic response of any duration, or stable disease for ≥12 weeks without other indicators of progression
- **Secondary endpoints:** for first-line therapy were duration of therapy, time to PSA progression, time to any progression, PFS. Additional were OS, safety and toxicity, proportion of patients who were eligible for crossover to second-line therapy and who received second-line therapy within the trial
- **Exploratory endpoints:** for second-line therapy were CBR, time to PSA progression, time to any progression, and PFS. Additional were OS from time of crossover, predictive and prognostic utility of cell-free DNA biomarkers

Results

Patient Characteristics

- Patient characteristics are shown in Table: Select Baseline Characteristics.

Select Baseline Characteristics[7a]

Baseline Characteristic	Group A (n=45)	Group B (n=50)[b]	*P*-value
Median age, years (IQR)	68.0 (59.0-73.0)	67.5 (60.3-71.0)	0.785
ECOG performance status 0-1, n (%)	41 (91)	48 (96)	0.418
Castration resistance within 12 months of ADT start, n (%)	41 (91)	42 (84)	0.364
<36 months from start of ADT to enrollment, n (%)	38 (84)	42 (84)	1.000
Prior docetaxel for mCSPC, n (%)	13 (29)	12 (24)	0.645
Prior docetaxel for mCRPC, n (%)	12 (27)	14 (28)	1.000
Bone metastases, n (%)	36 (80)	44 (88)	0.399
Lung metastases, n (%)	11 (24)	12 (24)	1.000
Liver metastases, n (%)	5 (11)	12 (24)	0.116
≥4 poor prognosis features,[c] n (%)	13 (29)	18 (36)	0.516

Abbreviations: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; ARPI, androgen receptor pathway inhibitor; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; LDH, lactose dehydrogenase; mCRPC, metastatic castration-resistant prostate cancer; mCSPC, metastatic castration-sensitive prostate cancer; ULN, upper limit of normal.
[a]Patients in group A received cabazitaxel. Patients in Group B received ARPI therapy with either ZYTIGA plus prednisone or enzalutamide daily.
[b]There were 27 patients who received ZYTIGA plus prednisone and 23 patients who received enzalutamide in group B.
[c]Patients were eligible for the trial if they had liver metastases, developed CRPC within 12 months of ADT start for metastatic disease, or ≥4 of the following 6 poor prognosis features: LDH>ULN, ECOG performance status 2, visceral metastatic disease, serum albumin ≤4 g/dL, ALP>ULN, or <36 months from start of initial ADT to study enrollment.

Efficacy

- Efficacy results for both treatment groups are reported in Table: Efficacy of First-Line Cabazitaxel vs ARPI Therapy in ARPI-Naïve Patients with Poor-Prognosis mCRPC.
- Median treatment duration for first-line therapy was 6.6 months and 5.5 months for group A and group B, respectively.
- No differences were observed for the following secondary endpoints: median OS (37.0 vs 15.5 months; HR, 0.58; *P*=0.073), time to progression (5.3 vs 2.8 months; HR, 0.87; *P*=0.52), time to PSA progression (6.6 vs 5.0 months; HR, 1.01; *P*=0.98), or PFS (5.3 vs 2.8 months; HR, 0.87; *P*=0.52) on first-line treatment.[11]

- Eighty-five patients stopped first-line therapy before data cut-off, of which 58 (68%) were eligible for crossover. Twenty-five (56%) of 45 patients in the cabazitaxel group and 30 (60%) of 50 patients in the ARPI group crossed over to receive the opposite treatment.
    - CBR for second-line ARPI and second-line cabazitaxel were 54% and 63%, respectively (*P*=0.58).
    - No differences were observed in PSA response, radiographic response, or stable disease for second-line ARPI and cabazitaxel.

Efficacy of First-Line Cabazitaxel vs ARPI Therapy in ARPI-Naïve Patients with Poor-Prognosis mCRPC[7a]

Endpoint, n (%)	Group A (n=45)[b]	Group B (n=50)[c]	*P*-value
CBR	35/44 (80%)	31/50 (62%)	0.039
PSA response ≥50%	25/44 (57%)	27/50 (54%)	0.84
Radiographic response	5/23 (22%)	5/24 (21%)	1.00
Stable disease ≥12 weeks	33/44 (75%)	28/50 (56%)	0.083

Abbreviations: ARPI, androgen receptor pathway inhibitor; CBR, clinical benefit rate; OS, overall survival; PSA, prostate-specific antigen.
[a]Patients in group A received cabazitaxel. Patients in group B received ARPI therapy with either ZYTIGA plus prednisone or enzalutamide.
[b]One patient never started treatment (required anticancer therapy not specified in the protocol) and was excluded due to missing data for all 3 constituents of the endpoint.
[c]There were 27 patients who received ZYTIGA plus prednisone and 23 patients who received enzalutamide in group B.

