SYNOPSIS

Title of the registry:	Non-interventional study to record the quality of life of patients with metastatic hormone refractory prostate carcinoma under cabazitaxel, who previously have received a docetaxel containing chemotherapy Registry number CABAZ_L_05763
Design:	Non-interventional
Objectives:	Primary objective: Correlation between health related quality of life in metastatic hormone refractory prostate carcinoma (mHRPC) patients, who have been treated with cabazitaxel (Jevtana®), and their biochemical Prostate-specific antigen (PSA)-response. Secondary objectives: • Impact of cabazitaxel on other quality of life dimensions/scales • Impact of toxicity on quality of life • Impact of pre-existing symptoms on quality of life • Predictive factors for improvement of quality of life after four cycles • Investigation of serious adverse drug reactions/events • Comparison of the quality of life of PSA-responders and non-responders before measurement or notification of the first PSA-value
Treatment:	Treatment of mHRPC with cabazitaxel according to labeled indication: Patients should be treated with cabazitaxel in the recommended dose of 25 mg/m² applied as i.v. infusion over 1 h, q3w Cabazitaxel treatment should be combined with 10 mg Prednisone or Prednisolone, taken daily p.o.
Scientific committee	Not applicable
Publications (reference):	Not applicable
Introduction - Background/rationale:	It has been shown by Tannock et al. in 2004 that mHRPC patients receiving an effective therapy reveal an increase in health related quality of life (QoL) independent of adverse reactions of the treatment itself (NEJM 351: 1502-1512, 2004). In this randomized phase III study that compared mitoxantrone plus prednisone against docetaxel plus prednisone, docetaxel administered every 3 weeks was associated with better pain control and quality of life and more frequent PSA responses compared to mitoxantrone despite an increase in adverse effects. Similarly QoL improvements were also reported in a randomized phase II study comparing weekly docetaxel regime plus prednisolone versus prednisolone alone (Fossa et al. Eur Urol 2007, 52: 1691-99). As of today, a correlation between PSA-response and health related QoL has not been evaluated. This NIS was conducted to examine the health related QoL under cabazitaxel therapy. Firstly, the correlation of health related QoL after 4 cycles of cabazitaxel with biochemical (PSA) response was

	examined, whereby PSA response was defined as an at least 50% decrease of PSA-value compared to PSA value before cabazitaxel therapy. Secondly, factors influencing health related QoL and safety of the cabazitaxel treatment were evaluated.
Methodology:	(a) Site and patient selection: It was planned to recruit 999 patients with mHRPC into the trial. Clinics and medical practices in Germany with experience in the therapy of mHRPC patients could participate. Except the conditions specified in the summary of product characteristics no further inclusion criteria were applied. (b) Data collection: For data capturing and data management, a web-based validated software was employed. Physicians documented the anamnesis and therapy data into electronic case report forms (eCRF). Patients were asked to fill in the EORTC QLQ-C30 questionnaires before every cabazitaxel therapy. These questionnaires were faxed to the CRO (Alcedis GmbH), where double data entry into the CRF was carried out. (c) Safety data collection: All adverse events (serious and non-serious, related and not-related) that occurred after first dose of cabazitaxel and until 28 days after last dose administered had to be reported using the applicable eCRF. All adverse events (AEs) had to be documented within 24 hours after they had become known by the sites. After saving the form an automatically generated e-mail informed Sanofi Pharmacovigilance (PV) about the AE. In the case electronic reporting was not possible, paper forms in the investigator's file were at the doctor's disposal for notification AEs by conventional fax to Sanofi PV. Another possibility in such cases was to report the AE by phone to Sanofi. If a conventional fax was received by Sanofi PV, the PV of the CRO was informed and asked the site to document the SAE into the eCRF. Reconciliation between the PVs of Sanofi and CRO were carried out at regularly intervals. (d) Data management, review, validation: Validity of documented data was ensured by validations in the eCRF, which indicated missing or implausible data entries. Patients could only be registered if they had been informed about the trial by the treating physician and had given their written consent before start of cabazitaxel therapy. The date of informed consent was documented into the eCRF and had to be before the date of the first documented cycle. The documentation of patients which was completed and signed by the investigator was reviewed on a regularly basis by the data management of the Alcedis GmbH. Queries were made directly in the eCRF and the sites were asked to answer the queries. To further ensure the validity of the data, quality control on-site was performed at 5% of participating sites by monitors of Alcedis GmbH according to the guidelines of Sanofi. (e) Statistical considerations: For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter were created. For continuous variables, the mean, median, standard deviation, minimum and maximum values were calculated. For categorical variables the $\chi 2$-test or Fisher's exact test were used to test for differences between subgroups, for continuous variables Wilcoxon's test. All analyses were descriptive. Therefore no correction for multiple testing took place. The EORTC-questionnaire was analyzed according to the manual. Analyses of adverse and serious adverse events were based on the Sanofi PV database. Overall survival (OS): OS was measured from the date of the first dose given until date of death. Survival time for subjects not known to have died was censored at the date of last contact. Time to progression (TTP): TTP was measured from the date of the first dose given until date of progression. Time to progression for subjects without progression was censored at the date of last contact. EORTC QLQ-C30: If more than 50% of the items collected in an EORTC-questionnaire were missing all items of the respective patient were set to missing, otherwise only the single item was set to missing (according to the EORTC manual). The global scale of the quality of life was measured according to the EORTC-LQ-Manual for each

