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Safety of cabazitaxel plus prednisone in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: cohort compassionate-use programme

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Introduction

- Cabazitaxel is a next generation taxane developed to overcome docetaxel resistance that frequently develops in patients with metastatic castration-resistant prostate cancer (mCRPC).[1]
- In the Phase III TROPIC trial (NCT00417079), cabazitaxel plus prednisone significantly improved overall survival compared with mitoxantrone plus prednisone in patients with mCRPC whose disease had progressed during or after prior docetaxel treatment (hazard ratio 0.70; $P < 0.0001$).[2]
- Based on these results, cabazitaxel in combination with prednisone is approved for the treatment of patients with mCRPC who have previously been treated with a docetaxel-containing regimen, providing a much-needed second-line chemotherapy option for this challenging patient group.[3,4]

Objectives

- The survival benefit observed in the TROPIC trial supported the initiation of compassionate use (CUP) and early access programmes (NCT01254279) to provide access to cabazitaxel ahead of approval and assess the safety and tolerability of cabazitaxel in the real-world setting.
- Here, we present the final analysis of the CUP.

Methods

- Patients were enrolled in the CUP across 58 centres in Europe, Asia and Latin America (Figure 1).
- Eligible patients received cabazitaxel 25 mg/m^2 intravenously every 3 weeks in combination with prednisone 10 mg oral, daily, until disease progression, death, unacceptable toxicity or physician's decision.
  - In some countries, commercial availability also required discontinuation.
- Patients were followed for ≥ 30 days after last dose.
- Granulocyte colony-stimulating factor (G-CSF) was recommended per the American Society of Clinical Oncology (ASCO) guidelines[5] in patients with factors predisposing to neutropenic complications and was administered per the physician's decision.

Results

Patient characteristics

- In total, 451 patients were enrolled across 12 countries (58 sites) worldwide (Figure 1).
- The median age of patients was 68 years (range 43–84), most patients (90.0%) had Eastern Cooperative Oncology Group performance status ≤ 1 and 59.9% had ≥ 2 metastatic sites (Table 1).
- The median time from last docetaxel dose to first cabazitaxel plus prednisone dose was 4.4 months and the median cumulative dose of the last docetaxel administration was 675 mg/m^2 (Table 1).
- Of the 445 patients with progression dates available at inclusion, 108 patients (24.3%) progressed during last-line docetaxel (Table 1).

Figure 1. *Enrolment per country (N = 451)*

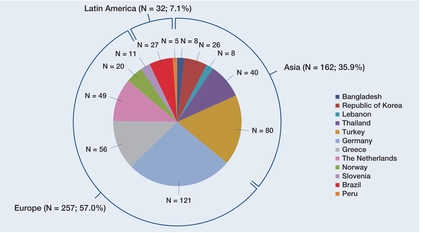


Table 1. *Baseline patient characteristics*

	Total (N = 451)
Age, years, median (range)	68.0 (43–84)
ECOG performance status, n (%)	N = 450
0	174 (38.7)
1	231 (51.3)
2	45 (10.0)
Missing	1
	N = 413
Time since initial diagnosis, months, median (range)	54.7 (9.1–229.9)
Missing	38
	N = 438
Cumulative dose of last docetaxel administration, mg/m², median (range)	675 (75–5145)
Missing	13
Cumulative dose of last docetaxel administration by class, n (%)	N = 438
< 225 mg/m²	12 (2.7)
225–450 mg/m²	81 (18.5)
450–675 mg/m²	124 (28.3)
675–900 mg/m²	94 (21.5)
≥ 900 mg/m²	127 (29.0)
Missing	13
	N = 451
Number of previous docetaxel lines, n, median (range)	1 (1–5)
Time since last docetaxel treatment to first cabazitaxel dose, months, median (range)	N = 446 4.4 (0.5–53.6)
Missing	5
Patients progressing during and after last docetaxel dose, n (%)	N = 445
During last docetaxel dose	108 (24.3)
< 3 months since last docetaxel dose	165 (37.1)
3–6 months since last docetaxel dose	62 (13.9)
≥ 6 months since last docetaxel dose	110 (24.7)
Missing	6
Type of progression with prior docetaxel treatment, n (%)	N = 451
Clinical progression	128 (28.4)
Increased PSA	400 (88.7)
Bone scan	144 (31.9)
Measurable lesions	88 (19.5)
Number of metastatic sites, n (%)	N = 451
No metastatic site	2 (0.4)
1 metastatic site	179 (39.7)
≥ 2 metastatic sites	270 (59.9)
Main metastatic sites, n (%)	N = 451
Bone	411 (91.1)
Regional lymph nodes	136 (30.2)
Distant lymph nodes	119 (26.4)
Lungs	49 (10.9)
Pelvis	49 (10.9)
Liver	45 (10.0)

ECOG = Eastern Cooperative Oncology Group; PSA = prostate specific-antigen.