Safety

- Treatment-related grade ≥3 AEs of interest were reported in 50% of patients receiving cabazitaxel and 10% receiving an ARPI.
    - The most common first-line treatment-related grade ≥3 AEs were neutropenia (32% vs 0%), diarrhea (9% vs 0%), infection (9% vs 0%), and fatigue (7% vs 5%) for the cabazitaxel vs ARPI groups, respectively.
- The most common reasons for treatment discontinuation were disease progression (84% and 88% in the cabazitaxel and ARPI groups, respectively) and treatment-related AEs (11% and 0% in the cabazitaxel and ARPI groups, respectively).
- Dose reductions were required for 24% and 6% of patients receiving first-line cabazitaxel and an ARPI, respectively (*P*=0.018).
- Serious AEs during first- and second-line therapy were reported in 16% and 20% of patients receiving cabazitaxel and 0% of patients receiving an ARPI.

Observational Studies

Romero-Laorden et al (2020)[8] evaluated radiographic and clinical PFS, and OS in 95 of 419 patients in the PROREPAIR-B study (NCT03075735) who met CARD trial eligibility and received either an AR signaling inhibitor (n=35; either ZYTIGA or enzalutamide) or cabazitaxel (n=60), including 14 gHRR carriers. Radiographic PFS was improved in patients who received cabazitaxel compared to AR signaling inhibitors (median 6 months vs 3.7 months, respectively; *P*=0.03), as was clinical PFS (median 4.4 months vs 3.4 months, respectively; *P*=0.01), and PSA50 responses (39% vs 17%, respectively; *P*=0.027). No difference in OS was observed. gHRR carriers had a worse prognosis than non-carriers, and cabazitaxel was not superior to AR signaling inhibitors for radiographic and clinical PFS and OS. No safety data were reported.

Puente et al (2019)[9] described the efficacy and safety of second-line treatments, including ZYTIGA plus prednisone and cabazitaxel plus prednisone, administered after first-line docetaxel in patients with mCRPC (N=150).

Study Design/Methods

- Prospective, multicenter, observational study (CAPRO Study) including 10 consecutive patients with mCRPC at each site who had progression after first-line, docetaxel-based chemotherapy with or without other agents; and were administered a second-line treatment for mCRPC according to routine clinical practice.
- **Primary endpoint:** describe patterns of second-line treatments of patients with mCRPC after docetaxel
- **Secondary endpoints:** identify factors associated with treatment patterns and to compare efficacy and safety of the most common treatments

Results

Patient Characteristics

- A total 150 patients were recruited into the study.
  - All patients received docetaxel monotherapy (median 6 cycles) and androgen-deprivation therapy (ADT; 18 [12%] patients had ≥3 hormonal manipulations).
  - Sixty-three (42%) patients progressed during first-line treatment, 31 (20.7%) ≤3 months after finalizing first-line treatment, and 56 (37.3%) >3 months of finalizing first-line treatment.
- As second-line treatment, 100 patients received ZYTIGA plus prednisone and 44 patients received cabazitaxel plus prednisone; 6 patients received other treatments not discussed further.
- Demographic and clinical characteristics are noted in Table: Demographic and Clinical Characteristics.

Demographic and Clinical Characteristics[9]