	documented point in time. The questionnaire includes six functional scales and the global health status and furthermore a number of multi-item scales and single items assessing financial impact and a range of physical symptoms common among patients with cancer. The scales and single items were linearly transformed such that all scales/items range from 0 to 100, with a higher score representing a higher level of functioning/symptomatology/problems. PSA response was defined as at least 50% decrease of the PSA-value after 4 cycles compared to the baseline value before the cabazitaxel- therapy. Minor PSA responses of at least 20% and at least 30% decrease of the PSA-value after 4 cycles compared to the baseline value were also provided. Change of global health after 4 cycles: Difference between global health after cycle 4 and baseline global health divided by baseline global health. Change of mean global health: Difference between mean of all post-baseline measurements of global health status until cycle 4 (at least two are necessary) and baseline global health divided by baseline global health status (in percent). Predictive factors: To determine potential predictors for improvement of global health status after four cycles the dependent variable of global health status was categorized into yes (=Improvement after 4 cycles) and no (=No improvement after 4 cycles). For a first overview the following independent covariates - PSA response after 4 cycles (Yes/No) - Toxicity (Yes/No) - Pre-existing symptoms (Yes/No) - Baseline ECOG (<2/≥2) - Age (<60/≥ 60) were looked at in a univariate regression. Afterwards, all of the above mentioned independent covariates were entered into a stepwise multivariate logistic regression. The entry level was p=0.5 and the stay level p=0.1. All covariates being significant were considered as potential predictors of the event in question. AEs and SAEs were coded according to MedDRA-SOC and PT and were displayed both on a patient and event basis. Missing values were not replaced. Analysis based on two data sets: 1. Safety population (SP) = Intent-to-treat (ITT): All patients who were signed by Alcedis data management and who received at least one dose of cabazitaxel (Jevtana®). 2. Primary Endpoint Set (PES): All patients who have been treated with cabazitaxel (Jevtana®) for at least 4 cycles and provided sufficient information about the PSA response. Sample size calculation was based on the high rate of drop outs in QoL investigations and the statistical precision of the estimated correlation coefficient. It was assumed that only 80% of data could be provided with only 60% for the time point “after 4 cycles”. Thus 999 patients were needed for getting evaluable data of 480 patients. With 480 patients and an expected correlation coefficient of r=0.5, the lower limit of a one-sided 97.5% CI for r will be 0.430.
RESULTS	
Participants (actual):	(a) Overall participation status: Between November 2011 and May 2014 a total of 587 patients with mHRPC, who previously had received a docetaxel containing chemotherapy, were included in the study by 158 sites (clinics and medical practices) in Germany. (b) Participation per period of the registry:

