Single Technology Appraisal (STA)

Abiraterone acetate for the treatment of metastatic hormone relapsed prostate cancer not previously treated with chemotherapy [ID503]

List of attachments:
Details of references from Figure 2 (32 docetaxel refs)
New Figure 2
302 model KM Curves and Cumulative Functions
302 model KM Curves with Number of Patients at Risk
302 model Parametric Function Parameters
302 model P values for Univariate Analysis and Full Model

Section A: Clarification on effectiveness data

A1. **Priority Question**: Please provide the *mean* survival in the BSC group in COU-AA-302 for the overall population and for the subgroup of patients from UK centres.

Janssen is unable to answer this question. Mean survival time in the COU-AAA-302 trial is essentially meaningless: as the majority of patients are still alive at end of follow-up and the trial is still on-going (note that 63.4% of patients in the AAP arm and 56.8% of patients in the PP arm were censored at the 3rd interim analysis, the latest data cut available), the calculated mean number of days of survival is by definition an under-estimation of the actual survival (and more so in the AAP arm compared to the PP arm, as more AAP-treated patients were still alive at data-cut). In order to calculate a mean, one requires the full data set. Consequently, in oncology clinical trials of this nature, the median overall survival is used as the measure of efficacy, as opposed to the mean.

A2. **Priority Question**: Please provide the *mean survival gain* of abiraterone (AAP) compared with BSC (PP) in COU-AA-302 for the overall population and for the subgroup of patients from UK centres.

Please refer to Question A1 above.

A3. **Priority Question**: Please provide the following data for the subgroup of people who received docetaxel following AAP or PP in each treatment arm respectively:

- rPFS results as reported in table 19
- OS results as reported in table 20
- Iterative parameter estimate and Rank preserving failure model HRs as reported in table 22.
- Time on docetaxel treatment

Janssen is unable to answer this question. The data requested is a *post-hoc* analysis of patients in the COU-AA-302 trial who subsequently receive docetaxel. This group of patients progressed more quickly, and therefore moved onto docetaxel treatment earlier than the other patients in the trial. This *post-hoc* analysis violates the principles of randomisation, and in effect, selects for the patients with the worst prognosis (ie those that progress quickly and move onto chemotherapy), which renders any interpretation of these results meaningless.

A4. Please provide references for all studies listed in Figure 2. For each reference please provide:

- the line of treatment in which AA, docetaxel or prednisone was taken
- the performance status or severity of symptoms of the trial population

Please provide the text which is hidden in the text boxes in Figure 2.

All of the references from Figure 2 are detailed in the document "Details of references from Figure 2". The tables contain information on line of treatment for AA, docetaxel, prednisone, although it should be recognised that all studies were in patients with mCRPC, so all patients would have received medical or surgical castration. PS and symptom information, when available, is also detailed in the attached document. Please see "New Figure 2" for full details of the hidden text. Please note that this new Figure 2 has some alterations to the numbers of studies in each category, as some studies had previously been categorised incorrectly.

A5. Please provide a full data extraction of the 32 RCTs included under post-ADT, pre-chemotherapy in Figure 2 that included docetaxel. This should include data on the population, intervention, comparators and primary outcomes. Please state whether each study is relevant to the decision problem and if not the reasons that the study is not relevant.

Information for the docetaxel pre-chemotherapy RCTs is contained in Table 1 of "Details of references from Figure 2".

In addressing this question, Janssen wishes to reiterate that this request is not relevant to the appraisal. We maintain that docetaxel is not a comparator to abiraterone acetate in this pre-chemotherapy setting. All docetaxel trials included in the above data extraction are in conducted in a population who are clinically indicated for chemotherapy – a population who are explicitly excluded from that covered under the terms of our marketing authorisation. Furthermore, to be consistent with the scope of a NICE technology appraisal, it is fundamentally important that the population and choice of comparator are consistent with the terms of the license. The exclusion of docetaxel is explicity clear, given our licensed wording, which states 'for the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) **in whom chemotherapy is not yet clinically indicated**'. This licensed indication clearly mandates that abiraterone acetate is to be used **prior** to the initiation of chemotherapy and in patients who are not yet candidates for it, thereby eliminating docetaxel as a relevant comparator.

However, for completeness, and to address this specific question, we provide an answer to this question below.

Of the 32 docetaxel trials that were conducted in patients who were chemotherapy naïve at the start of the study (Table 1), the majority were small phase II studies, and 31 of these studies compared docetaxel with other experimental regimens that are not relevant to the decision problem and therefore do not contribute to any network of evidence that could be used to compare abirateronewith docetaxel. Only one trial (TIPC [1]) compared docetaxel + prednisolone with prednisolone alone and can be used to construct a network, with the caveat that the population here and in the 302 trials are not comparable. The TIPC study ([1;2]) compared docetaxel + prednisolone with prednisolone alone (n=109) and the primary endpoint was ≥50% PSA reduction of the baseline level at 6 weeks; overall survival was a secondary endpoint. At study baseline for the TIPC study, 50% of patients had an ECOG status of ≥1, 51% of patients had a pain score of 1 or more (Scale 0-5) and approximately 47% of patients were receiving analgesics to treat pain. The major limiting factor for comparing outcomes from COU-AA-302 and the TIPC study, was that 56% of subjects in the

PP arm of the COU-AA-302 study went on to receive docetaxel, hence the outcomes observed from the PP arm of the COU-AA-302 study are not directly comparable to the PP arm of the TIPC study.

A6. Please explain why *radiographically assessed* progression-free survival (rPFS) was chosen as a primary outcome in this trial and not another definition of progression such as the disease state progression outcomes which were secondary outcome measures in COU-AA-302 (time to opiate use for cancer pain; time to initiation of cytotoxic chemotherapy, time to PSA progression or time to deterioration in ECOG PS). Please discuss any other measures of progression used in clinical trials for treatments for metastatic castrate resistant prostate cancer that were not used in COU-AA-302, and the reason why they were not measured in COU-AA-302.

rPFS is a commonly used efficacy endpoint in trials for prostate cancer (e.g. the PREVAIL study evaluating enzalutamide), and indeed other tumour types. It is an effective endpoint because it is easily measured using serial radiographic imaging; and it is objective, with validated assessment tools available (particularly RECIST [www.eortc.be/recist]). Hence, it was selected as a co-primary endpoint in the COU-AA-302 trial because the sensitivity and specificity of this measure is considerably higher than comparative measures used to assess progression free survival in prostate cancer, e.g. aspecific PSA rise.

Specifically, at the time Study COU-AA-302 was designed, there was a problem in using PFS endpoints in prostate cancer and a number of studies had failed with these endpoints. While the primary reason may have been lack of efficacy, there were issues with how the endpoints (composites) were defined. The Prostate Cancer Working Group developed criteria to address these issues. Study COU-AA-302 was the first successful pivotal study to use the definition of rPFS. Advice on the Study COU-AA-302 design was obtained from the US FDA in May 2008 and the Medicines and Healthcare Products Regulatory Agency (MHRA) in July 2008. Scientific Advice was subsequently sought from the CHMP in November 2008 (CHMP scientific advice procedure number EMEA/H/SA/985/1/FU/2008/SME/II) on a single clinical study (COU-AA-302) with co-primary endpoints (rPFS and OS), in which rPFS and secondary endpoints directly associated with clinical benefit could generate data to support a Conditional Approval. The CHMP concurred that the co-primary and secondary endpoints were appropriate and provided advice on the study design, which was incorporated into the final protocol.

rPFS is based on parameters defined by Prostate Cancer Working Group 2 (PCWG2) and is the time from randomisation to the occurrence of one of the following:

1. Bone scan with the appearance of ≥ 2 new lesions on the first assessment. A confirmatory bone scan obtained ≥ 6 weeks later shows ≥ 2 additional new lesions.
2. Soft tissue lesions measured by CT or MRI as defined in PCWG2 criteria.
3. Death from any cause.

rPFS, as defined above, is objective and there is biological plausibility that this correlates with clinical benefit. Progression of metastatic bone disease is of paramount importance to mCRPC patients since it is potentially associated with the onset of severe symptoms associated with skeletal morbidity: pathological fracture, pain, spinal cord compression or pre-emptive surgery. In addition, painful bone metastasis often requires radiation, chemotherapy or radionuclide therapy. Similarly, soft tissue metastasis is associated with clinically significant morbidity. Prevention or delay of disease progression in pelvic and para-

aortic lymph nodes reduces the risk for urinary tract obstruction. Liver metastasis, once present, could lead to organ failure and death.

The secondary outcome measures used in COU-AA-302 (ie time to opiate use for cancer pain; time to initiation of cytotoxic chemotherapy, time to PSA progression or time to deterioration in ECOG PS) were not appropriate to include as co-primary endpoints because they have not been validated as such in other phase III trials in mCRPC, and would not be accepted as primary endpoints to support licensing submissions with authorities such as the FDA and EMA. They are also less objective than rPFS: for example, determining when a patient needed to start opiate analgesia or cytotoxic chemotherapy would vary by clinician, thereby leading to inconsistently reported measures.

A7. The methods for iterative parameter estimate (IPE) and rank preserving failure time model (RPFT) reported in table 22 are not included in the methods section. Please provide a description of this methodology.

Switching is common in clinical trials in that ITT results can be heavily biased, per-protocol analysis is often not appropriate where switching occurs, and adjustment is not routinely applied. In the COU-AA-302 trial, adjustment for switching was applied (Table 22 in the main submission) as a matter of course. Notwithstanding this, the impact of treatment switching was minimal in that only 3 patients crossed-over from PP to AAP in the 3rd interim analysis (55% data cut).

Rank Preserving Structural Failure Time models (RPSFT) is a method developed by Robins and Tsiatis (1991) for survival analysis where patients can switch from the control group to the treatment group. The principle is to compare survival times that would have been observed if no treatment had been administered (counterfactual). Examples of counterfactual outcomes include the following:

– the treatment that patient i would have had if they had been randomised to treatment A

– the outcome that would have been observed if patient i had received treatment A

In the context of a two arm trial with treatment A (experimental intervention) and treatment B (no treatment), each patient (i) has an observed time to event or censoring time T(i). Each patient also has a counterfactual event time Ui which is the event time which would have been observed if no treatment had been received. Ti is equal to Ui in control arm patients who do not switch treatment, meaning that their counterfactual event time is observed. Ui is unobserved for all other patients. The patient's randomised treatment arm Ri is equal to A or B; the assumption being made that Ui is independent of Ri due to randomisation balance.

This method makes a number of assumptions. Specifically, the rank-preserving assumption may not be reasonable due to biological factors in certain patients who either experience more or less benefit than other patients on different types of treatments. Furthermore, it may not be possible to test using real data for any contravention of this assumption. Additionally, the same effect is assumed for those patients switching to a treatment as for those initially allotted to it.

The Iterative parameter estimate (IPE) method as described by Branson and Whitehead (2002) is used to estimate the treatment effect and its associated confidence interval under an Accelerated Failure Time model (AFT). This retains all patients to the treatment group to

which they were initially randomised. The authors build on the method put forward by Robins and Tsiatis above by substituting a test-based estimation for a likelihood-based analysis. This method employs similar assumptions as to those highlighted in the Robins and Tsiatis method (1991), e.g. common treatment assumption and extends the method with an added assumption to the effect that survival times follow a parametric distribution. The authors suggest that given a real dataset, a parametric form is chosen which fits the observed data most closely.