Characteristic	Second-line therapy		
	ZYTIGA plus Prednisone (n=100)	Cabazitaxel plus Prednisone (n=44)	Total[a] (N=150)
Median age, years (range)	73.9 (50.9-89.6)	69.7 (51.4-84.4)	72.6 (49-89.6)
PSA	n=99	n=43	n=147
Median, ng/mL (range)	42.8 (1.2-3222)	74.6 (0.9-3846)	60 (0.9-3846)
Gleason score	n=92	n=41	n=139
Median (range)	7 (4-10)	8 (6-10)	7 (4-10)
≤6, n (%)	24 (26.1)	2 (4.9)	27 (19.7)
7, n (%)	30 (32.6)	17 (41.5)	47 (34.3)
≥8, n (%)	38 (41.3)	22 (53.7)	63 (46)
ECOG performance status	n=79	n=40	n=122
0	22 (27.8)	7 (17.5)	31 (25.4)
1	46 (58.2)	24 (60.9)	70 (57.4)
2	10 (12.7)	9 (22.5)	20 (16.4)
3 or 4	1 (1.3)	0 (0)	1 (0.8)
Disease location, n (%)			
Bone metastases	76 (76)	40 (90.9)	119 (79.9)
Visceral metastases	24 (24)	9 (20.5)	35 (23.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.
[a]Patients receiving treatments other than ZYTIGA plus prednisone or cabazitaxel plus prednisone are not presented, but included in the total sample. Therefore, the total sample is not only comprised of the pool of ZYTIGA plus prednisone and cabazitaxel plus prednisone groups. Median age total n=149.

Efficacy

- Treatment with ZYTIGA plus prednisone resulted in a 43% reduction in the risk of clinical/radiographic progression compared to cabazitaxel plus prednisone (median 8.7 vs 6.4 months; HR, 0.565; 95% CI, 0.377-0.848; *P*=0.005).

- The median OS was increased for patients treated with ZYTIGA plus prednisone (not reached) compared to cabazitaxel plus prednisone (20.3 months) (HR, 0.4; 95% CI, 0.21-0.76; *P*=0.004).
- There was no statistically significant difference in the median biochemical PFS between both treatment groups (ZYTIGA plus prednisone: 9.2 months vs cabazitaxel plus prednisone: 9.9 months; HR, 0.78; 95% CI, 0.49-1.24; *P*=0.290).
- A PSA response was observed in 43 of 91 evaluable patients treated with ZYTIGA plus prednisone (47.3%; 95% CI, 37-57.5%) and in 10 of 31 evaluable patients treated with cabazitaxel plus prednisone (32.3%; 95% CI, 15.8-48.7%), a difference that was not statistically significant (relative risk, 1.5; 95% CI, 0.8-2.6; *P*=0.146).

Safety

- The most frequent (≥10%) AEs reported during treatment are described in Table: Most Frequent (≥10%) AEs Reported During Treatment. A total of 302 of 357 (84.6%) and 112 of 210 (53.3%) AEs were unrelated to drug treatment in the ZYTIGA plus prednisone and cabazitaxel plus prednisone groups, respectively.

Most Frequent (≥10%) AEs Reported During Treatment[9]

AE, n (%)	ZYTIGA plus Prednisone (n=100)				Cabazitaxel plus Prednisone (n=44)			
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total
Asthenia	16 (16)	14 (14)	1 (1)	31 (31)	14 (31.8)	8 (18.2)	2 (4.5)	24 (54.5)
Pain	14 (14)	11 (11)	3 (3)	28 (28)	3 (6.8)	3 (6.8)	3 (6.8)	9 (20.5)
Anemia	7 (7)	7 (7)	1 (1)	15 (15)	6 (13.6)	3 (6.8)	1 (2.3)	10 (22.7)
Edema	13 (13)	2 (2)	0 (0)	15 (15)	3 (6.8)	1 (2.3)	2 (4.5)	6 (13.6)
Vomiting	7 (7)	0 (0)	2 (2)	9 (9)	4 (9.1)	1 (2.3)	0 (0)	5 (11.4)
Diarrhea	6 (6)	2 (2)	0 (0)	8 (8)	7 (15.9)	5 (11.4)	2 (4.5)	14 (31.8)
Anorexia	6 (6)	1 (1)	0 (0)	7 (7)	5 (11.4)	3 (6.8)	1 (2.3)	9 (20.5)
UTI	1 (1)	5 (5)	1 (1)	7 (7)	1 (2.3)	3 (6.8)	2 (4.5)	6 (13.6)
Abbreviations: AE, adverse event; UTI, urinary tract infection.								