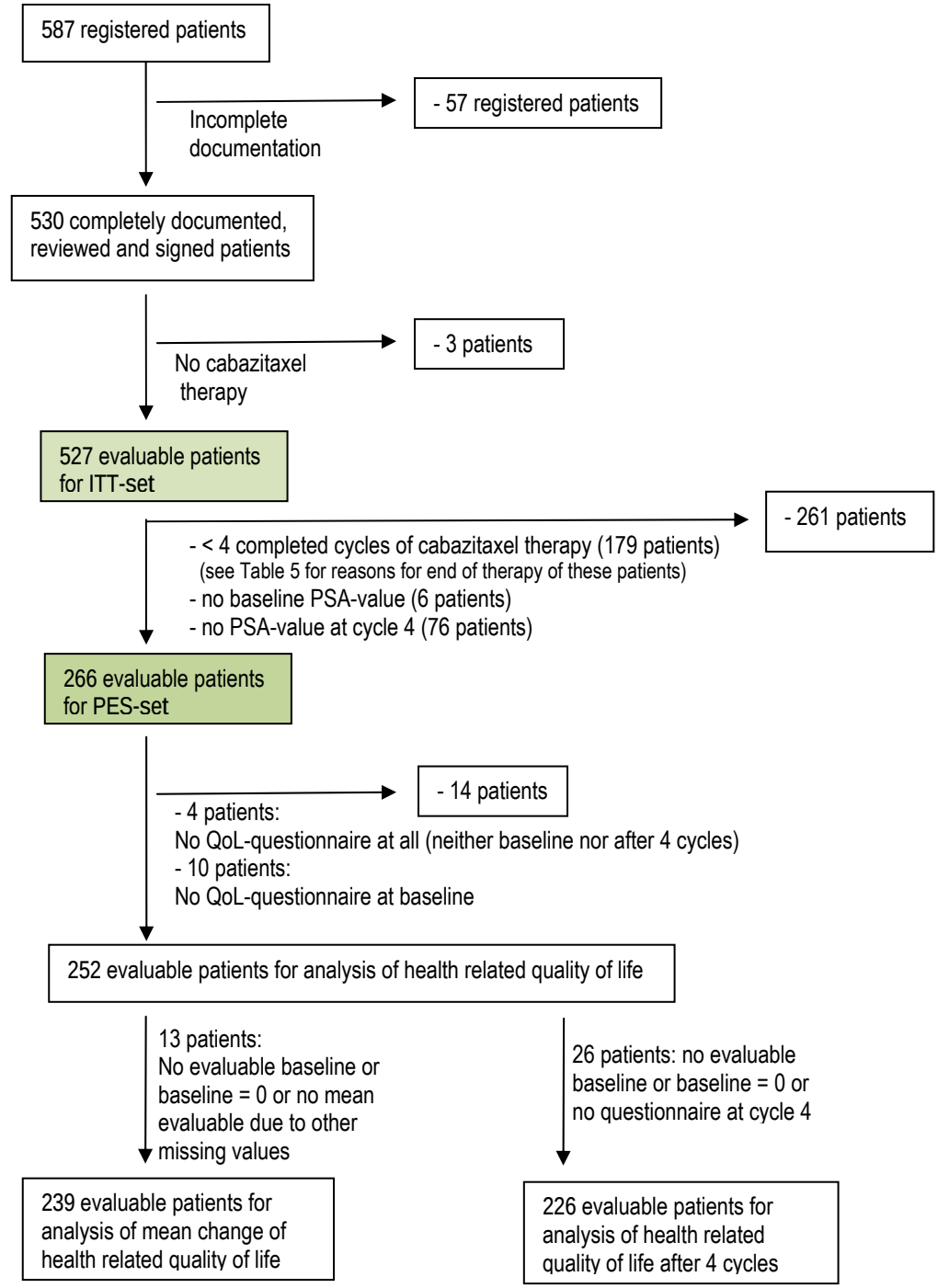


Figure 1: CONSORT-Scheme

Participant characteristics and primary analyses:

(a) Descriptive data:
527 male patients aged from 43 – 90 years were included. An overview of patient data is given in Table 11. Nearly 81% were older than 65 years. Median age was 72 years. Median BMI was 27.04 kg/m².

Table 1: Demographics at baseline

Demographics at baseline	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
Height [cm]	527	174.72	6.67	160.00	170.00	174.00	179.00	191.00	156.00	210.00	0
Weight [kg]	527	82.86	13.08	58.00	74.00	82.00	90.00	121.60	47.00	137.00	0
BMI [kg/m²]	527	27.16	4.16	18.83	24.30	27.04	29.61	39.04	16.41	46.31	0
BSA [m²]	527	1.98	0.16	1.67	1.87	1.97	2.07	2.39	1.45	2.43	0

About 90% of the patients had an ECOG of 0 or 1.

Histology of the tumor was mostly adenocarcinoma (82%), thus representing a typical patient population in this indication.
The most often documented tumor classification at study entry time was T3 (15.4%), N1 (31.7%) and M1 (37.8%). More than half of the patients suffered from bone metastases, followed by metastases in lymph nodes and liver. 247 patients (46.9%) had one location of metastasis only:

Table 2: Location of metastasis (patients with one location only)

Location of metastasis	N	%
Lymph node only	30	12.15
Bone only	211	85.43
Lung only	2	0.81
Liver only	3	1.21
Other only	1	0.40
Total	247	100.00

280 patients (53.1%) had multiple locations of metastasis. A list of all metastases is included in table 11 (appendix).

55.2% of the tumors had a grading of G3 (55.2%).
The median Gleason score sum was 8, ranging from 4 – 10.

Table 3: Gleason score sum

	N	Mean	Std	P1	P25	Median	P75	P99	Min	Max	NMiss
Gleason-score sum	409	7.91	1.12	5.00	7.00	8.00	9.00	10.00	4.00	10.00	118

Disease progression at enrollment and during course of the NIS was evaluated according to the investigator's decision. No specification was made concerning the method for evaluating the tumor or the time points.
Evaluation of the symptom "pain" at enrollment was done by using the patient's own assessment as documented in the baseline EORTC questionnaire. 25.8% and 26.4% of the 527 patients had no pain at all and a little pain, respectively. 16.1 % started cabaziaxel therapy with very much pain.

As therapy prior to cabazitaxel treatment only chemotherapy with docetaxel and mitoxantrone was

requested to be documented. The use of new agents such as abiraterone, which was authorized in the European Union as treatment post docetaxel only shortly before start of the NIS, and enzalutamide, which was authorized towards the end of the NIS, was not assessed. At the time these drugs were not part of daily clinical practice. Furthermore, the aim of this NIS was to answer specific questions around QoL and the eCRF and protocol were not amended to document abiraterone and enzalutamide according to their consecutive availabilities.