Using an AFT model, the authors derive an initial estimate of the treatment effect by fitting a parametric failure time model to the original unadjusted ITT data. The failure times of switching patients are subsequently re-estimated using this with the iterative procedure continuing until the new estimate is said to have 'converged' i.e. when it is very close to the previous estimate.

Both RPSFT and IPE are considered to be consistent under conditions alluded to above although IPE has 100% successful estimation, returns estimates of the Weibull parameters and results are robust to additional censoring. The Cancer Research Clinical Trials Unit (CRCTU) at the University of Birmingham recommend that the IPE method of Branson and Whitehead (2002) be used in the analysis of clinical trials that feature treatment switching.

A8. Please provide an estimate of the number of patients who currently may receive docetaxel in UK clinical practice whose symptoms meet the following criteria:

- BPI-SF question # 3 score of 0-3
- ECOG PS grade 0-1
- PSA progression following discontinuation of antiandrogen treatment (using the definition of PSA progression used in COU-AA-302)

We are unaware of any available data that can provide a reliable estmate of this. In addition, we would again reiterate that a prerequistite for treatment with abiraterone in the pre-chemotherapy setting is that a patient is not yet clinically indicated for treatment with docetaxel, therefore the number of patients receiving docetaxel is not relevant to the current decision problem.

A9. Section 6.3.3 describes the patient population in the COU-AA-302 study. Is the population who were eligible to participate in COU-AA-302 mutually exclusive from the population who could receive docetaxel in clinical practice?

- If yes, please state which of the eligibility criteria would exclude patients who may receive docetaxel in routine UK clinical practice from participating in COU-AA-302.
- If no, please state the number of patients included in COU-AA-302 for whom docetaxel may have been considered suitable in routine UK practice

The populations are not 100% mutually exclusive because the population determined by the license was requested by the regulators on the basis of the study results, rather than as a result of the study being designed to specifically for patients who are not yet suitable for docetaxel. This is an important nuance to be aware of.

However, the COU-AA-302 trial population inclusion criterion 7 states "Patients who are asymptomatic or mildly symptomatic from prostate cancer, and a score of 0-1 on BPI-SF Question #3 (worst pain in last 24 hours) will be considered asymptomatic, and a score of 2-3 will be considered mildly symptomatic". This inclusion criterion would select for a group of patients who would not routinely be treated with docetaxel in UK clinical practice, as docetaxel is usually reserved for patients who have more significant symptoms. In patients

who are asymptomatic or mildly symptomatic, the risks of docetaxel treatment (i.e. associated toxicity) would be considered to outweigh the benefits in most patients. This is supported by guidelines as outlined in section 2.6 of our submission.

Notwithstanding the above, the most important differentiating factor between those patients that would receive docetaxel and those that would receive abiraterone acetate in clinical practice is our licensed indication in the pre-chemotherapy setting. The licensed indication is clearly mutually exclusive from the population who could receive docetaxel in that the license states that abiraterone is for use in patients **who are not yet clinically indicated for chemotherapy**.

A10. The 3rd interim analysis was after unblinding. Please explain the potential consequences of unblinding for the primary outcomes, reporting of adverse events, treatment discontinuations and all secondary outcomes.

As mentioned in sections 1.6. and 6.3.8., distinct cross-over as opposed to patients receiving subsequent therapies following respective study interventions amounted to only three patients crossing over from PP to AAP, and only a maximum of 52 days before the 3rd interim analysis.

Accordingly, any effect on all outcomes is expected to be minimal. The relative lack of impact may be observed in Table 22 in the submission where the hazard ratio calculated using both the Iterative Parameter Estimate and the Rank preserving failure time model is 0.78 (95% CI: 0.63, 0.93 and 0.64, 0.95 respectively) which are comparable to 0.79 (0.66, 0.96) in the ITT 3rd interim analysis population.

Section B: Clarification on cost-effectiveness data

B1. **Priority Question**: **HRQoL- post docetaxel treatment**
Page 113 of the MS states that "*The post-docetaxel utility increment of 0.046 (derived from COU-AA-301 trial data) was not applied since the majority of patients were assumed to already have been receiving AAP in this setting. Hence, it was assumed this utility gain was captured in the UK mCRPC Utility Study and to apply it, would be double-counting. These assumptions were explored in sensitivity analyses".* This is inconsistent with the modelling in TA259, as in that submission an on treatment utility gain was applied to the Abiraterone comparator. Also, the sensitivity analysis referred to in the quoted text is not reported in the methods section (Table 62), nor in the results (Table 73).

In TA259, the two comparators requested by NICE were mitoxantrone and BSC. In the economic model, an on treatment utility gain was only applied to abiraterone and mitoxantrone. A utility gain was not applied to the BSC comparator. To be consistent with the modelling approach in TA259, an on treatment utility gain has not been applied for BSC in this submission.

An on treatment utility gain was not applied for abiraterone in the model as at the time the UK mCRPC utility study was conducted abiraterone was the only NICE-approved treatment for patients who progressed on or after a docetaxel-based chemotherapy regimen.
As abiraterone is now widely used in the UK in this setting, the assumption was made that patients who took part in the utility study were likely to be already receiving abiraterone and therefore the on treatment utility was already captured in these patients. To add the on treatment utility increment of 0.046 (derived from the COU-AA-301 trial) would therefore overestimate the utility gain associated with abiraterone in the post-chemotherapy setting.

a. Please provide a description of the treatments received by the people in the mCRPC utility study post ADT.

As indicated in our submission, no medication use was recorded in the UK mCRPC Utility Study, apart from chemotherapy treatment as part of the screening/eligibility criteria. Rather, the study aimed to collect health utility values for mCRPC stratified by treatment phases, not by treatment.

b. Please explain why the fact that the majority of patients in the UK mCRPC Utility Study were assumed to have already been receiving AAP prohibited the use of differential utility scores for AAP vs BSC in the post-docetaxel phase.

Janssen accepts this is a valid scenario to explore and has presented the scenario results in Table 1 below.

c. Please provide the results of a scenario using the value resulting from the UK mCRPC Utility Study as the utility for patients receiving AAP and subtract the 0.046 for patients receiving BSC in the model

Table 1: Results with 0.046 subtracted from BSC (PP) post-docetaxel

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.56	46,917

B2 **Priority Question: utility value estimates post docetaxel**
In TA259 the utility value at baseline at which time patients had received docetaxel was based on FACT-P data from COU-AA-301. This utility value is higher than the utility value estimated from the UK mCRPC utility study for the post docetaxel treatment phase in the current submission. Please provide the reason for this difference.

The baseline utility value used in TA259 was 0.78. The equivalent treatment phase in the UK mCRPC utility study reported a utility of [redacted]. The discrepancy in these utility values could be attributed to a number of reasons:

1. The TA259 value was FACT-P mapped to EQ-5D from patients in an RCT whereas the UK mCRPC utility study used EQ-5D directly
2. The COU-AA-301 study population may have differed from the UK mCRPC utility study population. The utility study was designed to specifically to derive utility data for mCRPC patients to inform the current submission in the pre-chemotherapy setting, whereas the COU-AA-301 trial was designed to study patients in the post-chemotherapy setting.
3. The FACT-P scores in COU-AA-301 were all elicited at the start of the study, when patients had to meet the inclusion criteria prior to the commencement of study medication. In the utility study, the inclusion criteria were not controlled in this way and thus patients could have been further along their period of progression.

Notwithstanding this, we recognise the validity of the 0.78 utility value from TA259, and therefore we have re-run the economic model using this value in two different scenarios below.

The first adopts the utilities as shown in Table 2 below, whereby the AAP post-docetaxel on treatment utility increment of 0.046 is applied, consistent with methodology used in the TA259. Results from this analysis are presented in Table 3.

Table 2: Scenario 1 adopting the utility value of 0.78 post-docetaxel

Treatment Phase	**Utility**
BSC (post-docetaxel)	0.78
BSC (PP post-docetaxel)	0.78
AAP (post-docetaxel)	0.826 *(i.e. 0.78 + 0.046)*

Table 3: Results from Scenario 1 adopting the utility value of 0.78 post-docetaxel

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.55	48,316

The second possible scenario deducts the AAP post-docetaxel on treatment utility increment of 0.046 from the comparator arm, consistent with the methodology previously requested under Clarification Question B1. The utilities for this scenario are shown in Table 4. Results from this analysis are presented in Table 4.

Table 4: Scenario 2 adopting the utility value of 0.78 post-docetaxel

Treatment Phase	**Utility**
BSC (post-docetaxel)	0.78
BSC (PP post-docetaxel)	0.734 *(i.e. 0.78 – 0.046)*
AAP (post-docetaxel)	0.78

Table 5: Results from Scenario 2 adopting the utility value of 0.78 post-docetaxel

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremental QALYs	ICER, £/QALY
BSC (PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.55	47,936

Whilst both scenarios result in a moderate increase in the ICER, there is little discrepancy between the two scenarios and hence supports the rationale that adopting 0.78 as the post-docetaxel baseline utility has little impact on the ICER.

B3 **Priority Question: HRQoL- utility increment on abiraterone**.
The concept of the on-treatment utility increment in favour of Abiraterone seems questionable as it is clear that AAP leads to significantly more adverse events (both overall and grade 3/4) than BSC. The submission states that the utility increment assigned to patients in the AAP was to capture *"patient benefits experienced on AAP compared with BSC (PP) with respect to pain and fatigue"* (MS P. 94) but the impact of other adverse events on HRQoL were not considered. Although it is possible that patients have a higher HRQoL during treatment with AAP, in spite of experiencing more adverse events, the choice of not incorporating the impact of adverse events on HRQoL is not sufficiently justified. In addition, it appears as if the effect of varying rates of grade 3/4 AEs is only taken into account in the costs in the docetaxel phase. So, the AE difference between AAP and BSC (PP) is not accounted for, in either HRQoL, or in costs.
Therefore:

a. Please demonstrate how the utility increment for abiraterone reflects the benefits experienced on abiraterone compared to BSC with respect to pain and fatigue in COU-AA-302

Findings from the COU-AA-302 trial indicated that the AE rates were similar between arms. Treatment-emergent AEs of any grade occurred in 99.3% of AAP patients and 97.0% of PP patients [3]. Treatment-emergent grade 3/4 AEs occurred in 49.3% of AAP patients and 43.5% of PP patients [3]. The detailed AE incidence of all grades, and grade 3/4, are shown in Table 5.

Table 6: AEs of interest reported in the COU-AA-302 study (third interim analysis - 22 May 2012, 55% data cut-off)

Adverse event	AAP (n = 542), %		PP (n = 540), %	
	All grades	Grades 3/4	All grades	Grades 3/4
Fatigue	39.7	2.4	34.6	1.9
Fluid retention/oedema	29.3	0.4	24.1	0.9
Hypokalaemia	17.2	2.6	12.8	1.9
Hypertension	21.8	4.2	13.5	3.1
Hyperglycaemia	8.7	2.6	8.0	2.0
Weight gain	5.2	0	7.2	0
Cardiac disorders	17.3	5.2	14.8	2.4
ALT increased	12.0	5.5	5.0	0.7
AST increased	11.1	3.1	4.8	0.9
Neuropathy	2.0	0.0	1.1	0.0
Neutropaenia	0.6	0.4	0.7	0.4
Febrile neutropaenia	0.0	0.0	0.2	0.2
Thrombocytopaenia	2.0	0.4	1.5	0.7
Anaemia	11.3	2.4	9.6	1.9

Oedema		0.4		0.9
Arthralgia	29.3	1.8	24.4	1.9
Asthenia	8.7	0.2	8.7	1.3
Diarrhoea	23.4	1.1	18.1	0.9
Dyspnoea	12.5	2.6	10.2	0.9
Nausea	24.0	0.9	23.0	0.2
Vomiting	14.2	0.7	0	0

Source: [3].

