IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. A11-24

# Cabazitaxel –

# Benefit assessment according to § 35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Cabazitaxel – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 12.01.2012).. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

# Publishing details

**Publisher:**
Institute for Quality and Efficiency in Health Care

**Topic:**
Cabazitaxel – Benefit assessment according to § 35a Social Code Book V

**Contracting agency:**
Federal Joint Committee

**Commission awarded on:**
17.10.2011

**Internal Commission No.:**
A11-24

**Address of publisher:**
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IQWiG thanks the external expert for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect the advisor's opinion.

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**Keywords:** cabazitaxel, prostate carcinoma, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| AM-NutzenV | Arzneimittel-Nutzenbewertungsverordnung<br>(Regulation for Early Benefit Assessment of New Pharmaceuticals) |
| BSC | best supportive care |
| CTCAE | Common Terminology Criteria for Adverse Events |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen<br>(Institute for Quality and Efficiency in Health Care) |
| mHRPC | metastatic hormone-resistant prostate cancer |
| PPI | Present Pain Intensity |
| SGB | Sozialgesetzbuch (Social Code Book) |

# 2. Executive summary

## 2.1 Executive summary of the benefit assessment

### Background

On 17.10.2011, in accordance with § 35a SGB (Social Code Book) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug cabazitaxel. The assessment was based on a dossier compiled by the pharmaceutical company.

### Research question

The present benefit assessment relates to the treatment of metastatic hormone-refractory prostate cancer (mHRPC) in patients previously treated with a docetaxel-containing treatment regimen and was carried out separately for 2 patient populations.

### *Best supportive care* population

The *best supportive care* population consists of patients for whom further treatment with docetaxel is no longer an option.

The appropriate comparator therapy (ACT) for this patient population is palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone, as well as *best supportive care* (BSC) (e.g. adequate pain therapy). BSC means the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life.

The first objective of the present report is therefore to assess the added benefit of cabazitaxel in combination with prednisone or prednisolone compared to dexamethasone, prednisone, prednisolone or methylprednisolone as well as BSC in patients with metastatic, hormone-refractory prostate cancer, for whom further treatment with docetaxel is no longer an option.

This benefit assessment was able to take account of studies that compared cabazitaxel together with prednisone or prednisolone in combination with BSC or without BSC versus treatment with the ACT. One study could be included in the assessment. This study compared cabazitaxel in combination with prednisone and BSC (cabazitaxel/prednisone/BSC) with a treatment consisting of mitoxantrone in combination with prednisone and BSC (mitoxantrone/prednisone/BSC). Here, mitoxantrone was classed as a component of BSC. The assessment was undertaken in respect of patient-relevant outcomes.

### Docetaxel retreatment population

The docetaxel retreatment population comprises patients for whom further treatment with docetaxel is still an option.

The ACT for this patient population is docetaxel in combination with prednisone or prednisolone.

A further objective of the present report is therefore to assess the added benefit of cabazitaxel in combination with prednisone or prednisolone compared to docetaxel in combination with prednisone or prednisolone in patients with metastatic, hormone-refractory prostate cancer, for whom further treatment with docetaxel is still an option.

**Results**

One relevant study was available for the benefit assessment (TROPIC). This was an open-label, randomized and active-controlled study. The study medication consisted, in one treatment arm, of cabazitaxel in combination with prednisone or prednisolone and, in the other arm, of mitoxantrone in combination with prednisone or prednisolone. In addition, patients in both treatment arms received supportive therapy in the sense of *best supportive care,* i.e. the study compared cabazitaxel/prednisone/BSC versus mitoxantrone/prednisone/BSC. In the Institute's view, the study arm in which patients received mitoxantrone/prednisone/BSC corresponded to the ACT of the *best supportive care* population, because mitoxantrone can be construed as a component of *best supportive care.* On the basis of this study (direct comparison) data on the *best supportive care* population were therefore available. No data were submitted for the docetaxel retreatment population.

The following conclusions were reached for the 2 named populations:

***Best supportive care* population**

The risk of bias of the study included in the benefit assessment was low, both at the study level and also for the individual outcomes, with 2 exceptions. At the outcome level, because of the open design of the study, there was a high risk of bias for the outcome "overall survival" (analysis including all patients who started further anticancer therapy after scheduled or premature discontinuation of the study treatment) as well as for the subjective outcome "change in PPI (Present Pain Intensity) score". From the evidence available (one study), unless outcome-specific aspects weakened the informative value, at most "indications" - e.g. of an added benefit – could be inferred from the data. Despite the above-mentioned high risk of bias, the informative value for "overall survival" was not however classified as being weakened, because after inspection of the actual data on further anticancer therapies used after the ending of the study medication, an overestimation of the effect of cabazitaxel appears unlikely.

***Mortality***

Over the entire observation period, treatment with cabazitaxel/prednisone/BSC produced a statistically significant prolongation of overall survival in the total population in comparison with treatment with mitoxantrone/prednisone/BSC. In this context, there was an indication that the results differ depending on age ($< / \geq 65$ years) (interaction test $p < 0.2$). The result was statistically significant in the subgroup of patients $\geq 65$ years, but not in the subgroup $< 65$ years. Therefore the certainty of results of the conclusion regarding overall survival in the subgroup of patients $< 65$ years is downgraded.

Overall, there is an indication of added benefit of cabazitaxel/prednisone/BSC for patients ≥ 65 years. On the other hand, there is only a hint of added benefit of cabazitaxel/prednisone/BSC in comparison with mitoxantrone/prednisone/BSC for patients < 65 years.

***Morbidity***

*Change in PPI score (pain)*

The differences in the proportion of patients with a change in PPI score (improved, stable, worsened) were not statistically significant under cabazitaxel/prednisone/BSC compared with mitoxantrone/prednisone/BSC. An added benefit in terms of the outcome "change in PPI score (pain)" is not proven.

***Health-related quality of life***

No data on health-related quality of life were available in the dossier of the pharmaceutical company. An added benefit regarding this outcome is not proven.