Nearly all patients received previous chemotherapy (96.6%). In this context, median docetaxel dose was 540 mg/m² and median mitoxantrone dose was 44 mg/m². A previous chemotherapy with cabazitaxel was administered to 9.6% of the patients, for a median of 6 cycles, ranging from 1-20 cycles. Further on, 66.4% of the patients had concomitant diseases, mainly cardiovascular (40.5%).

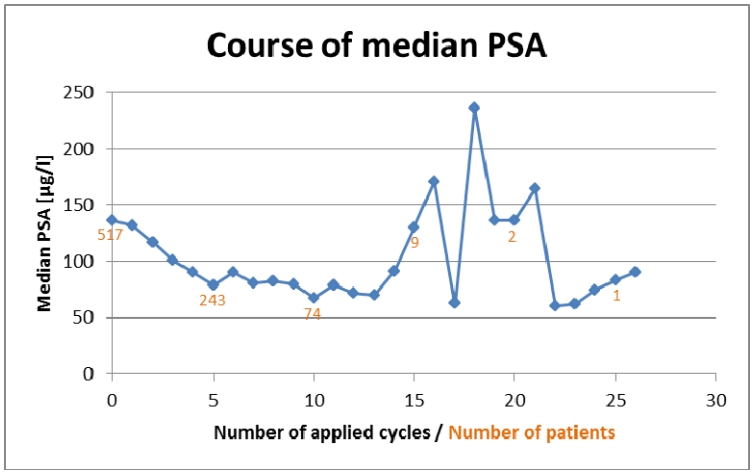
A total of 3220 cabazitaxel cycles were recorded: Patients received 1 to 26 cycles of cabazitaxel therapy with a median of 6 cycles. In median the recommended single dose of 25 mg/m² was administered, ranging from 10 – 25 mg/m². In 80.2% of the applied cycles cabazitaxel was administered with the recommended dose of 25 mg/m²:

Table 4: Cabazitaxel- Single dose (over all cycles), categorical

Single dose (over all cycles)	N	%
<20 mg/m²	129	4.01
20 mg/m²	323	10.03
>20-<25 mg/m²	88	2.73
25 mg/m²	2678	83.17
>25 mg/m²	2	0.06
Total	3220	100.00

197 cycles (6.1%) were applied with reduced cabazitaxel dose compared to the previous cycle. All dose reductions of cabazitaxel took place during the first ten cycles, mostly because of hematological toxicities. In addition, therapy delays were documented for nearly every cycle, mainly because of organizational reasons.
159 (30.2%) and 340 patients (64.5%) had dose recuctions and therapy delays, respectively.74 patients (14%) had a dose reduction due to toxicities, whereas 83 patients (15.8%) had a therapy delay because of toxicities.

The median PSA value before cabazitaxel therapy was 136 µg/l.
Figure 2 shows the development of median and mean PSA-values during cabazitaxel therapy. Table 16 lists the PSA values per each cycle.
In the first 10 cycles a decrease of median and mean PSA values could be observed. But it has to be noted that the number of patients with documented PSA values was not the same in each cycle: During therapy number of patients with reported PSA values decreased from 517 patients at baseline to 1 patient (from cycle 22 on).



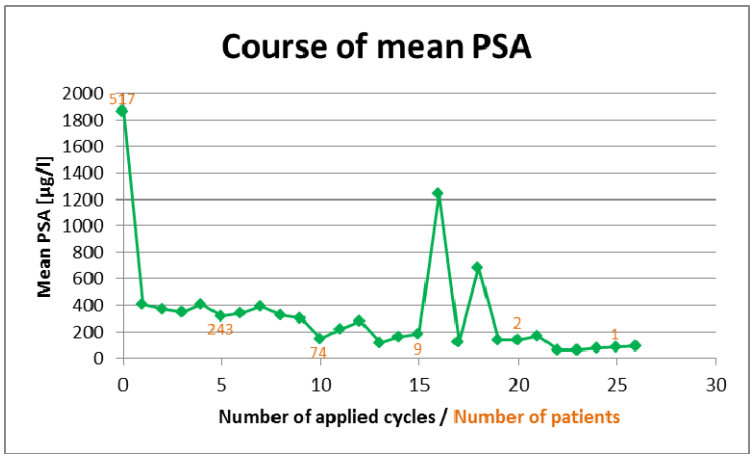


Figure 2: Course of median / mean PSA values

(b) Primary endpoint (Evaluation for the Primary Endpoint Set)
50.5% of the 527 evaluable patients were available for the Primary Outcome Set (266 patients).
261 patients could not be taken into account for the evaluation of primary endpoint due to the following reasons:
PSA-values at baseline or cycle 4 were not documented for 6 and 76 patients, respectively, and 179 patients had < 4 completed cycles of cabazitaxel therapy. The following Table 5 lists the causes for the end of therapy ot these 179 patients.