Treatment characteristics

- The median number of cabazitaxel plus prednisone cycles received by a patient was five (range 1–34) (Table 2).
- During the study, 248 patients (55.0%) received G-CSF at ≥ 1 cycle, with 214 patients (47.5%) receiving it at Cycle 1 (Table 2).

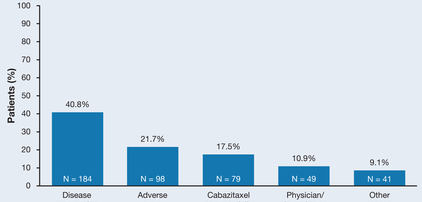
Table 2. *Treatment characteristics*

	N = 451
Number of cabazitaxel cycles per patient, n, median (range)	
Total population (N = 451)	5 (1–34)
In patients receiving G-CSF for at least one cycle (N = 248)	6 (1–34)
In patients who did not receive any G-CSF (N = 203)	5 (1–21)
Duration of dosing, weeks, median (range)	15.9 (3.0–104.1)
Cumulative dose, mg/m², median (range)	124.4 (19.2–817.1)
Relative dose intensity, %, median (range)	99.2 (80.1–106.5)
Patients who received G-CSF, n (%)	
In Cycle 1	**214 (47.5)**
Therapeutic	29 (6.4)
Prophylactic	137 (30.4)
Both	48 (10.6)
At least one cycle*	**248 (55.0)**
Therapeutic	40 (8.9)
Prophylactic	211 (46.8)
Both	72 (16.0)

* A patient can be considered in more than one category.
G-CSF = granulocyte colony-stimulating factor.

- Treatment was discontinued due to progression in 40.8% and adverse events (AEs) in 21.7% (Figure 2).

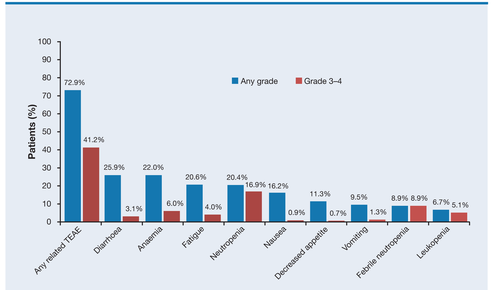
Figure 2. *Reasons for treatment discontinuation (N = 451)*



Safety

- In patients with prior docetaxel exposure, cabazitaxel had a predictable, manageable safety profile comparable to that observed in the TROPIC trial.[2]
- Any-grade treatment-emergent AEs (TEAEs) occurred in 83.4% of patients.
  - Grade 3–4 TEAEs occurred in 51.0% of patients.
- Any-grade TEAEs considered possibly related to cabazitaxel plus prednisone treatment occurred in 72.9% of patients (Figure 3).
  - Grade 3–4 TEAEs possibly related to cabazitaxel occurred in 41.2% of patients.
  - The most frequent Grade 3–4 TEAEs possibly related to cabazitaxel were neutropenia (16.9%), febrile neutropenia (8.9%), anaemia (6.0%), leukopenia (5.1%) and fatigue (4.0%).

Figure 3. *Most frequent all-grade (reported in > 6% of patients) and Grade 3–4 treatment-emergent adverse events (TEAEs) possibly related to cabazitaxel treatment (N = 451)**



* Clinically significant haematological TEAEs are reported.

- In patients with prophylactic G-CSF use (without therapeutic G-CSF use) at Cycle 1 (N = 137, 30.4%), Grade 3–4 neutropenia occurred in 2.2% of patients and febrile neutropenia occurred in 0.7%.
  - In patients without G-CSF use at Cycle 1 (N = 237; 52.5%), the respective rates of Grade 3–4 neutropenia and febrile neutropenia were 6.3% and 1.7%.