***Adverse events***

There was a statistically significant difference to the disadvantage of cabazitaxel/prednisone/BSC for the overall rate of all adverse events, for the overall rate of adverse events of the Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3, the overall rate of serious adverse events and the overall rate of discontinuations due to adverse events. Because of the marginal effect size, greater harm for the outcome "overall rate of adverse events" is not proven. For the remaining 3 outcomes, there is an indication of greater harm of cabazitaxel/prednisone/BSC in comparison with mitoxantrone/ prednisone/BSC.

**Docetaxel retreatment population**

No data were submitted by the pharmaceutical company for the docetaxel retreatment population. An added benefit of cabazitaxel/prednisone in comparison with docetaxel/prednisone is not proven.

**Probability and extent of the added benefit, patient groups with therapeutically important added benefits**

Based on the results presented and taking outcome categories and effect sizes into account, the extent and probability of the added benefit of the drug cabazitaxel are assessed as follows:

- for patients ≥ 65 years, for whom further treatment with docetaxel is no longer an option (*best supportive care* population), there is an indication of a considerable added benefit of cabazitaxel/prednisone/BSC over mitoxantrone/prednisone/BSC.
- for patients < 65 years, for whom further treatment with docetaxel is no longer an option (*best supportive care* population), there is a hint of an added benefit (extent "not

quantifiable", at most "considerable") of cabazitaxel/prednisone/BSC over mitoxantrone/prednisone/BSC.

These overall conclusions concerning the extent of added benefit are based on the aggregation of the extents of added benefit derived at the outcome level.

For patients for whom further treatment with docetaxel is still an option (docetaxel retreatment population), an added benefit of cabazitaxel in combination with prednisone or prednisolone over docetaxel in combination with prednisone or prednisolone is not proven.

The procedure for deriving an overall conclusion of the added benefit is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

## 2.2 Research question

The pharmaceutical company designated mitoxantrone in combination with prednisone or prednisolone as the appropriate comparator therapy (ACT) for the investigation of added benefit of cabazitaxel in patients with metastatic hormone-refractory prostate cancer previously treated with a docetaxel-based treatment regimen. The company thus deviated from the specification of the G-BA, who divided the therapeutic indication into 2 different populations and determined the suitable ACT for each of them.

The Institute undertook the benefit assessment using the ACTs specified by the G-BA. The individual populations and the ACT associated with each of them are shown in Table 1.

Table 1: Populations and appropriate comparator therapies

| **Characteristics of the population** | **Appropriate comparator therapy** |
|---|---|
| Patients with metastatic, hormone-refractory prostate cancer who show progression during or after docetaxel-containing chemotherapy and for whom further treatment with docetaxel is no longer an option.<br>Hereinafter called the "*best supportive care* population". | Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as *best supportive care* (BSC) (e.g. adequate pain therapy). BSC means the therapy that provides the patient with the best possible individually optimized supportive treatment to alleviate symptoms and improve the quality of life. |
| Patients with metastatic, hormone-refractory prostate cancer who show progression during or after docetaxel-containing chemotherapy, but in whom adequate docetaxel-containing chemotherapy is still, in principle, an option ("Rechallenge").<br>Hereinafter called the "docetaxel retreatment population". | Docetaxel in combination with prednisone or prednisolone |

The objective of this report is therefore to assess the added benefit of:

- cabazitaxel in combination with prednisone or prednisolone vs. dexamethasone, prednisone, prednisolone or methylprednisolone as well as BSC (as defined in Table 1) in patients of the *best supportive care* population and

- cabazitaxel in combination with prednisone or prednisolone vs. docetaxel in combination with prednisone or prednisolone in patients of the docetaxel retreatment population.

For the benefit assessment in the *best supportive care* population, studies that compared cabazitaxel in combination with prednisone or prednisolone with or without BSC versus treatment consisting of the ACT could be considered.

In the assessment of the *best supportive care* population, one randomized, active-controlled trial (TROPIC) could be included. In this trial, patients in the cabazitaxel/prednisone treatment arm as well as those in the mitoxantrone/prednisone treatment arm received a concomitant treatment rated as BSC. The trial thus compared the administration of cabazitaxel in combination with prednisone or prednisolone and BSC with a combination of mitoxantrone in combination with prednisone or prednisolone and BSC. In the Institute's view, the study arm in which patients received mitoxantrone/prednisone/BSC corresponded to the ACT of the *best supportive care* population, because mitoxantrone can be construed as a component of *best supportive care*. To make the comparison quite clear in the report, the treatment arms of this trial are named as follows in this assessment report: "cabazitaxel/prednisone/BSC" and "mitoxantrone/prednisone/BSC".

The assessment was carried out in relation to patient-relevant outcomes.

*Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.*

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following information:

- Studies of cabazitaxel in metastatic, hormone-refractory prostate cancer completed by the pharmaceutical company (no date for the study status was given in the dossier).
- Results of a bibliographical literature search and a search in trial registries for studies on cabazitaxel (up to 18.02.2011 and 15.03.2011 respectively, searches by the company).
- Own searches by the Institute for cabazitaxel in bibliographical databases and trial registries (search date 02.11.2011) to check the company's search results. In addition, a check of the contents of the company's information retrieval took place using the inclusion criteria specified by the Institute, which deviated markedly from those of the company in respect of the comparator therapy. The check produced no deviations from the study pool presented in the company's dossier.

The resulting study pool thus corresponded to that of the company. However, the relevant study was only used for one of the populations to be assessed (*best supportive care* population), which is explained in more detail in Section 2.3.1 below.

*Further information about the inclusion criteria for studies in the benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.*

### 2.3.1 Studies included

The assessment diverges substantially from the procedure of the company in respect of the division of the overall therapeutic indication into different populations. This is because when selecting the ACT, the company deviated from that specified by the G-BA (see Section 2.2). The dossier provides data only for part of the research questions. The submitted TROPIC study supplied data only for the *best supportive care* population; no data were available for the docetaxel retreatment population.

The study included in the benefit assessment is listed in the following table.