Prospectively Maintained Database

Schmidt et al (2020)[10] explored the efficacy of treatments administered after docetaxel and ADT in 93 patients with mCRPC, including ZYTIGA plus prednisone and cabazitaxel plus prednisone. Patients treated with docetaxel for hormone-sensitive metastatic disease were identified from a prospectively maintained multisite database of Australian patients treated in community and academic settings. Median age was 65 years (range, 43-85 years). A total of 58% of patients had a Gleason score ≥8, the median PSA at diagnosis was 53 ng/mL (range, 0.67-7086 ng/mL), and 65% of patients had de novo metastatic disease. Median time to mCRPC was 14.8 months (range, 1.3-56.9 months), and the median time to treatment after docetaxel was 16.3 months (range, 2.1-57.2 months). Most patients (91%) received ≥1 additional treatment for mCRPC; outcomes for the patients who received ZYTIGA plus prednisone and cabazitaxel plus prednisone are described in Table: mCRPC Outcomes.

mCRPC Outcomes[10]

Treatment	ZYTIGA plus Prednisone (n=23)	Cabazitaxel plus Prednisone (n=7)
First line duration, months (95% CI)	7.2 (5.1-9.3)	6 (0-12)
Historical pre-docetaxel first line duration, months	13.8	7.2
Historical post-docetaxel first line duration, months	8	2.8
PSA response >50%, n/N (%)	10/19 (53%)	3/7 (43%)
Historical pre-docetaxel PSA response >50%, %	62	60
Historical post-docetaxel PSA response >50%, %	29	39

Patients receiving second line therapy, n/N (%)	9/13 (69)	4/4 (100)
First line start to second line start, months (95% CI)	6.9 (4.2-9.5)	7.7 (0.2-15.3)
Abbreviations: CI, confidence interval; mCRPC, metastatic castration-resistant prostate cancer; PSA, prostate-specific antigen.		

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) was conducted on 01 June 2023. Summarized in this response are relevant data limited to prospective studies.

REFERENCES

1. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus abiraterone or enzalutamide in metastatic prostate cancer. *N Engl J Med*. 2019;381(26):2506-2518.
2. Fizazi K, Kramer G, Eymard JC, et al. Quality of life in patients with metastatic prostate cancer following treatment with cabazitaxel versus abiraterone or enzalutamide (CARD): an analysis of a randomised, multicentre, open-label, phase 4 study. *Lancet Oncol*. 2020;21(11):1513-1525.
3. Tombal BF, Castellano D, Kramer G, et al. CARD: overall survival (OS) analysis of patients with metastatic castration-resistant prostate cancer (mCRPC) receiving cabazitaxel versus abiraterone or enzalutamide [abstract]. *J Clin Oncol*. 2020;38(suppl):Abstract 5569.
4. de Wit R, Wulfing C, Castellano D, et al. Baseline neutrophil-lymphocyte ratio as a predictive and prognostic biomarker in patients with metastatic castration-resistant prostate cancer treated with cabazitaxel vs abiraterone or enzalutamide in the CARD study. *ESMO Open*. 2021;6(5):100241.
5. Sternberg CN, Castellano D, de Bono J, et al. Efficacy and safety of cabazitaxel versus abiraterone or enzalutamide in older patients with metastatic castration-resistant prostate cancer in the CARD study. *Eur Urol*. 2021;80(4):497-506.
6. van der Zande K, van der Noort V, Busard M, et al. First results from a randomized phase II study of cabazitaxel (CBZ) versus an androgen receptor targeted agent (ARTA) in patients with poor-prognosis castration-resistant prostate cancer (mCRPC) [abstract]. *J Clin Oncol*. 2021;39(suppl 15):Abstract 5059.
7. Annala M, Fu S, Bacon JVW, et al. Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. *Ann Oncol*. 2021;32(7):896-905.
8. Romero-Laorden N, Lozano R, Perez CL, et al. Cabazitaxel versus enzalutamide/abiraterone in CARD eligible mCRPC patients with or without germline HRR defects [abstract]. *J Clin Oncol*. 2020;38(suppl):Abstract 5554.
9. Puente J, González-del-Alba A, Sala-Gonzalez N, et al. Efficacy and safety of abiraterone acetate plus prednisone vs. cabazitaxel as a subsequent treatment after first-line docetaxel in metastatic castration-resistant prostate cancer: results from a prospective observational study (CAPRO). *BMC Cancer*. 2019;19(766):1-10.
10. Schmidt AL, Anton A, Wong SS, et al. Treatment outcomes for metastatic castrate-resistant prostate cancer (mCRPC) patients (pts) following docetaxel (D) for hormone sensitive disease [abstract]. *J Clin Oncol*. 2020;38(6 suppl):Abstract 78.
11. Annala M, Fu S, Bacon JVW, et al. Supplement to: Cabazitaxel versus abiraterone or enzalutamide in poor prognosis metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase II trial. *Ann Oncol*. 2021;32(7):896-905.