Table 5: Patient without four complete cycles- Reason for end of study

Reason for end of study	N	%
Planned number of cycles applied	7	3.91
Tumor progression	63	35.20
Death	23	12.85
Adverse event	25	13.97
Patient's wish	38	21.23
End of documentation	1	0.56
Other reasons	22	12.29
Total	179	100.00

Of these 266 patients, that entered the PES analysis, 34.6%, 49.6% and 58.3% had a PSA decrease after 4 cabazitaxel cycles of at least 50%, 30% and 20%, respectively (Table 6).

Table 6: PSA response

PSA or minor PSA response	At least 50% PSA decrease		At least 30% PSA decrease		At least 20% PSA decrease	
	N	%	N	%	N	%
No	174	65.41	134	50.38	111	41.73
Yes	92	34.59	132	49.62	155	58.27
Total	266	100.00	266	100.00	266	100.00

The development of the global health status during different time points for patients with or without a PSA-decrease of at least 50% is shown in the next table.

Table 7: PES EORTC QLQ-C30: Global health status/Quality of life with respect to PSA response after 4 cycles

Global health status		N	Mean	95% CI	Std	Median	Min	Max	p-Value (Wilcoxon Two-Sample test)
Baseline	**≥ 50% PSA decrease**	87	51.53	46.45-56.61	23.83	50.00	0.00	100.00	0.81
	< 50% PSA decrease	162	51.18	47.75-54.61	22.11	50.00	0.00	100.00	
	Total	249	51.31	48.47-54.14	22.68	50.00	0.00	100.00	
Cycle 1	**≥ 50% PSA decrease**	88	47.06	42.78-51.35	20.22	50.00	0.00	100.00	0.21
	< 50% PSA decrease	160	50.73	47.35-54.11	21.65	50.00	0.00	100.00	
	Total	248	49.43	46.78-52.08	21.18	50.00	0.00	100.00	
Cycle 2	**≥ 50% PSA decrease**	88	49.91	45.49-54.32	20.82	50.00	0.00	100.00	0.95
	< 50% PSA decrease	161	50.10	46.86-53.35	20.85	50.00	0.00	100.00	
	Total	249	50.03	47.44-52.63	20.80	50.00	0.00	100.00	
Cycle 3	**≥ 50% PSA decrease**	89	50.94	46.81-55.07	19.60	50.00	0.00	91.67	0.42
	< 50% PSA decrease	159	50.26	46.81-53.72	22.06	50.00	0.00	100.00	
	Total	248	50.50	47.86-53.15	21.17	50.00	0.00	100.00	
Cycle 4	**≥ 50% PSA decrease**	83	50.50	46.34-54.66	19.05	50.00	0.00	91.67	0.26
	< 50% PSA decrease	162	47.27	43.92-50.63	21.64	50.00	0.00	100.00	
	Total	245	48.37	45.75-50.99	20.82	50.00	0.00	100.00	

No statistically significant differences could be seen between baseline and after 4 cycles for PES-patients neither for the global health status (p=0.62, Wilcoxon signed-rank test) nor for the mean global health status (p=0.36, Wilcoxon signed-rank test).

Additionally, the change in global health status (p=0.69, Wilcoxon Two-Sample test) or in mean global health status (p=0.65, Wilcoxon Two-Sample test) did not differ statistically significantly between patients with ≥ 50% PSA decrease and with < 50% PSA decrease.
The correlation coefficient between change in PSA and global health status after cycle 4 was -0.14 (95% CI: -0.26 – (-0.01); p=0.03), which indicates an inversely proportional relation: If the PSA value tends to increase, the global health status after cycle 4 tends to be lower. No correlations could be found between change in PSA and baseline global health, between change in PSA and change of global health and between change in PSA and change of mean global health.

Other analyses:

With regard to the changes of EORTC QLQ-C30 items between baseline and cycle 4, significant differences between the subgroups of PSA responders (≥ 50% decrease and < 50% decrease) only occurred for pain (p=0.01, Wilcoxon Two-Sample test) and Physical functioning (p=0.05, Wilcoxon Two-Sample test).

Table 8: PES Changes between baseline and cycle 4 according to PSA response after 4 cycles [absolute)