Table 2: Study pool – RCT with the drug to be assessed, direct comparison

| **Population**<br>Study | **Study category** | | |
|---|---|---|---|
| | **Pivotal study for approval of the drug to be assessed (yes/no)** | **Sponsored study[a] (yes/no)** | **Third-party study (yes/no)** |
| ***Best supportive care* population** | | | |
| EFC 6193 (TROPIC) | yes | yes | no |
| **Docetaxel retreatment population** | | | |
| – | No study submitted. | | |
| a: Study for which the company was sponsor, or in which the company was otherwise financially involved. | | | |

One randomized, controlled trial (TROPIC) with the drug to be assessed was submitted for the assessment of cabazitaxel in the *best supportive care* population.

No study was submitted for the assessment of cabazitaxel in the docetaxel retreatment population.

Section 2.6 contains a list of data sources named by the company for the study included in its assessment.

*Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.*

### 2.3.2 Study characteristics

Tables 3 and 4 describe the study for the benefit assessment. This study (TROPIC) was the pivotal study for the approval of cabazitaxel. The Institute concurs with the basic estimation of the company, that the TROPIC study can be used to draw conclusions about the *best supportive care* population. In Sections 2.7.1., 2.7.2.3.2, 2.7.2.4.1 and 2.7.2.4.3 of the full dossier assessment, it is explained why, despite some uncertainties, the Institute used this

study for the benefit assessment. These sections also explain why the Institute refers back to the data on the total study population and does not use – as encouraged by the company – the data of a post-hoc defined subgroup of "certainly docetaxel-refractory patients" (patients, who showed progression within 20 days from the last docetaxel dose).

In summary, the study is suitable for the benefit assessment on the *best supportive care* population; however it is not suitable for drawing conclusions about the docetaxel retreatment population.

Table 3: Characteristics of the included study – RCT for the direct comparison cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Study | Study design | Population | Interventions (number of randomized patients) | Duration of study | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| TROPIC | RCT, open-label, parallel, 2-arms | Patients with metastatic hormone-refractory prostate cancer and documented disease progression during the 6 months following previous hormone therapy and after docetaxel-containing treatment. | Cabazitaxel/prednisone/ BSC<br>(N = 378)<br><br>Mitoxantrone/ prednisone/BSC<br>(N = 377) | Screening phase of 28 days<br>Treatment: Every patient was treated until disease progression, death, inacceptable toxicity or for a maximum of 10 cycles (30 weeks).<br>Cycle length: 3 weeks<br>Follow-up: as soon as a patient progressed or started further anticancer therapy, follow-up visits were planned and carried out every 3 months for a maximum of 2 years. Patients who completed the full treatment also underwent 2 years of follow-up until the end of the study. | 146 centres in 26 countries (including the USA)<br>01/2007–09/2009 | Primary: overall survival<br>Secondary: change in PPI score (pain), adverse events |

a: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available endpoints for this benefit assessment.

BSC: best supportive care; RCT: randomized controlled trial

Table 4: Characteristics of the interventions – RCT for the direct comparison cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Study | Cabazitaxel/prednisone/BSC | Mitoxantrone/prednisone/BSC | Comedication in both arms of the study |
|---|---|---|---|
| TROPIC | 25 mg/m$^2$ cabazitaxel intravenously every 3 weeks and prednisone[a] 10 mg orally, daily | 12 mg/m$^2$ mitoxantrone given intravenously over 15–30 minutes every 3 weeks and prednisone[a] 10 mg orally, daily | Systemically administered antihistamine, corticosteroid or $H_2$-antagonists; optional and/or on demand analgesics, G-CSF, blood substitutes, blood transfusions, antiemetics and other drugs (e.g. bisphosphonates, antibiotics). |
| a: In countries where prednisone was not available, prednisolone could be given. To improve readability, reference to prednisolone is not made when naming the study arms.<br>BSC: best supportive care, G-CSF: granulocyte colony stimulating factor, RCT: randomised controlled trial | | | |

The TROPIC study is a randomized, active-controlled, open-label study in which patients, treating physicians and outcome assessors were not masked to treatment allocation. Patients with metastatic hormone-refractory prostate cancer and documented progressive disease during the 6 months after previous hormone therapy and docetaxel-containing treatment were enrolled. The study treatment was administered according to a treatment regimen that corresponded to the description in the respective Summary of Product Characteristics (Table 4, [1,2]). Each patient was treated in 21-day cycles until disease progression, death or inacceptable toxicity occurred, or for a maximum of 10 cycles (30 weeks). In addition to the study treatment, patients in both study arms were treated with the necessary concomitant and/or on-demand medication as part of the *best supportive care* (Table 4). In the Institute's view, the study arm in which patients received mitoxantrone/prednisone/BSC corresponded to the ACT of the *best supportive care* population, because mitoxantrone can be construed as a component of *best supportive care*. Of the total of 755 randomized patients, 377 were allocated to the mitoxantrone arm and 378 patients to the cabazitaxel arm. The primary outcome was overall survival. After the treatment phase of the study (i.e. following the development of progression, inacceptable toxicity, after a maximum of 10 cycles or when the patient started further anticancer therapy), patients were followed up for a maximum of 2 years or until study completion. Follow-up consisted of study visits every 3 months.

Table 5 shows the characteristics of patients in the study included in the assessment for the *best supportive care* population.

Table 5: Characteristics of the study population – RCT for the direct comparison cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| **Study** Group | **N**[a] | **Age (years) median (min-max)** | **Previous therapy [Dose of docetaxel given before start of study mg/m²] median (IQR)** | **Number of previous chemo-therapies n (%)** | **Number of patients with measurable tumour n (%)** | **Number of patients with progression during treatment and < 3 or 3 to < 6 months from last dose of docetaxel n (%)** |
|---|---|---|---|---|---|---|
| **TROPIC** | | | | | | |
| Cabazitaxel/ prednisone/ BSC | 378 | 68 (46–92) | 577 (408–761) | 1: 260 (69)<br>2: 94 (25)<br>≥ 3: 24 (6) | 201 (53) | During treatment and up to 3 months: 273 (72)<br>After 3 to < 6 months: 58 (15) |
| Mitoxantrone/ prednisone/ BSC | 377 | 67 (47–89) | 529 (381–787) | 1: 268 (71)<br>2: 79 (21)<br>≥ 3: 30 (8) | 204 (54) | During treatment and up to 3 months: 285 (76)<br>After 3 to 6 months: 50 (13) |

a: randomized patients
BSC: best supportive care, IQR: interquartile range, RCT: randomized controlled trial

At the start of the study there were no substantial deviations between the treatment groups in respect of age, level of administered dose of docetaxel, number of patients with measurable tumours and number of previous chemotherapy regimens. The frequency of progression during treatment, and up to 3 months and 3 to 6 months from the last docetaxel dose was also roughly the same in the two treatment groups. The median age of patients was 67 to 68 years.