In regression analysis of the COU-AA-302 trial, both grade 3/4 AEs and treatment were significant predictors of mapped utility values (Table 6). Model 2 directly estimates the utility effect of being on treatment (i.e. AAP). Any grade 3/4 AE is excluded because it is a mediating variable impacted by treatment. Therefore, in Model 2, the utility increment of 0.02126 reflects the direct effect of treatment, implicitly considering both the benefit from the treatment as well as the impact of AEs. If AE is added as a covariate to Model 2, the treatment effect of AAP vs PP remains unchanged (i.e. 0.024). This may also indicate that AAP patients had only slightly more AEs than PP patients.

Table 7: Results of multiple regression analyses: change from baseline in utility score over time

	Predictors	Model 1		Model 2	
		Baseline utility and any AE		Baseline utility and treatment	
		Estimate	p value	Estimate	p value
All Patients	Intercept	0.2198	<0.0001	0.1797	<0.0001
	Treatment group: AAP vs PP			0.02126	0.0014
	Baseline utility score	–0.2835	<0.0001	–0.2658	<0.0001
	Any Grade 3/4 AE	–0.06487	<0.0001		

AA, abiraterone acetate; AE, adverse event; BSC, best supportive care; PSA, prostate-specific antigen; ITT, intention-to-treat.

Of note, the approach used to determine the utility with AAP is consistent with the approach used in TA259 that was accepted by NICE. This utility increment is also consistent with the benefit of enzalutamide, as observed in the AFFIRM trial for enzalutamide versus placebo (TA Guidance ongoing).

In addition, the cost impact of AAP and BSC (PP) for AEs have been captured implicitly by the unplanned MRU cost based on the COU-AA-302 data. The unplanned MRU data captured the resource use from symptoms of disease or other AEs including treatment toxicity. To assess the differences in unplanned MRU and associated costs between treatment arms we conducted a statistical analysis of these data. Overall, the total resource use while patients were receiving treatment was similar between AAP and BSC (PP). When the treatment was tested as a predictor of MRU, utilisation was was higher for the AAP arm; however, the difference was not statistically significant (p=0.1298), especially when treatment duration was included in the analysis (p=0.3496). On the contrary, when analysed independently, treatment duration was a predictor of MRU with statistical significance (p=0.0017). In summary, these results indicate that MRU while on treatment was associated with treatment duration but not with type of treatment. Based on this result, the monthly unplanned MRU cost was applied to both treatment arms for the duration on treatment. AAP patients have higher total unplanned MRU cost because of longer treatment duration.

The approach of using trial based MRU for unplanned events (progression and AE costs is consistent with the approach used in (TA259).

The same rationale applies to the unplanned MRU cost inputs for the post-docetaxel treatment.

Table 8: Regression analysis to assess the impact of treatment and treatment duration on unplanned MRU cost

Analysis Of Maximum Likelihood Parameter Estimates (Treatment only)								
Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	6.7779	0.2913	6.2069	7.3489	541.23	<.0001
Treatment	AAP	1	0.6741	0.4450	–0.1981	1.5464	2.29	0.1298
Treatment	PP	0	0.0000	0.0000	0.0000	0.0000	.	.
Scale		1	0.2104	0.0231	0.1696	0.2609		
Analysis Of maximum likelihood parameter estimates (treatment and treatment duration)								
Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.8163	0.3873	5.0573	6.5753	225.58	<.0001
Treatment	AAP	1	0.4165	0.4452	–0.4561	1.2890	0.88	0.3496
Treatment	PP	0	0.0000	0.0000	0.0000	0.0000	.	.
Treatment duration_weeks		1	0.0154	0.0054	0.0049	0.0258	8.24	0.0041
Scale		1	0.2212	0.0244	0.1782	0.2745		
Analysis Of Maximum Likelihood Parameter Estimates (Treatment duration only)								
Parameter		DF	Estimate	Standard Error	Wald 95% Confidence Limits		Wald Chi-Square	Pr > ChiSq
Intercept		1	5.9504	0.3696	5.2261	6.6748	259.23	<.0001
Treatment duration_weeks		1	0.0165	0.0053	0.0062	0.0268	9.83	0.0017
Scale		1	0.2200	0.0242	0.1772	0.2730		

* GLM regression analysis shows that the total cost per PFS state is independent of treatment group and disease free duration

b. Please provide the observed FACT-P scores from COU-AA-302 equivalent to all treatment phases in the model, per treatment, for the ITT population.

The COU-AA-302 trial did not collect FACT-P data beyond the point of disease progression (treatment discontinuation). The FACT-P scores by cycle in the COU-AA-302 trial are provided in Figure 4, Table 8 and Table 9.

Figure 1: FACT-P (total scores) during the COU-AA-302 trial by treatment arm

[redacted]

Table 9: FACT-P (total scores) during the COU-AA-302 trial by treatment arm

[redacted]

Table 10: BPI-SF and FACT-P (total and subscores) during the COU-AA-302 trial by treatment arm

c. Please provide utility decrements (FACT-P and/or EQ-5D) for all AEs separately (based on ITT population), either by performing a regression or by finding utility decrements in the literature.

Sample sizes for individual clinically significant AEs i.e. grade 3/4 are too small for meaningful analysis. Rather, we used a regression analysis (as described above) to evaluate the impact of AEs on utility. In regression analysis of the COU-AA-302 mapped utility data exploring the baseline utility over time, the AE decrement effect is –0.06487.

In order to make a comparison of the disutility of 0.065 associated with a grade 3/4 AE (as calculated by analysis of the COU-AA-302 trial data), we performed a targeted review of the solid tumor literature (i.e. non-systematic) to get an understanding of the range of values and elicitation techniques. We found numerous sources for AE disutilities which apply a variety of methods [4-11]. Elicitation methods included the EQ-5D, SG, the QWB self-administered questionnaire, TTO, and the visual analog scale (VAS) with SG. Disutility values for specific AEs varied (Table 10). For example, the disutility values located for febrile neutropaenia ranged from 0.09002 to 0.257. Some AEs were not located in the search, including thrombocytopaenia, hypokalaemia, and oedema. In the AAP post-docetaxel submission, the disutility per episode of any grade 3/4 AEs was reported as 0.078. Overall, our calculated disutility value of 0.065 appears to be consistent with the range of values calculated for grade 3/4 AEs of all types, and given the heterogeneity of available results, no other data sources appear to be superior.

Table 11: Disutility of AEs from the published literature

Source	[4]	[5]	[6]	[10]	[8]	[11]	[7]	[9]
Elicitation method/tool	EQ-5D	SG	SG	TTO	EQ-5D	SG	VAS and SG	TTO
Disease Area; AE Grade	NSCLC; Unknown	MBC; 3/4	CLL; Unknown	Chemotherapy-related anaemia	NSCLC; Unknown	NSCLC; "Severe"	NSCLC; Unknown	MRCC; 3
Diarrhoea	0.126	0.103					0.0468	0.261
Nausea	0.136						0.04802	0.255
Vomiting		0.103					0.04802	
Neutropenia	0.127						0.08973	
Febrile neutropaenia	0.257	0.15					0.09002	
Neuropathy	0.145							
Fatigue		0.115					0.07346	0.204
Asthenia		0.115						
Thrombocytopaenia								
Anaemia			0.09	0.25–0.38				0.119
Arthralgia						0.069		
Hypokalaemia								
Oedema								
Hypertension								0.153
Dyspnoea					0.29	0.05		

AE, adverse event; CLL, chronic lymphocytic leukaemia; EQ-5D, EuroQol 5-Dimension; MBC, metastatic breast cancer; MRCC, metastatic renal cell carcinoma; NSCLC, non-small cell lung cancer; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.

d. Adapt the model by
- removing the on treatment utility increment,
- incorporating utility decrements for each separate AE,
- incorporating per-event costs for AEs for the pre- and post-docetaxel treatment phases as well.

The model was adapted according to the above request and the cost effectiveness results are presented in Table 11 below.

Table 12: Scenario analysis results

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremenal QALYs	ICER, £/QALY
BSC(PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,383	0.62	0.52	50,880

Three additional scenario analyses were conducted to demonstrate the effect of implementing each consecutive model adaptation. Results are presented in Table 12. Given that utility decrements for AEs are already considered in the treatment effect, incorporating utility for each separate estimate is not appropriate as explained above. Also, incorporating costs from AEs in the pre- and post-docetaxel state is not appropriate either as the trial based analysis of unplanned MRU already considers these costs (see explanation above).

Table 13. Scenario analyses applying requested adaptations individually

	Total costs, £	Total LYG	Total QALYs	Incremental costs, £	Incremental LYG	Incremenal QALYs	ICER, £/QALY
o Removing the on treatment utility increment							
BSC(PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.53	50,120
o Incorporating utility decrements for each separate AE for all treatment phases							
BSC(PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,404	0.62	0.56	47,415
o Incorporating per-event costs for AEs for all treatment phases							
BSC(PP)	[redacted]	[redacted]	[redacted]				
AAP	[redacted]	[redacted]	[redacted]	26,383	0.62	0.57	46,686

B4. **Priority Question**: **Estimation of prediction equations (Appendix 16 MS) - *Issues that may introduce bias and need additional analyses and an updated model***

a. Figure 37 shows that the time to discontinuation is similar in the selected group used in the model (analysable data set of 902 patients with information on baseline characteristics) and the ITT group for best supportive care but that time to discontinuation appears higher for abiraterone in the modelled group compared with the ITT population. The manufacturer concluded that times to APP/BSC (PP) discontinuation for the 902 people with analysable data are similar to the ITT group.

o Please provide the results of analyses to determine the similarity of TTD and OS in the ITT group and the selected group of 902 people used in the model.

The COU-AA-302 trial enrolled 1088 patients (546 AAP and 542 PP). A total of 902 patients (459 AAP and 443 BSC (PP)) from the COU-AA-302 trial were used in the economic model. A total of 186 patients (87 for AAP and 99 for BSC (PP)) were excluded due to missing baseline data that were used as predictors (e.g. BPI). A logrank test was conducted to compare the time to treatment discontinuation (TTD) for ITT population and analysed patients. The p-value is 0.7481 for the AAP group and 0.7745 for the BSC (PP) group, indicating that there is no statistically significant difference in terms of TTD between the ITT population and analysed patients. A similar analysis was conducted for OS and no statistically significant difference was identified either (p value 0.3117 for the AAP group and 0.6328 for the BSC (PP) group).

By visually analysing these graphs (Figure 5 to Figure 8) , OS KM curves are identical and analysed patients who were treated with AAP had slightly longer TTD (but not statistically significant), which implies that results of the model are conservative given that treatment duration is slightly longer, contributing to slightly higher cost for model population vs ITT population.