Change for other EORTC QLQ-C30 scales		N	Mean	Median	p-Value (Wilcoxon Two-Sample test)
Physical functioning (PF)	**≥ 50% PSA decrease**	80	-1.75	0.00	0.05
	< 50% PSA decrease	154	-7.00	-6.67	
	Total	234	-5.21	-6.67	
Role functioning (RF)	**≥ 50% PSA decrease**	81	-4.94	0.00	0.16
	< 50% PSA decrease	156	-10.79	-16.67	
	Total	237	-8.79	0.00	
Emotional functioning (EF)	**≥ 50% PSA decrease**	80	-1.08	0.00	0.10
	< 50% PSA decrease	156	-4.43	0.00	
	Total	236	-3.30	0.00	
Cognitive functioning (CF)	**≥ 50% PSA decrease**	80	-4.17	0.00	0.83
	< 50% PSA decrease	156	-3.95	0.00	
	Total	236	-4.03	0.00	
Social functioning (SF)	**≥ 50% PSA decrease**	80	-0.62	0.00	0.33
	< 50% PSA decrease	155	-5.05	0.00	
	Total	235	-3.55	0.00	
Fatigue (FA)	**≥ 50% PSA decrease**	81	2.13	0.00	0.16
	< 50% PSA decrease	156	8.76	11.11	
	Total	237	6.49	0.00	
Nausea and vomiting (NV)	**≥ 50% PSA decrease**	81	-3.50	0.00	0.18
	< 50% PSA decrease	156	4.81	0.00	
	Total	237	1.97	0.00	
Pain (PA)	**≥ 50% PSA decrease**	81	-7.61	0.00	0.01
	< 50% PSA decrease	155	3.44	0.00	
	Total	236	-0.35	0.00	
Dyspnoea (DY)	**≥ 50% PSA decrease**	81	4.12	0.00	0.71
	< 50% PSA decrease	155	7.53	0.00	
	Total	236	6.36	0.00	
Sleep disturbance (SL)	**≥ 50% PSA decrease**	81	-3.70	0.00	0.08
	< 50% PSA decrease	153	1.96	0.00	

	Total	234	0.00	0.00	
Appetite loss (AP)	**≥ 50% PSA decrease**	79	-5.06	0.00	0.12
	< 50% PSA decrease	153	2.18	0.00	
	Total	232	-0.29	0.00	
Constipation (CO)	**≥ 50% PSA decrease**	78	-3.85	0.00	0.19
	< 50% PSA decrease	156	3.21	0.00	
	Total	234	0.85	0.00	
Diarrhea (DI)	**≥ 50% PSA decrease**	78	10.26	0.00	0.81
	< 50% PSA decrease	155	8.60	0.00	
	Total	233	9.16	0.00	
Financial impact (FI)	**≥ 50% PSA decrease**	80	1.25	0.00	0.32
	< 50% PSA decrease	155	3.87	0.00	
	Total	235	2.98	0.00	

Comparison of the median changes of EORTC Items between baseline and cycle 4 in the PSA subgroups (≥ or < 50% decrease) yielded for patients with < 50% PSA-decrease statistically significant p-values for the reduction of PF, RF and EF. The same was found for mean changes of the symptoms FA, NV, and DY, whereas deterioration of DI was statistically significant for both subgroups. FI was statistically significant worse for the patients with < 50% PSA-decrease. The results are summarized in Table 19.

In contrast to these findings, PA improved significantly for patients with a PSA decrease of at least 50%. For this subgroup of patients mean changes of other symptoms, e.g. SL or AP improved, too, although without statistical significance. For patients with < 50% PSA decrease no symptom improvement could be found.

Analysis of changes of global health status according to hematological and non-hematological toxicities as well as according to pre-existing symptoms did not reach statistically significant p-values.

Further univariate and multivariate logistic regressions for improvement of global health status reveals that none of the parameters tested had a p-value smaller than 0.16, which implies, that no value is considered as possible predictor.

Tumor evaluation and overall survival:

Time points and methods of tumor staging were performed according to the normal routine of the physicians and according to the investigator's decision..No specifications were made for methods or timepoints for tumor evaluation. Response could be evaluated by PSA analysis, bone scan, clinical evaluation or imaging examination.

Best response as evaluated by the investigator for most patients was stable disease (39.1%), followed by partial remission (33.4%) or progressive disease (9.5%). Only nine of the 527 patients showed a complete remission as best response (1.7%).

Table 9: Best response as evaluated by the investigator (response = imaging method, PSA value, clinical)

Best response	N	%	% (adj.)
Complete remission	9	1.71	1.84
Partial remission	176	33.40	35.99
Stable disease	206	39.09	42.13
Progression	50	9.49	10.22
Not appraisable	48	9.11	9.82
Missing	38	7.21	.

Total	527	100.00	.

Tumor progression was the main reason for documentation of “end of study” form (30.0%), followed by planned number of cycles applied (27.5%) and patient’s wish (14.6%).

Table 10: Reason for documentation of “end of study”-form

Reason	N	%
Planned number of cycles applied	145	27.51
Tumor progression as evaluated by the investigator	158	29.98
Death	37	7.02
Adverse event	33	6.26
Patient's wish	77	14.61
End of documentation	31	5.88
Other reasons	46	8.73
Total	527	100.00

Median time to progression amounted to 8.3 months.
Altogether 135 patients of the 527 analyzed patients died within the observational period (25.6%). In the majority of cases (82%) the reason for the death was tumor-related. Median overall survival was 16.8 months.
In the observational plan the time period for the documentation of adverse events was defined from date of first application of cabazitaxel to 28 days after end of last therapy cycle. After this time point only adverse events with causal relation to cabazitaxel have to be documented. For all deaths which occurred thereafter and which are not causally related to cabazitaxel no AE/SAE form was filled in the eCRF.
Altogether, 53 patients died during observational period and for these patients an SAE form was filled in and PV of Sanofi was informed. 80 patients died after this observational period and death was not associated with cabazitaxel. Thus, no SAE was reported for these patients.