The risk of bias at the study level is shown in Table 6.

Table 6: Risk of bias at the study level – RCT for the direct comparison cabazitaxel/ prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Study | Adequate randomization sequence generation | Group allocation concealment | Blinding | | Indications of selective outcome reporting | Other potential sources of bias | Risk of bias at the study level |
|---|---|---|---|---|---|---|---|
| | | | Patient | Treating persons | | | |
| TROPIC | yes | yes | no | no | no | no | low |
| BSC: best supportive care; RCT: randomized controlled trial | | | | | | | |

The risk of bias at the study level was rated for the study as low. This accords with the company's estimation.

*Further information about the study design and the study populations and the risk of bias at the study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 of the dossier and in Sections 2.7.2.2., 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.*

## 2.4 Results concerning added benefit

This assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - change in PPI score (pain)
- Health-related quality of life
  - no data available
- Adverse events
  - adverse events
  - adverse events of CTCAE Grade ≥ 3
  - serious adverse events
  - discontinuation due to adverse events

Regarding the choice of patient-relevant outcomes, the Institute deviated from the choice of the pharmaceutical company, which used additional outcomes in the dossier (Module 4) (for the reasons for the Institute's choice of outcomes, see Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows the data available for the particular outcomes in the study included in the assessment. Table 8 provides the risk of bias for these outcomes.

Table 7: Matrix of outcomes – RCT for the direct comparison cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Study | Overall survival | Change in PPI score (pain) | Health-related quality of life[a] | AEs | AEs of CTCAE Grade ≥ 3[a] | Serious AEs | Discontinuation due to AEs |
|---|---|---|---|---|---|---|---|
| TROPIC | yes | yes | -[b] | yes | yes | yes | yes |

a: Adverse events of CTCAE Grades 3 - 5.

b: Parameter was not recorded.

AE: adverse event ; BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, PPI: present pain intensity, RCT: randomized controlled trial

Table 8: Risk of bias at study and outcome level – RCT for the direct comparison cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Study | Study level | Overall survival | Change in PPI score (pain) | Health-related quality of life | AEs | AEs of CTCAE, Grade ≥ 3[c] | Serious AEs | Discontinuation due to AEs |
|---|---|---|---|---|---|---|---|---|
| TROPIC | low | high[a] | high | -[b] | low | low | low | low |

a: Because the analysis considered patients who, after scheduled or premature ending of the study treatment, started further anticancer therapy, with open-label study design (see Section 2.7.2.4.2 of the full dossier assessment)

b: Parameter was not recorded.

c: Adverse events of CTCAE Grades 3 –5.

AE: adverse event; BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, PPI: present pain intensity, RCT: randomized controlled trial

Except for health-related quality of life, for which no data had been recorded, the availability of data for the study can be presumed to be good.

In contrast to the company's estimation, the risk of bias for the outcome "overall survival" is classed as high. Inspection of the study data shows that patients who started further anticancer therapy after scheduled or premature ending of the study treatment, were included in the analysis of the outcome "overall survival". In the Institute's view, the open-label study design is another potential risk of bias for this outcome. However, this does not lead to a downgrading of the certainty of results of the conclusions regarding added benefit for this outcome, because after inspection of the actual data on these further anticancer therapies, an overestimation of the effect of cabazitaxel appears unlikely (see Section 2.7.2.4.2 of the full dossier assessment).

The risk of bias for the outcome "change in PPI score (pain)" is likewise rated as high, since this is a subjective outcome in an open-label study design and the data were analysed only for patients for whom a value was recorded at the start of the study and during treatment (88 and 86% of patients respectively). The pharmaceutical company did not estimate the risk of bias regarding this outcome. The outcomes "AEs", "AEs of CTCAE Grade ≥ 3", "serious AEs" and "discontinuation due to AEs" were assessed to have a low risk of bias. This concurs with the estimation of the company, which admittedly did not carry out an assessment at the outcome level, but for adverse events as a whole.

*Further information about choice of outcome and risk of bias at the outcome level can be found in Module 4, Sections 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.*

### 2.4.1 Results on the *best supportive care* population

Table 9 and Table 10 summarize the results of the benefit assessment for the comparison cabazitaxel/prednisone/BSC and mitoxantrone/prednisone/BSC in patients in the *best supportive care* population. Table 11 gives additional information about individual AEs. The data correspond to those submitted by the company and were, in part, supplemented by the Institute's own calculations where these were not reported in the dossier. In addition, information from Module 5 of the dossier were added.

Table 9: Mortality, morbidity and health-related quality of life – RCT for the direct comparison of cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| | **Cabazitaxel/ prednisone/BSC** | | **Mitoxantrone/ prednisone/BSC** | | **Cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC** | |
|---|---|---|---|---|---|---|
| **Mortality** | | | | | | |
| | **Total** | **Median [95% CI] months** | **Total N** | **Median [95% CI] months** | **Hazard ratio [95% CI][a]** | **p-value[b]** |
| Overall survival | 378 | 15.1 [14.1; 16.3] | 377 | 12,7 [11.6; 13.7] | 0,70 [0.59; 0.83][c] | < 0.001 |
| **Morbidity** | | | | | | |
| Change in PPI score (pain) | **Total N** | **Patients with event n (%)** | **Total N** | **Patients with event n (%)** | **Odds ratio [95% CI][h]** | **p-value[h]** |
| Improved[d] | 333[g] | 71 (21.3) | 324[g] | 59 (18.2) | 0,94 [0.70; 1.25] | 0.658 |
| Stable[e] | | 154 (46.2) | | 161 (49.7) | | |
| Worsened[f] | | 108 (32.4) | | 104 (32.1) | | |
| **Health-related quality of life** | No data available. | | | | | |

a: Cox regression stratified according to the variables ECOG performance status and disease measurability at the start of the study.

b: Stratified log rank test (see footnote a).

c: No conclusions on the basis of the overall effect because of an indication of a relevant effect modification by the characteristic “age” (see end of this section).

d: An improvement was assumed, if a patient’s worst PPI score during treatment was lower than his PPI score at baseline.

e: No change in PPI score during treatment. It remains unclear whether patients whose PPI score changed by one point were assigned to the category “unchanged”.

f: A worsening was assumed, if a patient’s PPI score during treatment increased more than 1 unit compared to baseline.

g: All patients for whom the PPI score was recorded at the start of the study and during treatment were included in the analysis.

h: Institute’s calculation: logistic regression (proportional odds model).