Figure 2: Comparison of Analysed patients (DES) versus ITT population: TTD, AAP arm

[redacted]

Figure 3: Comparison of Analysed patients (DES) versus ITT population: OS, AAP arm

[redacted]

Figure 4: Comparison of Analysed patients (DES) versus ITT population: TTD, BSC(PP) arm

[redacted]

Figure 5: Comparison of Analysed patients (DES) versus ITT population: TTD, BSC(PP) arm

[redacted]

- Please provide an updated version of all prediction equations incorporating all ITT patients (with censoring at the time patients deviated from the pathway specified in the model; thus including patients with missing baseline data), with assigned treatment (i.e. BSC (PP), AAP) included as only covariate if significant at p-value of 0.10 (thus excluding other baseline characteristics as this information is missing in a subset of the patients). For this purpose, please perform the model selection (exponential, Weibull, log-normal or log-logistic distribution) as performed for the prediction models described in Appendix 16 and provide the AIC and BIC statistics.

The ITT population was used in the model/parametric function selection. Therefore, AIC and BIC presented in the report were based on ITT patients. Predictors were then selected based on best fit/selected parametric functions. Patients were excluded due to missing baseline predictors at this stage. Please refer to the attached excel file named “302 model Parametric Function Parameters” for the prediction equations with only treatment as a covariate. Please note that each sheet contains one event (e.g. time to AAP/BSC(PP) discontinuation).

- Please provide graphs comparing the observed KM-curve for these updated prediction equations (from the ITT population with censoring at the time patients deviated from the pathway specified in the model). Please add the number of patients at risk to the graphs (reported per 0.5 year).

Please refer to the attached excel file named “302 model KM Curves and Cumulative Functions” for the graphs comparing observed KM curve and the parametric functions based on ITT population. Please refer to attached excel file named “302 model KM Curves with Number of Patients at Risk” for the KM graphs with the number of patients at risk. Please note that each sheet contains one event (e.g. time to AAP/BSC (PP) discontinuation).

- Please provide updated cost-effectiveness results and an updated version of the DES model with these updated prediction equations. For this purpose, the proportion of patients for whom docetaxel treatment is unsuitable might be calculated from observed data from the COU-AA-302 trial (instead of based on ECOG PS <2).

The model adopted a treatment pathway approach, which uses a series of equations to project patient experience with different stages of the disease and OS. These equations are connected through predictors. For example, the time to docetaxel start depends on how long the patients were treated in the AAP/BSC (PP) phase. Without these predictors, a given patient’s experience with different stages of the disease would be totally independent, which contradicts real world clinical practice. In real life, what happens to a patient earlier in their disease impacts what happens to them later on. Hence these predictors are integral to the DES and to remove them would generate incorrect results, as the model predictions and the trial observations would not calibrate.Therefore, we strongly believe that removing the predictors from the prediction equations is not appropriate. Figure 9 clearly shows that when predictors are removed, the projected OS is not consistent with trial observations. Henceforth, results from such a simulation model would be invalid.

Figure 6: Predicted OS Based on Equations without Predictors vs 302 Trial OS KM Curve

[redacted]

b. For the selection of covariates in the prediction equations, it is stated (Appendix 16): *"A p value of 0.10 was used to decide which variables had a univariate association. Significant predictors were then combined in a multivariate model, which was then manually trimmed to exclude predictors that become non-significant (p>0.1)."* However some covariates with a higher p-value than 0.10 were included in the model.

- Please provide the prediction equations and updated cost-effectiveness results when excluding the covariates and interaction terms with a larger p-value than the apprehended threshold of 0.10.
- Please provide an updated version of the DES model with these updated prediction equations.
- Please provide graphs comparing these prediction equations and the observed KM-curves (from the ITT population with censoring at the time patients deviated from the pathway specified in the model). Please add the number of patients at risk to the graphs (reported per 0.5 year).

In the model, the p-value of 0.10 was used as a cut-off with only a few exceptions.

Time from post-docetaxel treatment end to death, in which p=0.1899: We keep treatment as a predictor in this equation because the Kaplan Meier graph (Figure 10) shows clear survival difference between the two treatment groups and only 125 patients are included in this analysis (other patients had not reached this point in 302 trial) with 71 events. We believe the treatment effect is not statistically significant due to the small sample size.

Figure 7: KM Curve for Time To Death After Post-Docetaxel Active Treatment End

[redacted]

Other variables that are above the 0.10 p-value cut-off are those that are not independent variables (e.g. continuous variables that were broken into categorical variables to avoid extreme predictions). Some categories were not statistically significant but the overall effect of the categorical variables retained in the model was statistically significant at the 0.10 level.

In Time to AAP/BSC (PP) end, BPI 0-1 becomes non-significant only when the interaction terms are added to the model, otherwise in both the univariate model and in the model with other significant predictors but without interactions terms, BPI 0-1 is statistically significant (p<0.0001 in the univariate model and 0.004 in the model without interaction). In the model including interaction terms, the recommendation is to include main effects regardless of their significance after the interaction term is added. For this reason, the main effect (i.e. BPI 0-1) was retained in the final equation.

c. The DES model does not include the possibility of dying during AAP and BSC (PP). As some patients (N=5) died before AAP or BSC (PP) treatment end, it is appropriate to included probabilities to die during all phases in the model. The same applies for death during post-docetaxel treatment.

- Please provide an updated DES model that incorporates the possibility of dying during AAP or BSC (PP) treatment and during post-docetaxel treatment and updated cost effectiveness results.,
- Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to these updated prediction equations. Please add the number of patients at risk to the graphs (reported per 0.5 year).

In the 302 trial (55% of events data cut), only 5 patients died while on treatment (3 in the AA arm and 2 in the placebo arm); rather, death occurs after treatment stop. Therefore, prediction equations were developed to predict time to death from the time of AAP or BSC (PP) treatment discontinuation. Since so few deaths were recorded while on treatment, it was not possible to create a competing risk equation for death versus treatment stop, instead these deaths were considered in the derivation of survival post AAP/BSC (PP) treatment discontinuation (with time of death post AAP/BSC (PP) discontinuation set to 1 day for these 5 patients).

Similarly, while patients were treated with post-docetaxel active treatment, there were only 10 deaths for patients originally enrolled in the BSC (PP) arm and 3 deaths for the AAP arm, with most deaths occurring after discontinuation of post-docetaxel active treatment. The limited number of death events while on post-docetaxel treatment was not enough to power the statistical analysis to create a competing risk equation for death versus treatment discontinuation. As in the pre-docetaxel setting, prediction equations were developed to predict the time to death from the time of post-docetaxel active treatment discontinuation. The deaths observed while on post-docetaxel treatment were considered by setting the time of death to day 1 after discontinuation of post-docetaxel active treatment.

B5. **Priority Question**: **Estimation of prediction equations (Appendix 16 MS) - *Issues that are unclear or needed to examine the validity of the current model***

a. In appendix 16 (P298-299) it is stated: *"Observed Kaplan–Meier curves and cumulative hazard functions were examined graphically. If the exploratory analysis indicated that the shape of the cumulative hazard was similar in both treatment arms, then the two arms were modelled together and a treatment indicator was included as a predictor in the model; otherwise, each treatment arm was modelled separately."*

- Please provide the observed Kaplan–Meier (KM) curves and cumulative hazard functions for all equations that were used to perform the graphical examination.

Please refer to the attached excel file named "302 model KM Curves with Number of Patients at Risk" for the observed KM curves and cumulative hazard functions for all equations tested. Please note that each sheet contains one event (e.g. time to AAP/BSC (PP) discontinuation).

- Time from AAP/BSC (PP) end to death, unlike all other prediction equations, was estimated separately by arm (see Table 148). Please provide an updated version of the 'Time from AAP/BSC (PP) end to death' prediction equations using a single prediction equation for both arms (AAP and BSC (PP)) and a coefficient for treatment arm.

Separate prediction equations were estimated for time from AAP/BSC (PP) end to death because a single equation with treatment as predictor did not provide a good fit. Please refer to attached excel file named "302 model Parametric Function Parameters" sheet "TTDeathBeforeDox" for the estimates of the coefficients when a single equation is used.

b. It is unclear which candidate predictors are used for which prediction equation. Please list for each prediction equation separately, all candidate predictors and mark those that were significant in the initial univariate selection and also mark those that were significant in the multivariate model. In addition provide for each candidate predictor the p-value in the univariate selection and if applicable the p-value in the multivariate model.

Please refer to the attached excel file named “302 model P values for Univariate Analysis and Full Model” for the candidate predictors tested in the equations, their significance in univariate analysis and multivariate analysis. Please note that each sheet contains one event (e.g. time to AAP/BSC(PP) discontinuation).

c. Considering model selection for the prediction equations:

- How were the models selected in case the AIC and BIC were inconsistent on the best-fitting model?

AIC and BIC were not consistent in two cases: 1) time from docetaxel end to post-docetaxel treatment start; 2) time from post-docetaxel treatment end to death. In both cases, Weibull was finally selected. For time from docetaxel end to post-docetaxel treatment start, Weibull has the best AIC while exponential has the best BIC. As exponential is a special form of Weibull, we selected Weilbull. For time from post-docetaxel treatment end to death, exponential has the best BIC and lognormal has the best AIC. Weibull is used in this case given the small difference in AIC and BIC across the parametric functions and is clinically more plausible since the long tail of a lognormal distribution is often criticised for offering unrealistic survival benefit.

- Please clarify whether the AIC and BIC statistics reported in Table 142 were based on the prediction equations with selected covariates included? If not, please provide these statistics.

The model/parametric function selections were performed without considering predictors other than treatment. Therefore, AIC and BIC presented in the report were based on equations without predictors (except including treatment). Once the parametric functions were selected, predictors were then tested based on best fit/selected parametric functions. AIC and BIC were not estimated for equations with predictors, since only selected parametric functions were used for adding predictors. We do not expect that including predictors to parametric functions will change the decision on the parametric function selections.

- Please also clarify how the validity of the extrapolation was assessed, as fit to the observed data is not necessarily a good indication.

To test the validity of the projected survival curves, the predicted OS was first compared against the 302 trial KM curves to make sure the “trial period” prediction was accurate. In Figure 11, predicted OS is based on treatment pathway observed from the COU-AA-302 trial. These figures show that model predictions were consistent with COU-AA-302 trial results during the trial period.

Figure 8: Overall survival based on observations from COU-AA-302 trial

[redacted]

AAP, abiraterone acetate plus prednisolone; KM, Kaplan–Meier; PP, placebo plus prednisolone.

To further validate the predicted long-term survival, we used the phase III trial of sipuleucel-T (IMPACT trial). The IMPACT trial was conducted in a similar population as the 302 trial, and followed patients over 5 years. The comparison shows that the predicted 5-year survival of the BSC (PP) arm from the model is consistent with the observed 5-year survival rate (~10%) from the IMPACT trial.

Figure 9: OS comparison of model prediction and the IMPACT Trial results

[redacted]

Sipuleucel-T survival graph source: Provenge drug prescribing information (http://www.dendreon.com/prescribing-information.pdf).

d. In appendix 16 it is stated: *"Commonly used distributions such as exponential, Weibull, log-normal, and log-logistic were tested, and the one yielding the closest fit to the observed data was chosen (refer to the Model selection section below for details). Best fitting does not necessarily imply good fit; the best-fitting distribution may still deviate from the observed data. To ensure this was not the case, the observed versus predicted distributions by treatment group were examined."*

- Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) and the predictions using the four distributions (not only the best-fitted distribution) that were examined for selecting the distribution (Exponential, Weibull, log-normal or log-logistic). Please add the number of patients at risk to the graphs (reported per 0.5 year).
- Please provide the coefficients and standard errors for all these prediction equations.