Safety analysis (see Table 26 - Table 34):
Safety analysis based on the AE-database of Sanofi. In this database AEs were assigned as serious and non-serious, no further grade specification was provided. Therefore only the occurrence of AEs and SAEs but not the distribution among the grades could be evaluated.
For more than 50% of the 527 patients adverse events were documented:A total of 1357 adverse events occurred in 292 patients (55.4%). For 235 (44.6%) patients, no adverse events were reported. The most often reported event in this context was anemia at 10.4%, followed by diarrhea (6.6%), white blood cell count decreased (6%) and fatigue (5.8%). All other events had a share of less than 5%.
On a per-patient-basis 29.79%, 22.26% and 21.23% of the 292 patients suffered from anemia, fatigue and diarrhea, respectively. Referring to the ITT set of 527 patients, 16.51%, 12.33% and 11.76% of them developed anemia, fatigue and diarrhea, respectively. 3.8% of theITT patients suffered from neutropenia, whereas 3.61% had a febrile neutropenia. 2.09% and 3.04% of the patients had serious neutropenia and febrile neutropenia, respectively.
18 of the 20 patients with neutropenia and 12 of the 19 patients with febrile neutropenia received G-CSF. But altogether more than 50% (268 patients) received at least one administration of G-CSF, thus this medication was administered in most patients prophylactically.

The median duration of AE was eight days (range: 0-329 days). Most events were recovered (61.4%), but 4.2% had a fatal outcome. Assessed by Investigator, 58.9% of the events were associated with cabazitaxel, whereas assessment by company yielded 63.6% events which were associated with cabazitaxel. The AE “device related infection” was the only AE of special interest (0.1%). For 85.5% of the events no action was taken.

	32.7% of the events were serious. Of these 444 serious adverse events, anemia, occurred in 174 patients (33%). The main reason for seriousness was hospitalization or prolongation of hospitalization (66.8%), followed by other important medical events (12.5%) and patient's death (12%; Table 33). According to reporter, 36% of the serious events were associated with cabazitaxel; however, according to company 43% were associated. Further on, 54.7% of the events were recovered, 12.8% had a fatal outcome. Additionally, for 72.1% of the events no action was taken. In addition to the 1357 AEs described above another 61 adverse events were part of the Sanofi AE-database. These additional AEs occurred in patients who do not belong to the ITT analysis set because they were not enrolled into this NIS. or have not received any cabazitaxel therapy after enrollment or their documentation was incomplete (not being reviewed and signed by Alcedis data management). 49 of these 61 events were serious [further description and listing of these events is documented in Final Statistical Report (Listing 3 + 4 of non-safety set)]. These (serious) adverse events are not included in the analyses and tables of this product registry report.
Discussion:	587 patients with mHRPC treated with cabazitaxel and prednisolone or prednisone according to licensed indication were registered into the NIS by 158 German sites. There were no specifications concerning inclusion of patients or diagnostic and therapeutic measures, physicians could follow normal daily routine. Median age of the patients was 72 years with more than 80% of them being older than 65 years. Thus patients enrolled in this registry were in the median older than patients included into randomized clinical trials, in which older patients are often underrepresented due to special inclusion and exclusion criteria. In the TROPIC study which was the basis of approval of cabazitaxel, the median patient age was 68 years old (De Bono JS et al. 2010). The high age is accompanied by a large number of patients with concomitant diseases (> 60% of patients). Despite labelling requirements, 14 patients (2.66%) had not received previous chemotherapy and for 4 patients (0.76%) no information was given concerning this point. Only 50.5% of the registered patients were evaluable for primary objective (266 patients). Thus the statistically calculated number of 480 evaluable patients for the primary outcome could not be reached. Reasons were mainly incomplete documentation and that the time point for evaluation (= after application of 4 cycles cabazitaxel) was not reached. Therefore, statistical power for analyzing the primary objective may be affected. About one third of the evaluable patients achieved a PSA decrease of at least 50% after 4 cycles of cabazitaxel, nearly half and 60% of the patients had a PSA decrease of at least 30% and 20%, respectively. The change in global health status or in mean global health status showed no great differences between the patients with and without ≥ 50% PSA decrease. Likewise, no statistically significant difference between baseline and after 4 cycles could be seen for the global health status or for the mean global health. But regarding correlation results between changes in PSA after 4 cycles compared to baseline and global health status after 4 cycles a small inversely proportional relation was found (correlation coefficient -0.14): If the PSA value increases, the global health status after cycle 4 is lower. Hence, deterioration of global health status may be the result of disease progression rather than be caused by cabazitaxel therapy itself. Analysis of secondary objectives included evaluation of quality of life parameters of the EORTC questionnaire between baseline and cycle 4 of patients grouped into ≥ or < 50% PSA decrease. Comparing the median changes of EORTC Items between baseline and cycle 4 in the PSA subgroups (≥ or < 50% decrease) showed that CF and SF were not different between subgroups. But PF, RF and EF worsened for patients with < 50% PSA decrease. However, PA got better for patients with a PSA decrease of at least 50%. A trend to less pain was also seen by Bahl A et al. 2015 who investigated especially safety parameters of metastatic castration-resistant prostate cancer patients treated with cabazitaxel. Thus patients with a better PSA response have stabilization or even reduction of some tumor associated symptoms and functioning. None of the parameters - hematological toxicity, non-hematological toxicity, pre-existing symptoms - tested as possible predictors for improvement of global health status showed statistical significance.