BSC: best supportive care, CI: confidence interval, ECOG: Eastern Cooperative Oncology Group, N: number of patients in the analysis, n: number of patients with event, PPI: present pain intensity

Table 10: Adverse events – RCT for the direct comparison of cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| | **Cabazitaxel/ prednisone/BSC** | | **Mitoxantrone/ prednisone/BSC** | | **Cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC** | |
|---|---|---|---|---|---|---|
| | **Total N** | **Patients with event n (%)** | **Total N** | **Patients with event n (%)** | **Relative risk [95% CI][a]** | **p-value[b]** |
| **Adverse events** | | | | | | |
| AEs | 371 | 355 (95.7) | 371 | 328 (88.4) | 1.08 [1.04; 1.13] | < 0.001 |
| AEs of CTCAE Grade ≥ 3[c] | 371 | 213 (57.4) | 371 | 146 (39.4) | 1.46 [1.25; 1.70] | < 0.001 |
| Serious AEs | 371 | 145 (39.1) | 371 | 77 (20.8) | 1.88 [1.49; 2.38] | < 0.001 |
| Discont. due to AEs | 371 | 68 (18.3) | 371 | 31 (8.4) | 2.19 [1.47; 3.27] | < 0.001 |

a: Institute's calculation.

b: Institute's calculation, unconditioned exact test (CSZ method according to [3]).

c: AEs of CTCAE Grades 3–5.

AE: adverse event, BSC: best supportive care, CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events, CI: confidence interval, N: number of patients in the analysis, n: number of patients with event

Table 11: Number (%) of patients with AEs of CTCAE Grades 1–5 and Grade ≥ 3 with a relative frequency ≥ 3 % in at least one treatment group for AEs of CTCAE Grade ≥ 3 – RCT for the direct comparison of cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| **Adverse events**[a] | **Cabazitaxel/prednisone/BSC N = 371** | | **Mitoxantrone/prednisone/BSC N = 371** | |
|---|---|---|---|---|
| | **All grades n (%)** | **Grade ≥ 3**[b] **n (%)** | **All grades n (%)** | **Grade ≥ 3**[b] **n (%)** |
| Neutropenia | 81 (21.8) | 79 (21.3) | 40 (10.8) | 26 (7.0) |
| Febrile neutropenia | 28 (7.5) | 28 (7.5) | 5 (1.3) | 5 (1.3) |
| Diarrhoea | 173 (46.6) | 23 (6.2) | 39 (10.5) | 1 (0.3) |
| Fatigue | 136 (36.7) | 18 (4.9) | 102 (27.5) | 11 (3.0) |
| Asthenia | 76 (20.5) | 17 (4.6) | 46 (12.4) | 9 (2.4) |
| Leukopenia | 20 (5.4) | 14 (3.8) | 11 (3.0) | 5 (1.3) |
| Back pain | 60 (16.2) | 14 (3.8) | 45 (12.1) | 11 (3.0) |
| Anaemia | 40 (10.8) | 13 (3.5) | 20 (5.4) | 5 (1.3) |
| Disease progression | 2 (0.5) | 2 (0.5) | 11 (3.0) | 11 (3.0) |

a: Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA).
b: AEs of CTCAE Grade 3–5.
BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, N: number of patients in the analysis, n: number of patients with event

In the Institute's view, the particular requirements placed on the derivation of proof from a single study are not met for the TROPIC study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, unless outcome-specific aspects weakened the informative value, at most "indications" - e.g. of an added benefit – could be inferred from the data. Despite the above-mentioned high risk of bias, the informative value for "overall survival" was not however classified as being weakened, because after inspection of the actual data on further anticancer therapies used after the ending of the study medication, an overestimation of the effect of cabazitaxel appears unlikely (see Section 2.7.2.4.2 of the full dossier assessment).

## Mortality

### *Overall survival*

Over the entire observation period, treatment with cabazitaxel/prednisone/BSC produced a statistically significant prolongation in overall survival in comparison with treatment with mitoxantrone/prednisone/BSC. For the interpretation of the survival curve, see Section 2.7.2.4.3 of the full dossier assessment.

However, later on in the assessment of subgroup characteristics, there was an indication of an effect modification through the characteristic "age" (< / ≥ 65 years). This means that possible conclusions in terms of added benefit for this outcome are made on the basis of the

subgroups. The subgroup analyses and the related interpretation of the results and documentation of the evidence can be found at the end of this section.

**Morbidity**

***Change in PPI score (pain)***

There was no relevant difference in the proportions of patients with a change in PPI score (improved, stable, worsened) between cabazitaxel/prednisone/BSC and mitoxantrone/prednisone/BSC. The result was not statistically significant and an added benefit for this outcome is not proven.

**Health-related quality of life**

No data on health-related quality of life were available in the dossier of the pharmaceutical company. An added benefit of cabazitaxel/prednisone/BSC for this outcome is not proven.

**Adverse events**

Adverse events, adverse events of CTCAE Grade ≥ 3, serious adverse events and discontinuations due to adverse events occurred more frequently in the patients treated with cabazitaxel/prednisone/BSC than in those who received mitoxantrone/prednisone/BSC. There was a statistically significant difference to the disadvantage of cabazitaxel/prednisone/BSC for all 4 outcomes. Because the effect size is marginal, greater harm for the outcome "adverse events" is not proven. For adverse events of CTCAE Grade ≥ 3, serious adverse events and discontinuations due to adverse events there is an indication in each case of greater harm of cabazitaxel/prednisone/BSC in comparison with mitoxantrone/prednisone/BSC.