Please refer to the attached excel file named "302 model KM Curves and Cumulative Functions" for the comparison of observed KM curves vs the predictions using the four distributions (with treatment as the only predictor). Please refer to the attached excel file named "302 model KM Curves with Number of Patients at Risk" for the KM curves with number of patients at risk. Please refer to the attached excel file named "302 model Parametric Function Parameters" for the coefficients and standard errors for all prediction equations with different distributions. Please note that each sheet contains one event (e.g. time to AAP/BSC (PP) discontinuation).

B6. **Priority Question**: **Comparison of model outcomes and trial outcomes**

Table 68 provides a useful summary of the proportion of patients in the pre-docetaxel, on-docetaxel and post-docetaxel phases of the model, and the respective duration of time spent in that treatment phase. However, it is not possible to compare this to the observations in the subset of the trial population that followed pathways relevant to the UK setting.

a. Please provide these data for people receiving treatments after AAP/BSC corresponding to scenarios included in the model [figures 39 and 40] as observed in the COU-AA-302 trial (ITT population with censoring at the time patients deviated from the pathway specified in the model,) using exactly the same format as Table 68.

As patients were censored in the trial but followed up to death in the model, it is not appropriate to generate Table 68 based on trial data. The mean duration in each phase will

be significantly underestimated using censored patients, and the patient populations will not be comparable if the censored patients from the 302 trial are excluded. In order to compare the model prediction versus trial observations, we extracted the simulated patient profiles using “trial scenario” (that is without the “negative” treatment effect for AAP arm in the post-docetaxel phase, and without the ECOG restriction on docetaxel use) and compared their experiences in different phases using survival curves. Figure 13 to Figure 21 show that the model simulation closely matches the trial observations.

Figure 10: Time to AAP/BSC (PP) Treatment Discontinuation

[redacted]

Figure 11: Time from AAP/BSC (PP) Discontinuation to Docetaxel Start

[redacted]

Figure 12: Time from AAP/BSC (PP) Discontinuation to Death Before Docetaxel Start

[redacted]

Figure 13: Time from Docetaxel start to Docetaxel End

[redacted]

Figure 14: Time from Docetaxel Start to Death Before Docetaxel Discontinuation

[redacted]

Figure 15: Time from Docetaxel End to Post-Docetaxel Treatment Start

[redacted]

Figure 16: Time from Post-Docetaxel Treatment End to Death

[redacted]

Figure 17: Time from Post-Docetaxel Treatment Start to Discontinuation

[redacted]

Figure 18: Time from Post-Docetaxel Treatment Discontinuation to Death

[redacted]

B7 Currently, it is not possible to validate predicted data versus observed data for each (treatment) phase in the DES model. Please provide: the graphs for all prediction equations currently used in the DES model comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to the prediction equations used in the model (Appendix 16). Please add the number of patients at risk to the graphs (reported per 0.5 year).

Please see Figure 22 to Figure 31 comparing the observed curve from the 302 trial to the curves estimated by the prediction equations for each model phase. Please refer to attached excel file named "302 model KM Curves with Number of Patients at Risk" for the KM graphs with the number of patients at risk.

Figure 19: Time to AAP/BSC (PP) discontinuation

[redacted]

Figure 20: Time from AAP discontinuation to death before docetaxel start

[redacted]

Figure 21: Time from BSC (PP) discontinuation to death before docetaxel start

[redacted]

Figure 22: Time from AAP/BSC (PP) discontinuation to docetaxel start

[redacted]

Figure 23: Time from docetaxel start to docetaxel discontinuation

[redacted]

Figure 24: Time from docetaxel start to death before docetaxel discontinuation

[redacted]

Figure 25: Time from docetaxel discontinuation to death before third-line treatment starts

[redacted]

Figure 26: Time from docetaxel discontinuation to post-docetaxel treatment start

[redacted]

Figure 27: Time from third-line treatment start to post-docetaxel treatment discontinuation

[redacted]

Figure 28: Time from post-docetaxel treatment discontinuation to death

[redacted]

B8. It is unclear why patients in the BSC arm were censored after sequential AAP and Cabazitaxel treatment (post-docetaxel). The addition of Cabazitaxel could be corrected for (as done for the other pathways).

a. Please provide updated prediction equations, wherein patients in the BSC arm are not censored after sequential AAP and Cabazitaxel treatment.
b. Please provide graphs comparing the observed KM-curve (from the ITT population with censoring at the time patients deviated from the pathway specified in the model) to these updated prediction equations.
c. Please add the number of patients at risk to the graphs (reported per 0.5 year).
d. Please also provide an updated version of the 'negative treatment effect' for cabazitaxel using the same format as Table 35.

To correct our description in the submission report, patients who received another active treatment after post-docetaxel active treatment are not censored. Their time spent with these treatments was included in the time from post-docetaxel treatment end to death.

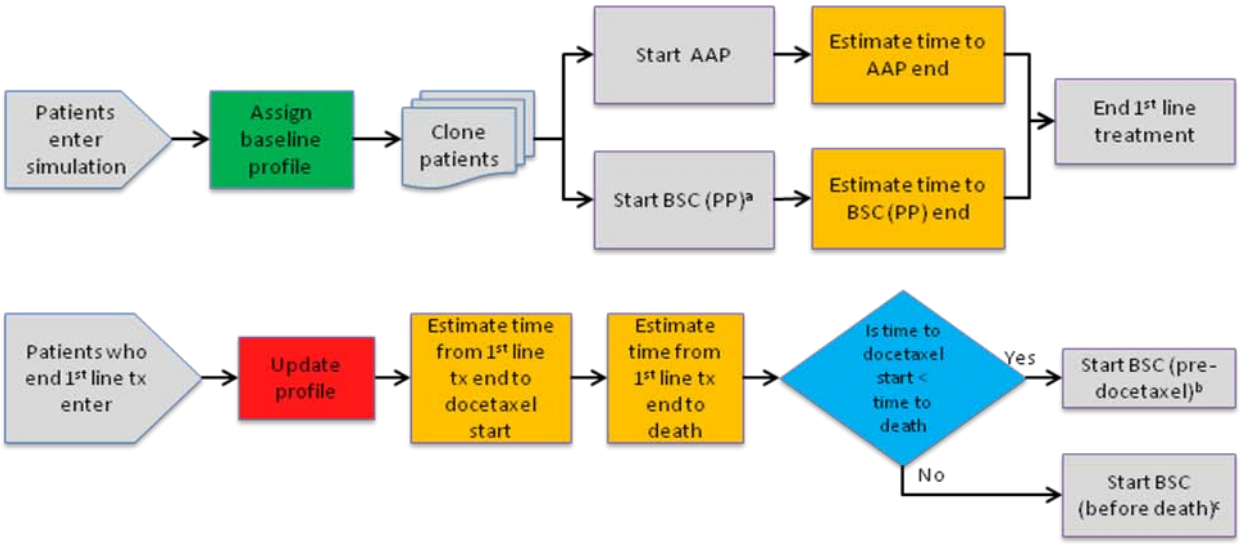
B9. Figure 11 is useful to understand the model structure, but unclear in distinguishing between types of BSC (e.g. active treatment and palliative treatment).

a. Please provide an updated figure with a distinction between different types of BSC

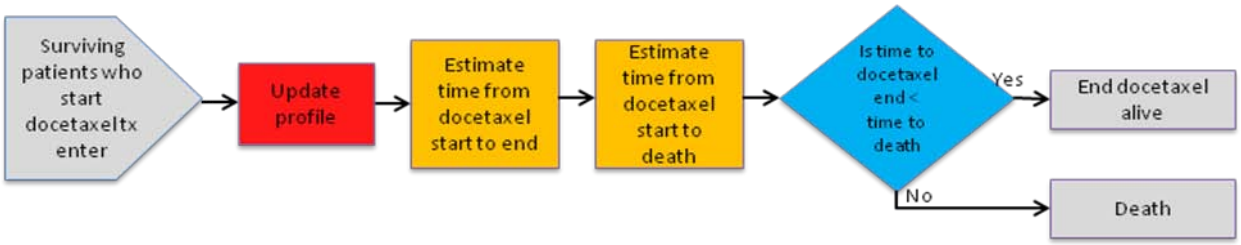
Figure 11 has been modified (please see Figure 32 in this document) to include a description of the various phases of BSC. The BSC (PP) arm serves as a proxy for an active monitoring strategy where patients are not receiving active treatments such as AAP or docetaxel that impact survival. However, the goal is that these patients will go on to receive docetaxel once their disease worsens therefore we use the terminology of "active monitoring" for this phase of BSC. We distinguish alternative types of BSC in the model that reflects phases where patients are awaiting active treatment with docetaxel (BSC pre-docetaxel) or after docetaxel (BSC post-docetaxel) or are near death and will not receive additional active treatments that may impact survival, but instead are managed for their pain or other symptoms (BSC before death).

Figure 29: Patient flow through the simulation

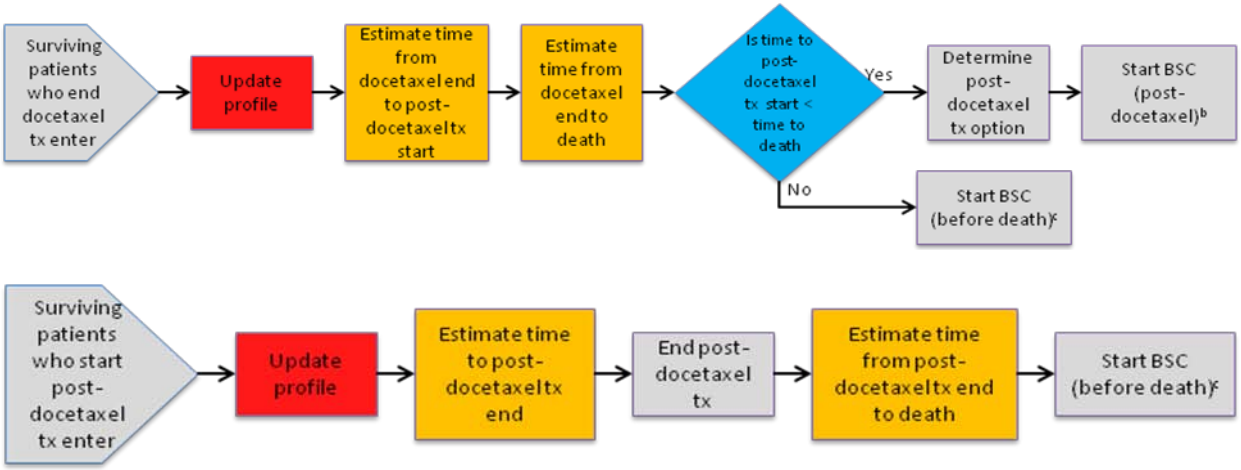
A



B



C



AAP, abiraterone acetate + prednisolone; BSC, best supportive care; PP, placebo + prednisolone; tx, treatment.
[a]BSC (PP), active monitoring comparator treatment arm where patients are not receiving active treatments such as AAP before docetaxel that impact survival
[b]BSC (pre-docetaxel / post-docetaxel), time before receiving an active treatment that has shown to impact overall survival where patients are still receiving treatments that palliate symptoms (e.g., corticosteroids) of disease
[c]BSC (before death), best supportive care "end of life" phase where patients are near death and will not receive additional active treatments that may impact survival, but instead are managed for their pain or other symptoms

Section C: Clarification on literature searches

Search strategies: General questions

C1. Please clarify whether the flow-diagrams report results from the update searches described in the submission. Are the results from the original searches conducted for NICE TA259 also included in the flow-diagrams?