Table 3. *Most frequent all-grade (reported in > 6% of patients) and Grade 3–4 treatment-emergent adverse events (TEAEs), classified by decreasing order of all-grade events in men ≥ 75 years of age*

Adverse event*, %	Total (N = 451)		< 70 years of age (N = 256)		70–74 years of age (N = 114)		≥ 75 years of age (N = 81)	
	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades
Any adverse event	51.0	83.4	48.4	82.8	52.6	88.6	56.8	77.8
Anaemia	6.7	26.6	6.3	25.0	6.1	27.2	8.6	30.9
Diarrhoea	3.3	28.6	2.7	26.2	2.6	32.5	6.2	30.9
Neutropenia	17.1	20.6	15.2	18.0	14.0	18.4	27.2	32.1
Fatigue	4.7	25.7	3.9	27.7	3.5	22.8	8.6	23.5
Decreased appetite	0.7	13.3	0.8	11.7	0.0	11.4	1.2	21.0
Nausea	0.9	18	0.8	21.5	0.9	13.2	1.2	13.6
Increased blood creatinine	0.2	7.1	0.0	5.1	0.9	7.9	0.0	12.3
Febrile neutropenia	8.9	8.9	7.4	7.4	9.6	9.6	12.3	12.3
Constipation	0.0	6.7	0.0	6.3	0.0	5.3	0.0	9.9
Peripheral oedema	0.2	5.5	0.4	3.5	0.0	7.0	0.0	9.9
Leukopenia	5.1	6.7	4.3	5.5	6.1	7.9	6.2	8.6
Pyrexia	0.7	5.5	0.0	4.7	0.0	5.3	3.7	8.6
Thrombocytopenia	1.3	6.2	2.0	5.9	0.9	5.3	0.0	8.6
Vomiting	1.6	10.9	0.0	11.7	2.6	10.5	4.9	8.6
Asthenia	0.4	4.2	0.0	2.3	0.0	6.1	2.5	7.4
Arthralgia	0.7	5.1	1.2	5.1	0.0	4.4	0.0	6.2
Dizziness	0.0	2.4	0.0	1.6	0.0	1.8	0.0	6.2
Increased aspartate aminotransferase	0.0	5.1	0.0	4.7	0.0	5.3	0.0	6.2

* Clinically significant haematological TEAEs are reported.

- The rate of some TEAEs (of any causality) had a trend to increase with patient age (Table 3).
  - Rates of haematological TEAEs, including anaemia, neutropenia and febrile neutropenia, appeared higher in patients ≥ 75 years of age.
  - Rates of some non-haematological TEAEs, including diarrhoea, decreased appetite and increased blood creatinine levels, appeared to be increased in the older patient groups.
- Cabazitaxel dose reductions occurred in 17.3% of patients and dose delays occurred in 36.4% of patients.
  - Dose reductions and delays were required due to TEAEs possibly related to cabazitaxel in 15.3% and 15.7% of patients, respectively.
- Cabazitaxel was discontinued due to TEAEs in 21.7% of patients (N = 98) (Figure 2).
  - A range of TEAEs led to the discontinuation of cabazitaxel.
  - The most common TEAEs leading to discontinuation were febrile neutropenia (N = 10; 2.2%), fatigue (N = 7; 1.6%), neutropenia (N = 6; 1.3%) and acute renal failure (N = 5; 1.1%).
- There were 30 deaths (6.7%); during the on-treatment period (which extended from first cabazitaxel dose to 30 days after last dose), deaths occurred due to disease progression, AE or other reason; during the follow-up period, deaths occurred due to possibly related AEs.

Discussion and conclusions

- Data from this worldwide CUP showed that in patients with prior docetaxel exposure, cabazitaxel plus prednisone treatment had a predictable and manageable safety profile comparable to that observed in the TROPIC trial.[2]
- It is important to closely monitor haematological AEs in patients treated with cabazitaxel.
- Prophylactic use of G-CSF has been shown to improve tolerability to cabazitaxel particularly when used at Cycle 1 and in men aged ≥ 75 years of age.[6]
- The lower rate of neutropenic complications in patients with prophylactic G-CSF use at Cycle 1 supports the use of G-CSF to prevent haematological AEs in patients at risk of developing neutropenia.

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