**Relevant subgroups**

The results of the TROPIC study were examined for the outcome "overall survival" regarding a possible effect modification through the characteristic "age", in order to detect possible effect differences between patient groups (age < / ≥ 65 years, established prospectively). The requirement for proof of different effects was a statistically significant homogeneity and/or interaction test ($p \leq 0.05$). A p-value between 0.05 and 0.2 provided an indication of different effects. From the interaction test presented in the dossier, there was an indication of an effect modification through age < / ≥ 65 years (interaction test $p = 0.110$, see also Section 2.7.2.4.3 of the full dossier assessment), which necessitates a separate consideration of the results in the two groups.

Table 12 shows the results of the subgroup analysis.

Table 12: Subgroup results according to age – RCT for the direct comparison of cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC (*best supportive care* population)

| Subgroup character-istic | Treatment arm | N | Median survival in months [95% CI] | Hazard ratio [95% CI] p-value | Interaction test p-value[a] |
|---|---|---|---|---|---|
| Age < 65 years | Cabazitaxel/prednisone/BSC | 133 | 15.1 [13.9; 16.5] | 0.81[0.61; 1.08]; 0.1461 | 0.110 |
| | Mitoxantrone/prednisone/BSC | 162 | 13.3 [12.0; 15.6] | | |
| Age ≥ 65 years | Cabazitaxel/prednisone/BSC | 245 | 15.0 [13.6; 17.3] | 0.62 [0.50; 0.78] < 0.001 | |
| | Mitoxantrone/Prednisone/BSC | 215 | 12.1 [10.6; 13.6] | | |
| a: from Cox regression with the variables of treatment, age and interaction term between treatment and age | | | | | |

For patients ≥ 65 years, treatment with cabazitaxel/prednisone/BSC over the entire observation period produced a statistically significant prolongation of overall survival in comparison with treatment with mitoxantrone/prednisone/BSC. There is an indication of an added benefit for this outcome in this population. The effect estimator of the subgroup was used to derive a conclusion concerning the extent of the added benefit.

For patients < 65 years, treatment with cabazitaxel/prednisone/BSC over the entire observation period admittedly produced a prolongation of overall survival in comparison with treatment with mitoxantrone/prednisone/BSC, but showed no statistically significant difference between the treatment groups. On the basis of these data, the indication of an interaction for this subgroup was interpreted as showing the presence of an added benefit for patients < 65 years to be associated with uncertainty. The certainty of results of the statistically significant finding for the total population was downgraded from “indication” to “hint”. There is therefore a hint of an added benefit for the outcome “overall survival” in the population of patients < 65 years. Because of the uncertainty present, the extent of this added benefit cannot be determined, neither based on the overall estimator of the study nor on the effect estimator of the subgroup. This fact is taken into account by the rating of the extent of added benefit as “not quantifiable”.

Because of these results, overall conclusions on added benefit must also be drawn separately for patients < / ≥ 65 years. For weighing up benefits and harms it would, where appropriate, be necessary to also use separate subgroup results for other outcomes. Subgroup results according to age (< / ≥ 65 years) - not to be found in the dossier, but in the study report – do not suggest an interaction for the outcomes “adverse events” and “adverse events of CTCAE Grade ≥ 3”. Therefore for the overall consideration of the benefit-harm ratio for patients < / ≥ 65 years, further outcome data of the total population can be used that were available in the dossier.

**Appraisal of the estimation of added benefit by the pharmaceutical company**

The estimation of the Institute concerning the *best supportive care* population deviates considerably from that of the pharmaceutical company, which claimed a major added benefit for cabazitaxel for docetaxel-refractory mHRPC patients in 2nd line treatment (progression within 20 days from last docetaxel dose, with the exception of patients with ≤ 3 cycles of docetaxel, Module 4, Section 4.4.3). This restriction of the patient group by the company does not, however, occur throughout the dossier (see Module 3, Section 3.2.4) and is therefore inconsistent. Taken as a whole, the Institute interprets the conclusions of the company as follows: the company does not differentiate between populations and subgroups that are relevant to the assessment. The company thus claims an added benefit of cabazitaxel for the entire therapeutic indication and derives an overall major added benefit for it. However, no explicit statements were made about certainty of results and accordingly no categorization as proof, indication or hint (either overall or at the outcome level).

*Further information about outcome results of the direct comparison for the best supportive care population can be found in Module 4, Section 4.3.1.3.1 of the dossier and in Section 2.7.2.4.3 of the full dossier assessment.*

### 2.4.2 Results for the docetaxel retreatment population

The company presented no data for investigating the added benefit of cabazitaxel in the docetaxel retreatment population. An added benefit in that population is not proven. This estimation differs substantially from that of the company, which although it derived no added benefit of cabazitaxel for this population, did not, however, consider it relevant in the first place. Instead, the company claimed an added benefit of cabazitaxel for the entire therapeutic indication, in accordance with the regulatory approval of the drug.

*The dossier contains no information about the docetaxel retreatment population; the Institute's assessment can be found in Section 2.7.2.4.3 of the full dossier assessment.*

## 2.5 Extent and probability of the added benefit

Derivation of the extent and probability of added benefit per patient population is discussed below at the outcome level, taking into account outcome categories and effect sizes. The methodology used is explained in Appendix A of Benefit Assessment A11-02 [4].

The added benefit is assessed separately for the *best supportive care* population and the docetaxel retreatment population.

The procedure for deriving an overall conclusion regarding added benefit based on the aggregation of the conclusions derived at the outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

### 2.5.1 Best supportive care population

#### 2.5.1.1 Evaluation of added benefit at the outcome level

The data presented in Section 2.4.1 produced an indication for patients ≥ 65 years and a hint for patients < 65 years of an added benefit of cabazitaxel/prednisone/BSC over mitoxantrone/prednisone/BSC. In contrast, there were indications of greater harm for both these groups of patients.

The extent of the respective added benefit at the outcome level was estimated and is shown in Table 13.