The study flow described in Figure 2 (CONSORT flow) includes all the references relevant to this submission. Searches used in the original review (NICE TA 259) and updates of searches pertinent to this submission (untill 27 Sep, 2012) are included in the flow diagram.

Search strategies: Clinical effectiveness and adverse events (Sections 6.1, 6.8, 6.9, Appendices 10.2, 10.6 and 10.8)

C2. Please clarify whether validated study design search filters were used for the RCT and non-RCT facets. If validated filters were used, please provide details of the source or reference of those filters.

The RCT and observational search filters have been adapted from those recommended by the Scottish Intercollegiate Guidelines Network (SIGN). The published SIGN guidelines are used directly to search Medline and Embase literature databases. The Embase.com platform was used to conduct these searches and therefore some MeSH require modification in order to search both Medline and Embase simultaneously. The search terms used in the searches described in this submission have been validated (unpublished).

No study design search filters were used within the databases searches performed. Only free text and controlled vocabulary terms were used to search for study design e.g. 'clinical trial'/exp.

C3. There appears to be an error in the date span used for the third Embase/Medline update search strategy (Table 100). The search was conducted on 27.09.12, and the date limit used in the strategy was '[27-09-12]/sd'. Please confirm whether the search was limited to one day or whether this is a reporting error. If the search was limited to a single day, please clarify the implications of potentially excluding references for the full date span.

This error is a typo. The updated literature search was conducted from 27/02/2012 to 27/09/2012.

C4. Please provide more details for the searches of conference proceedings, i.e. search strategies or search terms used, website addresses

Conference	Website	Years searched	Search terms used
American Society of Clinical Oncology (ASCO) Annual meeting	http://am.asco.org/past-meetings http://jco.ascopubs.org/content/by/year http://meetinglibrary.asco.org/ http://meetinglibrary.asco.org/abstractbysubcategory/2013%20ASCO%20Annual%20Meeting/559 http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_meeting_categories_view&confID=114	2006–2013	Prostate cancer
American Society of	http://gucasym.org/past-symposia	20060-	Prostate

Clinical Oncology Genitourinary Cancers Symposium (ASCO GU)	http://jco.ascopubs.org/content/by/year http://meetinglibrary.asco.org/ http://meetinglibrary.asco.org/abstractbysubcategory/2013%20Genitourinary%20Cancers%20Symposium/198 http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_category_abstracts_view&confID=116&subCatID=198	2013	cancer
American Urological Association (AUA)	https://www.auanet.org/ http://www.jurology.com/issues http://www.aua2013.org/program/posters-and-podiums.cfm http://www.aua2012.org/abstracts/abstracts.cfm	2006–2013	Prostate cancer
European Association of Urology (EAU)	http://www.uroweb.org/ http://www.uroweb.org/events/abstracts-online/	2006–2013	Prostate cancer
European Society for Medical Oncology (ESMO)	http://www.ejcancer.com/supplements#	2006–2012[a]	Prostate cancer

aAt the time of the search, ESMO 2013 had not yet taken place.

Search strategies: Cost effectiveness (section 7.1, appendix 10.10)

C5. Please explain why the cost-effectiveness searches used a date span that started from 2000.

The cost-effectiveness searches were conducted from 2000 as this timeframe would capture those studies most relevant to the decision problem. Abiraterone acetate received marketing authorisation in 2011. A search spanning 10 years earlier than this date is sufficient to identify any publications pertinent to the economic analysis in this decision problem.

C6. Despite reporting that the searches run from 2000, the first update search strategy for Embase/Medline appears to run from 14-12-2009 to 9-6-2011 (Table 116, search line #92). Please confirm whether the search was limited to this date span or whether this is a reporting error. If the search was limited to this date span, please clarify the implications of potentially excluding references for the full date span.

The original search was run from 1-1-2000 to 9-6-2011. There appears to be an error in the table. Furthermore, two update searches were conducted in 2012, one in Feburary (spanning 9-6-2011 to 28-2-2012) and the second in November (spanning 1-3-2012 to 20-11-2012). The search strategies for these two updates are provided in Appendix 1 (at the end of this document).

C7. The second update search strategy reports a date span of 20-11-2012 to 30-5-2013 (Table 117, search line #92). This would mean that over a year has been missed since the previous update search. Please clarify whether this is a reporting error, or whether the search conducted using this date span. Please clarify the implications of potentially missing references for this date span.

As for C6.

C8. In section 7.1.1 it is stated that conference proceedings from ISPOR International and ISPOR European conferences were hand searched. There are no details of these searches in 10.10. Please provide details for these searches.

Conference	Website	Years searched	Search terms used
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual International Meeting	http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	2006–2012	Prostate cancer
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress	http://www.ispor.org/RESEARCH_STUDY_DIGEST/research_index.asp	2006 - 2012	Prostate cancer

C9. Please explain why there are no Emtree (or MeSH) subject index terms for the named interventions in the Embase/Medline and Cochrane Library search strategies (Tables 116-121). Please clarify what impact this may have had on the search results.

In the literature search most relevant to this decision problem, an extensive list of interventions was included. All the interventions were searched as text terms using brand, generic and nomenclature used during the research and development phase. This is an extremely comprehensive list that was used to search the title and abstracts. In addition to this, a number of Emtree terms were also used, including corticosteroid, antiandrogen, gonadroreline agonist, LHRH agonist and cancer immunotherapy. Due to the comprehensive nature of the search terms used in combination with the Emtree terms, it is believed that no studies relevant to the decision problem were excluded from the search. It should be noted that in addition to the structured search, a bibliographic search was also conducted. This methodology ensures that all studies pertinent to the decision problem have been included.

Search strategies: Health related quality of life (section 7.4, appendix 10.12)

C10. In section 7.4.5 and 10.12.3 it is stated that the date span of the searches was from 2005 to 2013. However, the search strategies for embase.com and the Cochrane Library (Tables 130-131) indicate that the date span used was 2005 to 2012. Please confirm whether this is a reporting error or if the searches were conducted using this date span.

This is a reporting error. The updated tables of the HRQoL Cochrane search strategies are missing in the document. Please find them in Table 13 and Table 14.

Table 14: Utility – Cochrane Search Strategy executed on 30th May 2013

#	Key words	Hits
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees	
#2	(prostate or prostatic) near/2 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)	
#3	(utilit* near/1 approach*) or (health near/1 gain) or hui or hui2 or hui3 or (hui near/1 3) or (health next measurement* next (scale* or questionnaire*)) or (standard near/1 gamble*) or (categor* near/1 scal*) or (linear near/1 scal*) or (linear near/1 analog*) or (visual near/1 scal*) or (magnitude near/1 estimat*) or (time near/1 (tradeoff or tradeoffs or "trade off" or "trade offs")) or (rosser* near/1 (classif* or matrix or distress*)) or hrqol or (index near/2 wellbeing) or (quality near/2 wellbeing) or qwb or (multiattribute* next health	

	next ind*) or (multi next attribute next health next ind*) or (health next utilit* next index) or (health next utilit* next indices)	
#4	(multiattribute* near/1 theor*) or (multi next attribute* next theor*) or (multiattribute* near/1 analys*) or (multi next attribute* next analys*) or (health next utilit* next scale*) or (classification next of next illness next state*) or (15 near/1 dimension) or (health next state* next utilit*) or (well near/1 year*) or (multattribute* near/1 utilit*) or (multi next attribute* next utilit*) or (health next utilit* next scale*) or "euro qol" or "euro qual" or "eq-5d" or eq5d or "eq 5d" or euroqol or euroqoi or euroqual or qualy or qaly or qualys or qalys or "quality adjusted life year" or "quality adjusted life years" or "willingness to pay"	
#5	hye or hyes or (health* next year* equivalent*) or (person next trade next off*) or (person near/1 tradeoff*) or (time near/1 tradeoff*) or (time next trade next off*) or (theory near/1 utilit*) or sf36 or (sf near/1 36) or (short next form next 36) or (shortform near/1 36) or (sf near/1 thirtysix) or (sf next thirty next six) or (shortform near/1 thirtysix) or (shortform next thirty next six) or (short next form next thirtysix) or (short next form next thirty next six) or (sf near/1 6d) or (short next form next 6d)	
#6	((#1 or #2) and (#3 or #4 or #5))	
#7	#6 from 2012 to 2013, in Economic Evaluations	
#8	(#1 and #2) from 2012 to 2013, in Economic Evaluations	

Table 15: Utility – Cochrane Search Strategy executed on 2nd September 2013

#	Key words	Hits
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees	3020
#2	(prostate or prostatic) near/2 (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or tumour* or tumor*)	5065
#3	(utilit* near/1 approach*) or (health near/1 gain) or hui or hui2 or hui3 or (hui near/1 3) or (health next measurement* next (scale* or questionnaire*)) or (standard near/1 gamble*) or (categor* near/1 scal*) or (linear near/1 scal*) or (linear near/1 analog*) or (visual near/1 scal*) or (magnitude near/1 estimat*) or (time near/1 (tradeoff or tradeoffs or "trade off" or "trade offs")) or (rosser* near/1 (classif* or matrix or distress*)) or hrqol or (index near/2 wellbeing) or (quality near/2 wellbeing) or qwb or (multiattribute* next health next ind*) or (multi next attribute next health next ind*) or (health next utilit* next index) or (health next utilit* next indices)	5475
#4	(multiattribute* near/1 theor*) or (multi next attribute* next theor*) or (multiattribute* near/1 analys*) or (multi next attribute* next analys*) or (health next utilit* next scale*) or (classification next of next illness next state*) or (15 near/1 dimension) or (health next state* next utilit*) or (well near/1 year*) or (multattribute* near/1 utilit*) or (multi next attribute* next utilit*) or (health next utilit* next scale*) or "euro qol" or "euro qual" or "eq-5d" or eq5d or "eq 5d" or euroqol or euroqoi or euroqual or qualy or qaly or qualys or qalys or "quality adjusted life year" or "quality adjusted life years" or "willingness to pay"	6721
#5	hye or hyes or (health* next year* equivalent*) or (person next trade next off*) or (person near/1 tradeoff*) or (time near/1 tradeoff*) or (time next trade next off*) or (theory near/1 utilit*) or sf36 or (sf near/1 36) or (short next form next 36) or (shortform near/1 36) or (sf near/1 thirtysix) or (sf next thirty next six) or (shortform near/1 thirtysix) or (shortform next thirty next six) or (short next form next thirtysix) or (short next form next thirty next six) or (sf near/1 6d) or (short next form next 6d)	4672
#6	((#1 or #2) and (#3 or #4 or #5))	199

#7	#6 from 2012 to 2013, in Economic Evaluations	10
#8	(#1 and #2) from 2012 to 2013, in Economic Evaluations	22

C11. There appears to be a mistake in the final search line of the Cochrane Library (NHS EED) search strategy (Table 131, search line #8). Please confirm whether this is a reporting error or if the search lines #1 and #2 were combined for this search.

This is a typo. Search line #8 consists of #7 AND [2005-2012]/py [NHS EED only].

C12. Please clarify whether an update search in EconLit was conducted. It is not clear from section 10.12.1 whether this search was conducted or not.

No, EconLit was not searched. EconLit was not searched for HRQoL data.

Executive summary

C13. Please clarify the anticipated submission date to the Scottish Medicines Consortium for its appraisal of abiraterone.

Janssen anticipates that a submission will be made to the SMC in April 2014 with a decision expected in September 2014.