	Analyses of PSA response, hematological toxicity, non-hematological toxicity, pre-existing symptoms, age and ECOG as possible predictive factors for the improvement of quality of life did not yield any statistically significant results. But analysis at the time points “baseline” and “after 4 cycles” of cabazitaxel therapy may be impaired by cabazitaxel cycles administered before patient informed consent was obtained. 49 patients received from 1-20 cycles (median: 6 cycles) before documentation of cabazitaxel therapy cycles in the NIS. However, due to the primary purpose of the study being the evaluation of QoL under treatment, and the design being non-interventional, these patients were not excluded from the analysis. Instead, the first QoL assessment in the study was considered as baseline, i.e. these prior cycles are not considered for evaluation. Analysis of special items of the EORTC questionnaire showed that social and cognitive functioning are not impaired by the disease or therapy, irrespective of PSA response. On the other hand, patients with < 50% PSA decrease had worse physical, role and emotional functioning after cycle 4 compared with patients showing ≥50% PSA decrease. For the latter patient group pain symptoms improved statistically significantly. All patients had an improvement of the symptom “diarrhea” under cabazitaxel therapy. 185 patients (35.11%) responded to therapy with 9 patients achieving complete and 176 patients yielding partial response as Best response. 206 patients (39.09%) had stable disease as best response. Nearly 10% of the patients did not respond to therapy. Median time to progression amounted to 8.3 months. At the end of the study period 135 of the 527 patients were documented to have died with a median overall survival of 16.8 months. Despite the non-selected patient population of the NIS these data are better than those found in the TROPIC clinical trial, in which a PFS of 2.8 months was seen. But a PFS > 8 months was also found by Bracarda et all. 2014, who analyzed patients in an Italian early access program. Differences in PFS may be in part due to different specification for analysis (given time points for examination or defined methods). But even median overall survival of the patients in this NIS is better compared to the TROPIC trial: 16.8 months compared to 15.1 months. One reason may be that in the TROPIC study chemotherapy was administered for a maximum of 10 cycles whereas in the NIS a maximum of cabazitaxel cycles was not defined. Thus cabazitaxel therapy administered until progressive disease, if possible, seems to have a positive effect on overall survival. Post-cabazitaxel treatments may also have added to the relatively good overall survival. Over 50% of the patients developed at least 1 AE. Main AEs were anemia, fatigue and diarrhea. Neutropenia and febrile neutropenia occurred in 20 and 19 of the patients, respectively. But many more patients, namely 268 patients, received at least one administration of G-CSF. More than 60% of the 1357 AEs recovered/resolved, 5% recovered/ resolved with sequelae and 4% had a fatal outcome. Thus toxicities were in general manageable. Additionally only about 6% of cabazitaxel cycles had to be applied with a reduced dose, mainly due to hematological toxicity. 174 patients (33%) had at least 1 SAE, mostly anemia in 4.55% of patients followed by general physical health deterioration and leucopenia in 3.61% and 3.42%, respectively. 54.7% of the 444 serious events were recovered, 12.8% were fatal. For the great majority (72.1%) of the events no action was taken. In contrast to the findings in this NIS, neutropenia (as AE and SAE) was the most common toxicity found in other clinical trials (DeBono JS et al. 2010, Bracarda S. et al. 2014). Since this special AE can be managed by use of G-CSF prophylaxis, it appeared to be that most of the physicians acted accordingly.

Conclusions:	Therapy with cabazitaxel is generally well tolerated and leads to improvement of especially pain symptoms for patients having at least 50% decrease of PSA after cycle 4. Patients with <50% decrease have statistically significant worse physical, role and emotional functioning compared to patients with ≥ 50% decrease. In general it could be shown that an increase of PSA value results in lower global health status after cycle 4. PSA response after 4 cycles (Yes/No), Toxicity (Yes/No), Pre-existing symptoms (Yes/No), Baseline ECOG (<2/≥2) and Age (<60 years /≥ 60 years) had no influence on quality of life and are therefore not considered to be predictors for improvement of global health status during cabazitaxel therapy. Side effects of cabazitaxel therapy were mainly of hematological nature, predictable and manageable. Of note, the results of the event-related parameters time to progression and overall survival assessed in this non-interventional study are higher than the results of the international, randomized controlled TROPIC trial had indicated. Altogether, cabazitaxel is an effective therapy option for mHRPC patients with manageable side effects.
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