Table 13: Extent of the added benefit at the outcome level: cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC *(best supportive care* population)

| | | **Effect estimator [95% CI] / quantile of time to event or proportion of event cabazitaxel/prednisone/BSC vs. mitoxantrone /prednisone/BSC / p-value / probability[a]** | **Derivation of extent[b]** |
|---|---|---|---|
| **Mortality** | | | |
| Overall survival | Age < 65 years[c] | Not quantifiable<br><br>Probability: hint | Outcome category: survival period<br><br>Added benefit, extent: “not quantifiable” |
| | Age ≥ 65 years[c] | HR 0.62 [0.50; 0.78]<br>median: 15.0 months vs. 12.1 months<br>p<0.001<br>probability: indication | Outcome category: survival period<br>$CI_o$ < 0.85<br>Added benefit, extent: “major” |
| **Morbidity** | | | |
| Change in PPI score (pain) | | OR 0.94 [0.70; 1.25][d]<br>Improved: 21.3 % vs. 18.2 %<br>Stable: 46.2 % vs. 49.7 %<br>Worsened: 32.4 % vs. 32.1 %<br>p<0.658 | Lesser benefit / added benefit not proven |
| **Health-related quality of life** | | | |
| | | No evaluable data available | Lesser benefit / added benefit not proven |

(continued on next page)

Table 13: Extent of the added benefit at the outcome level: cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC *(best supportive care* population) (continuation)

| | **Effect estimator [95% CI] / quantile of time to event or proportion of event cabazitaxel/prednisone/BSC vs. mitoxantrone /prednisone/BSC / p-value / probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| **Adverse events** | | |
| AEs | RR[e] 1,08 [1.04; 1.13]<br>95.7 % vs. 88.4 %<br>RR[f] 0.93 [0.88; 0.96]<br>p<0.001 | Outcome category: non-serious / non-severe adverse events<br>$CI_o \geq 0.90$<br>Greater/lesser harm not proven[g] |
| AEs of CTCAE Grade ≥ 3[h] | RR[e] 1.46 [1.25; 1.70]<br>57.4 % vs. 39.4 %<br>RR[f] 0.68 [0.59; 0.80]<br>p<0.001<br>probability: indication | Outcome category: serious/severe adverse events<br>$0.75 < CI_o < 0.90$<br>Extent: "considerable" |
| Serious AEs | RR[e] 1.88 [1.49; 2.38]<br>39.1 % vs. 20.8 %<br>RR[f] 0.53 [0.42; 0.67]<br>p<0.001<br>probability: indication | Outcome category: serious/severe adverse events<br>$CI_o < 0.75$<br>Extent: "major" |
| Discont. due to AEs | RR[e] 2.19 [1.47; 3.27]<br>18.3 % vs. 8.4 %<br>RR[r] 0.46 [0.31; 0.68]<br>p<0.001<br>probability: indication | Outcome category: non-serious / non-severe adverse events<br>$CI_o < 0.80$<br>Extent: "considerable" |

a: Figure for probability, provided statistically significant differences are present that exceed an extent classed as "marginal".

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval ($CI_o$).

c: Splitting of the population because of an indication of an interaction and effect modification by the particular characteristic. The effect estimator of the subgroup analysis is used to derive a conclusion about the extent of added benefit for patients ≥ 65 years. See Section 2.4.1 for more detailed reasoning. The overall results for adverse event outcomes are used for the weighing up of benefits and harms, because there was no indication of an interaction for the characteristic "age (< / ≥ 65 years)" for the outcomes "AEs of CTCAE, all grades" and "AEs Grade ≥ 3".

d: Institute's calculation: logistic regression (proportional odds model).

e: Institute's calculation, proportion of events cabazitaxel/prednisone/BSC vs. mitoxantrone/prednisone/BSC.

f: Institute's calculation, proportion of events mitoxantrone/prednisone/BSC vs. cabazitaxel/prednisone/BSC (effect direction reversed to enable derivation of extent of added benefit).

g: Because upper limit of confidence interval is above the named threshold of 0.90.

h: AEs of CTCAE Grades 3–5.

AE: adverse event, BSC: best supportive care, CTCAE: Common Terminology Criteria for Adverse Events, HR: hazard ratio, CI: confidence interval, $CI_o$: upper limit of confidence interval, OR: odds ratio, PPI: present pain intensity, RR: relative risk

The extent of the added benefit for the outcome "overall survival" in the subgroup of patients < 65 years cannot be quantified on the basis of the data presented in the dossier. It remains unclear whether the identified added benefit should be classed as "minor", "considerable" or "major". According to the legislation, in situations where, on the basis of the scientific data, uncertainty prevails concerning the classification of the extent of the added benefit, the term "not quantifiable" must be applied as the assessment category (see Regulation for Early Benefit Assessment of New Pharmaceuticals (AM-NutzenV) Section 5 subsection 7).

#### 2.5.1.2 Overall conclusion on added benefit

The summary of results that determine the overall conclusion on added benefit is shown in Table 14 and Table 15, divided according to the relevant subgroups.

**Patients ≥ 65 years**

Table 14: Patients ≥ 65 years: Results contributing to the overall conclusion on added benefit (*best supportive care* population)

| **Positive Effects** | **Negative Effects** |
|---|---|
| Indication of a major added benefit<br>(survival period: overall survival) | Indication of greater harm –<br>extent: "considerable"<br>(serious/severe adverse events: AEs of CTCAE Grade ≥ 3[a]) |
| | Indication of greater harm –<br>extent: "major"<br>(serious/severe adverse events SUEs) |
| | Indication of greater harm –<br>extent: "considerable"<br>(non-serious/non-severe adverse events: discontinuation due to AEs) |
| a: AEs of CTCAE Grades 3–5.<br>AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events, SAE: serious adverse event. | |

In the global assessment (Table 14) positive and negative results show the same certainty of results (indication). On both sides, the extent "major" is achieved. Because the added benefit is opposed by the indication of a greater harm of "major" extent in relation to serious adverse events it appears, in the Institute's view, that the extent of the added benefit should be downgraded (from "major" to "considerable").