Reference List

[1] Fossa SD, Jacobsen AB, Ginman C, et al. Weekly docetaxel and prednisolone versus prednisolone alone in androgen-independent prostate cancer: a randomized phase II study. Eur Urol 2007 Dec;52(6):1691-8.

[2] Fossa SD. A randomized phase II trial comparing weekly taxotere plus prednisolone versus prednisolone alone in androgen-independent prostate cancer. Front Radiat Ther Oncol 2008;41:108-16.

[3] Janssen Research & Development. Report of Updated Data from Study COU-AAA-302. 22 May 2012 Data Cutoff. A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer. 2012.

[4] Negreiro F, Pereira C, Pereira H, Silva C. Economic analysis of erlotinib, docetaxel, pemetrexed, and best supportive care as 2nd and 3rd line treatment of non-small-cell lung cancer. 2008.

[5] Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer 2006 Sep 18;95(6):683-90.

[6] Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes 2010;8:50.

[7] Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84.

[8] Grutters JP, Joore MA, Wiegman EM, et al. Health-related quality of life in patients surviving non-small cell lung cancer. Thorax 2010 Oct;65(10):903-7.

[9] Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin 2010 May;26(5):1091-6.

[10] Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methods. Pharmacoeconomics 2007;25(3):223-37.

[11] Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer 2008 Dec;62(3):374-80.

Appendix 1

Table 16: Embase® and MEDLINE® database (searched on 28/02/2012)

#	Search History	Results
1.	'economics'/de	195 898
2.	'economic aspect'/de	98 390
3.	'cost'/de	48 804
4.	'health care cost'/exp OR 'health care cost'	172 764
5.	'drug cost'/de	50 130
6.	'hospital cost'/de	11 513
7.	'socioeconomics'/de	97 644
8.	'health economics'/de	31 828
9.	'pharmacoeconomics'/de	4235
10.	'fee'/exp	30 865
11.	'budget'/exp	16 749
12.	'economic evaluation'/exp	179 677
13.	'hospital finance'/de OR 'financial management'/de	96 586
14.	'health care financing'/de	10 643
15.	'health care utilization'/de	31 535
16.	'low cost'	21 875
17.	'high cost'	7333
18.	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*	177 154
19.	fiscal OR funding OR financial OR finance	320 182
20.	cost NEXT/1 estimate*	1618
21.	'cost variable'	35
22.	unit NEXT/1 cost*	1844
23.	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti	185 481
24.	cost* NEAR/3 (treat* OR therap*)	34 985
25.	health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization)	33 208
26.	resource NEXT/1 (utilisation OR utilization OR use)	10 267
27.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	946 020
28.	'prostate cancer'/exp	98 937
29.	'prostate tumor'/de	24 601
30.	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)	136 668
31.	crpc	812
32.	castrat* NEAR/3 resistant	1792
33.	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*	4 542 409
34.	#32 AND #33	1787
35.	#28 OR #29 OR #30 OR #31 OR #34	136 696
36.	'2,4-dioxo-5-fluoropyrimidine':ab,ti OR '5-fluoro-2,4(1h, 3h)-pyrimidinedione':ab,ti OR '5-fluorouracil':ab,ti OR '5-fluracil':ab,ti OR '5-fu':ab,ti OR accusite:ab,ti OR 'actino-hermal':ab,ti OR adrucil:ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efudex:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR 'fluoro uracil':ab,ti OR fluoroplex:ab,ti OR fluorouracil:ab,ti OR fluouracil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR 'ro 2-9757':ab,ti OR timazin:ab,ti	37 047
37.	abarelix:ab,ti OR plenaxis:ab,ti OR 'ppi 149':ab,ti OR 'r 3827':ab,ti OR ppi149:ab,ti OR r3827:ab,ti	54
38.	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti	248
39.	aflibercept:ab,ti OR 'ave0005':ab,ti OR 'vascular endothelial growth factor trap':ab,ti OR 'vegf trap r1r2':ab,ti OR 'vegf trap':ab,ti OR 'vasculotropin trap':ab,ti	239

#	Search History	Results
40.	'2-(p-aminophenyl)-2-ethylglutarimide':ab,ti OR '3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione':ab,ti OR 'alpha-(4-aminophenyl)-alpha-ethylglutarimide':ab,ti OR aminoblastin:ab,ti OR aminoglutethimide:ab,ti OR 'ba-16038':ab,ti OR cytadren:ab,ti OR elipten:ab,ti OR mamomit:ab,ti OR orimenten*:ab,ti OR orimeten:ab,ti OR rodazol:ab,ti	1562
41.	'abt 627':ab,ti OR atrasentan:ab,ti OR xinlay:ab,ti OR abt627:ab,ti OR 'a 147627':ab,ti OR a147627:ab,ti OR a1277*:ab,ti OR (a NEXT/1 1277*):ab,ti	407
42.	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'anti-vegf humanized monoclonal antibody':ab,ti OR 'anti-vegf rhumab':ab,ti OR 'recombinant humanized anti-vegf monoclonal antibody':ab,ti OR 'rhumab-vegf':ab,ti	9887
43.	bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR 'ici 176334':ab,ti OR ici176334:ab,ti OR raffolutil:ab,ti	1168
44.	'1-hydroxy-7beta,10beta-dimethoxy-9-oxo-5beta,20-epoxytax-11-ene-2alpha,4,13alpha-triyl 4-acetate 2-benzoate 13-[(2r,3s)-3-{[(tertbutoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate]':ab,ti OR cabazitaxel:ab,ti OR 'rpr 116258a':ab,ti OR 'taxoid xrp6258':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti	134
45.	'(sp-4-2)-diammine[1,1-cyclobutanedicarboxylato(2--)-o,o]platinum':ab,ti OR '1,1-cyclobutanedicarboxylic acid platinum complex':ab,ti OR blastocarb:ab,ti OR carboplatin:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR cbdca:ab,ti OR 'cis-diammine(1,1-cyclobutanedicarboxylato) platinum(ii)':ab,ti OR displata:ab,ti OR ercar:ab,ti OR 'jm-8':ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR paraplat*:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti	12 411
46.	'nsc 81340':ab,ti OR 'nsc 81430':ab,ti OR nsc81340:ab,ti OR nsc81430:ab,ti OR 'sh 714':ab,ti OR sh714:ab,ti OR sinovir:ab,ti OR virilit:ab,ti OR cyproterone:ab,ti	3032
47.	'corticosteroid'/exp	647 953
48.	'antiandrogen'/exp	41 040
49.	'gonadorelin agonist'/exp OR 'lhrh agonist'	9605
50.	'cancer immunotherapy'/exp	31 869
51.	dasatinib:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti OR sprycel:ab,ti	1668
52.	degarelix:ab,ti OR fe200486:ab,ti OR 'fe 200486':ab,ti	113
53.	dexamethasone:ab,ti OR 'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflog*:ab,ti OR arcodex*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR (dacort* NEAR/1 fue*):ab,ti OR dalalone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR decacort*:ab,ti OR dekacort*:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameto*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR d?xamethasone:ab,ti OR esacortene:ab,ti OR 'ex s1':ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR (fluor* NEAR/1 predniso*):ab,ti OR fluormethylpredniso*:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR dexa*:ab,ti OR hexadecad*:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isopto*:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazon*:ab,ti OR 'metisone lafi':ab,ti OR millicorten*:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR opticort*:ab,ti OR oradex*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR 'predni f tablinen':ab,ti OR 'prednisolone f':ab,ti OR prodex*:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti OR decadeltosona:ab,ti OR decadeltosone:ab,ti OR decadion*:ab,ti OR decadran:ab,ti OR decadron*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti	111 724
54.	'(e)-4,4-(1,2-diethyl-1,2-ethenediyl)bisphenol':ab,ti OR '3, 4-bis(p-hydroxyphenyl)-3-hexene':ab,ti OR acnestrol:ab,ti OR 'alpha,alpha-diethylstilbenediol':ab,ti OR antigestil:ab,ti OR apstil:ab,ti OR boestrol:ab,ti OR bufon:ab,ti OR 'cyren a':ab,ti OR des:ab,ti OR diastyl:ab,ti OR diethylstilbenediol:ab,ti OR diethylstilbestrolum:ab,ti OR diethylstilbestrol:ab,ti OR diethylstilboestrol:ab,ti OR distilbene:ab,ti OR domestrol:ab,ti OR estrobene:ab,ti OR estromenin:ab,ti OR estrosyn:ab,ti OR fonatol:ab,ti OR grafestrol:ab,ti OR makarol:ab,ti OR microest:ab,ti OR milestrol:ab,ti OR 'neo-oestronol i':ab,ti OR oestrogeni*:ab,ti OR oestromenin:ab,ti OR oestromensyl:ab,ti OR oestromon:ab,ti OR sexocretin:ab,ti OR sibol:ab,ti OR stilbestro*:ab,ti OR stilbetin:ab,ti OR stilboefral:ab,ti OR stilboestrol:ab,ti OR stilkap:ab,ti OR synestrin:ab,ti OR synthoestrin:ab,ti OR vagestrol:ab,ti OR hexanestrol:ab,ti OR hexestrofen:ab,ti OR hexital:ab,ti OR hexron:ab,ti OR hexypheen:ab,ti OR 'hi bestrol':ab,ti OR 'hormoestrol':ab,ti OR menostilbene:ab,ti OR 'meso hexestrol':ab,ti OR mesohexestrol:ab,ti OR micrest:ab,ti OR 'neo estranol':ab,ti OR 'nsc 3070':ab,ti OR 'nsc 35752':ab,ti OR 'nsc 9894':ab,ti OR oekolp:ab,ti OR oestrostilben:ab,ti OR oestrosyntal:ab,ti OR orestrol:ab,ti OR ovendosyn:ab,ti OR pabestrol:ab,ti OR pabestrosalve:ab,ti OR palestrol:ab,ti OR proestrin:ab,ti OR serral:ab,ti	430 745
55.	docetaxel:ab,ti OR taxotere:ab,ti	10 127
56.	'(8s-cis)-10-[(3-amino-2,3,6-trideoxy-alpha-l-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione':ab,ti OR '14-hydroxydaunomycin':ab,ti OR doxorubicin:ab,ti OR 'hydroxyl daunorubicin':ab,ti OR adriablastin*:ab,ti OR adriacin:ab,ti OR adriam?cina:ab,ti OR adriamycin:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR dexorubicin:ab,ti OR 'dox	43 264