In summary, for patients ≥ 65 years in the *best supportive care* population, i.e. for patients for whom further treatment with docetaxel is no longer an option, there is an indication of a "considerable" added benefit of cabazitaxel/prednisone/BSC over mitoxantrone/ prednisone/BSC.

**Patients < 65 years**

Table 15: Patients < 65 years: Results contributing to the overall conclusion on added benefit (*best supportive care* population)

| **Positive Effects** | **Negative Effects** |
|---|---|
| Hint of an added benefit –<br>extent: "not quantifiable"<br>(survival period: overall survival) | Indication of greater harm –<br>extent: "considerable"<br>(serious/severe adverse events: AEs of CTCAE Grade ≥ 3[a]) |
| | Indication of greater harm –<br>extent: "major"<br>(serious/severe adverse events: SUEs) |
| | Indication of greater harm –<br>extent: "considerable"<br>(non-serious/non-severe adverse events: discontinuation due to AEs) |
| a: AEs of CTCAE Grades 3–5.<br>AE: adverse events, CTCAE: Common Terminology Criteria for Adverse Events, SAE: serious adverse event | |

In the global assessment (Table 15), positive and negative results show different certainties of results ("hint" vs. "indication"). As regards the added benefit, the extent on the basis of the available data is "not quantifiable", whilst for greater harm, the extent "major" is reached. Since the added benefit cannot be quantified, no definitive assessment can be made as to whether a downgrading of the extent on the added benefit side would be reasonable. However, the question arises whether the negative effects fully outweigh the positive ones. In the Institute's view, it is not appropriate to completely query the hint of an added benefit in terms of overall survival on the basis of an indication of greater harm regarding serious adverse events.

However, on the basis of the above downgrading of the extent of added benefit for patients ≥ 65 years ("major" to "considerable"), for the available data on patients < 65 years it must at least be concluded that the remaining added benefit (extent not quantifiable) can be no more than "considerable".

In summary, there is a hint of an added benefit (extent "not quantifiable", at most, "considerable") of cabazitaxel/prednisone/BSC over the ACT mitoxantrone/prednisone/BSC for patients < 65 years.

### 2.5.2 Docetaxel retreatment population

As described in Section 2.4.2, the pharmaceutical company did not submit any data on the added benefit of cabazitaxel in the docetaxel retreatment population.

An added benefit of cabazitaxel in combination with prednisone or prednisolone over the ACT (docetaxel in combination with prednisone or prednisolone), for the docetaxel retreatment population is not proven.

### 2.5.3 Extent and probability of the added benefit – summary

An overview of the extent and probability of the added benefit for patient populations and subgroups relevant to the benefit assessment of cabazitaxel compared to the relevant ACTs is shown in Table 16.

Table 16: Cabazitaxel: extent and probability of the added benefit

| **Population** | **Subgroup** | **Appropriate comparator therapy** | **Comparison** | **Extent and probability of the added benefit** |
|---|---|---|---|---|
| *Best supportive care* population | Age < 65 years[a] | Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as *best supportive care* (e.g. adequate pain therapy) | Cabazitaxel/prednisone/BSC vs. mitoxantrone/ prednisone/BSC | Hint of an added benefit (extent "not quantifiable", at most "considerable") of cabazitaxel/prednisone/BSC |
| *Best supportive care* population | Age ≥ 65 years[a] | Palliative treatment with dexamethasone, prednisone, prednisolone or methylprednisolone as well as *best supportive care* (e.g. adequate pain therapy) | Cabazitaxel/prednisone/BSC vs. mitoxantrone/ prednisone/BSC | Indication of a "considerable" added benefit of cabazitaxel/prednisone/BSC |
| Docetaxel retreatment population | | Docetaxel in combination with prednisone or prednisolone | Cabazitaxel in combination with prednisone or prednisolone vs. docetaxel in combination with prednisone or prednisolone | Added benefit not proven |
| a: Splitting of the population due to effect modification.<br>BSC: best supportive care | | | | |

This overall assessment deviates from that of the pharmaceutical company, which, at the outset did not undertake any division into populations and claimed an added benefit of cabazitaxel for the entire therapeutic indication. The company claimed overall a major added benefit, but made no explicit statements about certainty of results and accordingly derived no proof, indication or hint (overall or at the outcome level).

*Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment*

## 2.6 List of included studies

**TROPIC**

De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376(9747): 1147-1154.

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Sanofi-Aventis. Jevtana value dossier Germany: draft version 3.0 [unpublished]. 2010.

Sanofi-Aventis. Modellierung der Überlebenskurven (overall survival) in der TROPIC-Studie (XRP6258_FC6193) zur Bestimmung der erwarteten (mittleren) Überlebenszeiten [Modelling of survival curves [overall survival] in the TROPIC Study [XRP6258_FC6193] for determination of the expected (mean) survival times] [unpublished]. 2011.

Sanofi-Aventis. A randomized, open label multi-center study of XRP6258 at 25 mg/m$^2$ in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen: study EFC6193; clinical study report [unpublished]. 2010.

Sanofi-Aventis. A randomized, open label multi-center study of XRP6258 at 25 mg/m$^2$ in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen: study EFC6193; amended clinical trial protocol 5 [unpublished]. 2008.

Sanofi-Aventis. A randomized, open label multi-center study of XRP6258 at 25 mg/m$^2$ in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen: study EFC6193; final statistical analysis plan (and amendments) [unpublished]. 2008.

Sanofi-Aventis. A randomized, open label multi-center study of XRP6258 at 25 mg/m$^2$ in combination with prednisone every 3 weeks compared to mitoxantrone in combination with prednisone for the treatment of hormone refractory metastatic prostate cancer previously treated with a Taxotere-containing regimen [online]. In: International Clinical Trials Registry Platform. 04.01.2011 [Accessed on: 25.11.2011]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00417079.

Sanofi-Aventis. XRP6258 plus prednisone compared to mitoxantrone plus prednisone in hormone refractory metastatic prostate cancer (TROPIC) [online]. In: ClinicalTrials.gov. 04.03.2011 [Accessed on: 25.11.2011]. URL: http://www.clinicaltrials.gov/ct2/show/NCT00417079.

**References for English extract (please see full dossier assessment for full reference list)**

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