#	Search History	Results
	sl':ab,ti OR doxil:ab,ti OR doxorubicin*:ab,ti OR 'fi 106':ab,ti OR lipodox:ab,ti OR 'liposomal doxorubicin':ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR 'pegylated liposomal doxorubicin':ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti	
57.	dutasteride:ab,ti OR 'gg 745':ab,ti OR 'gg745':ab,ti OR avodart:ab,ti OR avolve:ab,ti OR advodart:ab,ti OR duagen:ab,ti OR 'gi 198745':ab,ti OR gi198745*:ab,ti	564
58.	e7389:ab,ti OR 'e 7389':ab,ti OR eribulin:ab,ti OR 'halichondrin b analog':ab,ti	126
59.	estramustine:ab,ti OR 'leo 275':ab,ti OR 'leo 462':ab,ti OR 'nsc 89199':ab,ti OR 'ro 21 8837':ab,ti OR 'ro 22 2296 000':ab,ti OR leo275:ab,ti OR leo462:ab,ti OR nsc89199:ab,ti OR ro218837:ab,ti OR ro222296000:ab,ti	1122
60.	'4-demethylepipodophyllotoxin 9-[4,6-o-ethylidene-beta-d-glucopyranoside':ab,ti OR 'demethyl epipodophyllotoxin ethylidine glucoside':ab,ti OR epeg:ab,ti OR etoposide:ab,ti OR vepesid:ab,ti OR 'vp 16-213':ab,ti OR etomedac:ab,ti OR etopol:ab,ti OR lastet:ab,ti OR 'nk 171':ab,ti OR 'nsc 141540':ab,ti OR toposar:ab,ti OR vepesid*:ab,ti	17 446
61.	'(5alpha,17beta)-n-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide':ab,ti OR 'chibro-proscar':ab,ti OR finasteride:ab,ti OR finastid:ab,ti OR 'mk 906':ab,ti OR 'pro-cure':ab,ti OR propecia:ab,ti OR propeshia:ab,ti OR proscar:ab,ti OR prostide:ab,ti OR urprosan:ab,ti OR 'ym 152':ab,ti	2299
62.	flutamide:ab,ti OR apimid:ab,ti OR chimax:ab,ti OR eulexine:ab,ti OR flucinome:ab,ti OR flucinom:ab,ti OR flugerel:ab,ti OR fluken:ab,ti OR flulem:ab,ti OR 'fluta-gry':ab,ti OR flutabene:ab,ti OR flutacan:ab,ti OR flutamex:ab,ti OR flutamin:ab,ti OR flutan:ab,ti OR flutaplex:ab,ti OR flut:ab,ti OR fugerel:ab,ti OR grisetin:ab,ti OR oncosal:ab,ti OR profamid:ab,ti OR prostacur:ab,ti OR prostadirex:ab,ti OR prostica:ab,ti OR prostogenat:ab,ti OR 'sch 13521':ab,ti OR sch13521:ab,ti OR tafenil:ab,ti OR tecnoflut:ab,ti OR testotard:ab,ti OR drogenil:ab,ti OR euflex:ab,ti OR eulexin:ab,ti OR flumid:ab,ti OR niftolid:ab,ti OR niphtholid:ab,ti OR sebatrol:ab,ti	2690
63.	goserelin:ab,ti OR 'ici-118630':ab,ti OR 'ici 118 630':ab,ti OR 'ici 118630':ab,ti OR ici118630:ab,ti OR zoladex:ab,ti	1182
64.	'(11beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione':ab,ti OR 'aeroseb-hc':ab,ti OR 'barseb hc':ab,ti OR cetacort:ab,ti OR 'cort-dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortifan:ab,ti OR cortisol:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR domolene:ab,ti OR eldecort:ab,ti OR hautosone:ab,ti OR 'heb-cort':ab,ti OR hydrocortisone:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR 'komed-hc':ab,ti OR nutracort:ab,ti OR proctocort:ab,ti OR rectoid:ab,ti OR therapeutic:ab,ti AND hydrocortisone:ab,ti OR alphaderm:ab,ti OR barseb:ab,ti OR cetacort:ab,ti OR cobadex:ab,ti OR 'compound f':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortibel:ab,ti OR cortifan:ab,ti OR cortifoam:ab,ti OR cortiment:ab,ti OR cortiphate:ab,ti OR cortisol*:ab,ti OR cortoderm:ab,ti OR cortril:ab,ti OR dermolate:ab,ti OR dioderm:ab,ti OR duomedihaler:ab,ti OR 'ef cortelan':ab,ti OR efcortelan:ab,ti OR egocort:ab,ti OR eksalb:ab,ti OR eldecort:ab,ti OR ficortril:ab,ti OR hebcort:ab,ti OR hycort:ab,ti OR hydracort:ab,ti OR hydrasson:ab,ti OR 'hydro ricortex':ab,ti OR hydrocort:ab,ti OR hydrocorticosteroid:ab,ti OR hydrocortisate:ab,ti OR hydrocortis*:ab,ti OR hydrocortone:ab,ti OR hydroderm:ab,ti OR hysone:ab,ti OR hytone:ab,ti OR incortin:ab,ti OR medihaler:ab,ti OR mildison:ab,ti OR munitren:ab,ti AND 'neo cortef':ab,ti OR neocortef:ab,ti OR novohydrocort:ab,ti OR 'nsc 10483':ab,ti OR 'nsc 741':ab,ti OR nutracort:ab,ti OR otosone:ab,ti OR penecort:ab,ti OR prepcort:ab,ti OR proctocort:ab,ti OR proctosone:ab,ti OR rectocort:ab,ti OR schericur:ab,ti OR 'scherosone f':ab,ti OR 'solu cortef':ab,ti OR synacort:ab,ti OR vasocort:ab,ti	23
65.	'anti-cytotoxic t-lymphocyte-associated antigen-4 monoclonal antibody':ab,ti OR ipilimumab:ab,ti OR 'mdx-010':ab,ti OR 'mdx-ctla4':ab,ti OR 'bms 734016':ab,ti OR yervoy:ab,ti	350
66.	jm216:ab,ti OR 'jm 216':ab,ti	91
67.	ketoconazole:ab,ti OR fungarest:ab,ti OR fungoral:ab,ti OR ketoderm:ab,ti OR ketoisdin:ab,ti OR nizoral:ab,ti OR orifungal:ab,ti OR panfungol:ab,ti OR xolegel:ab,ti OR anisole:ab,ti OR cetonax:ab,ti OR 'dio 902':ab,ti OR dio902:ab,ti OR 'kw 1414':ab,ti OR kw1414:ab,ti OR micoral:ab,ti OR nisoral:ab,ti OR oxocanazole:ab,ti OR oxoconazole:ab,ti OR 'r 41 400':ab,ti OR r41400:ab,ti OR terzolin:ab,ti	7793
68.	leuprolide:ab,ti OR leuprorelin:ab,ti OR leuplin:ab,ti OR leupro*:ab,ti OR lucrin:ab,ti OR lupride:ab,ti OR lupron:ab,ti OR procrin:ab,ti OR prostap:ab,ti OR tap144:ab,ti OR 'tap 144':ab,ti	2339
69.	mdv3100:ab,ti OR 'mdv3100':ab,ti	77
70.	megastrol:ab,ti	6
71.	mitoxantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mito?antrone:ab,ti OR novanthron:ab,ti OR novantron*:ab,ti OR 'now 85 34':ab,ti OR 'now 8534':ab,ti OR now8534:ab,ti OR 'nsc 279836':ab,ti OR 'nsc 301739':ab,ti OR 'nsc 301739d':ab,ti OR nsc279836:ab,ti OR nsc301739:ab,ti OR nsc301739d:ab,ti	16 914
72.	nilutamide:ab,ti OR anandron:ab,ti OR nilandron:ab,ti OR anadron:ab,ti OR nitulamide:ab,ti OR 'rn 23908':ab,ti OR 'ru 23908':ab,ti OR rn23908:ab,ti OR ru23908:ab,ti	265
73.	'abi 007':ab,ti OR 'abi007':ab,ti OR abraxane:ab,ti OR 'bms 181339':ab,ti OR coroxane:ab,ti OR genexol:ab,ti OR hunxol:ab,ti OR intaxel:ab,ti OR 'nsc 125973':ab,ti OR paxceed:ab,ti OR paclitaxel:ab,ti OR paxene:ab,ti OR taxol:ab,ti OR yewtaxan:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti	24 268

#	Search History	Results
74.	'pamidronic acid':ab,ti OR pamidronate:ab,ti OR aredia:ab,ti OR aminomux:ab,ti OR 'gcp-23339a':ab,ti	2407
75.	prednison*:ab,ti OR prednisolon*:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR 'de cortin':ab,ti OR decortin:ab,ti OR 'de cortisyl':ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR 'delta(1)-cortisone':ab,ti OR 'delta-dome':ab,ti OR deltacortene:ab,ti OR deltacortisone:ab,ti OR deltadehydrocortisone:ab,ti OR deltasone:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR lisacort:ab,ti OR 'meprosona-f':ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR 'panasol-s':ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicorten:ab,ti OR predicor:ab,ti OR 'prednicen-m':ab,ti OR prednicort:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednisone:ab,ti OR prednisonum:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti OR 'sk-prednisone':ab,ti OR sterapred:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR decortancyl:ab,ti OR dekortin:ab,ti OR delitisone:ab,ti OR 'delta cortelan':ab,ti OR 'delta cortisone':ab,ti OR 'delta dome':ab,ti OR 'delta e':ab,ti OR 'delta prenovis':ab,ti OR deltacorten:ab,ti OR deltacortone:ab,ti OR 'di adreson':ab,ti OR diadreson:ab,ti OR encorton*:ab,ti OR enkorton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone:ab,ti OR orisane:ab,ti OR precort:ab,ti OR precortal:ab,ti OR pronison*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti	48 157
76.	samarium:ab,ti	1442
77.	sipuleucelt:ab,ti OR 'apc8015 vaccine':ab,ti OR 'apc8015':ab,ti OR 'pa2024 (pap/gm-csf)-loaded dendritic cell vaccine':ab,ti OR provenge:ab,ti OR 'sipuleucel-t':ab,ti OR 'apc 8015':ab,ti	239
78.	strontium:ab,ti	6215
79.	'tak-700':ab,ti OR 'tak 700':ab,ti OR 'tak700':ab,ti	17
80.	triptorelin:ab,ti OR '6-d-tryptophan-lh-rh':ab,ti OR '6-d-tryptophanluteinizing hormone-releasing factor':ab,ti OR 'ay-25650':ab,ti OR 'cl-118,532':ab,ti OR 'decapeptyl':ab,ti OR detryptoreline:ab,ti OR '[d trp 6] lhrh':ab,ti OR 'arvekap':ab,ti OR 'ay 25650':ab,ti OR 'ay25650':ab,ti OR 'd trp 6 lhrh':ab,ti OR 'd trp 6 luteinizing hormone releasing hormone':ab,ti OR 'gonadorelin [6 dextro tryptophan]':ab,ti OR 'gonadotropin releasing hormone [6 dextro tryptophan]':ab,ti OR 'lhrh (d trp 6)':ab,ti OR 'lhrh [6 dextro tryptophan]':ab,ti OR 'luteinizing hormone releasing hormone [6 dextro tryptophan]':ab,ti OR trelstar:ab,ti OR 'trelstar la':ab,ti OR tryptorelin:ab,ti	1003
81.	'le 29060':ab,ti OR 'le29060':ab,ti OR 'leukoblastin':ab,ti OR rozevin:ab,ti OR 'vin blastine':ab,ti OR vinblastin*:ab,ti OR vincaleucoblastin*:ab,ti OR vincaleukoblastin*:ab,ti OR vincoblastin*:ab,ti OR vincoleucoblastin*:ab,ti OR vincoleukoblastin*:ab,ti OR vinleucoblastine:ab,ti OR vlb:ab,ti	9518
82.	navelbine:ab,ti OR vinorelbine:ab,ti OR '3,4-didehydro-4-deoxy-c-norvincaleukoblastine':ab,ti OR '5-nor-anhydrovinblastine':ab,ti OR dihydroxydeoxynorvinkaleukoblastine:ab,ti OR 'nor-5-anhydrovinblastine':ab,ti	3619
83.	zd4054:ab,ti OR 'zd 4054':ab,ti OR zibotentan:ab,ti OR 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide':ab,ti	62
84.	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR reclast:ab,ti OR 'zol 446':ab,ti OR 'cgp 42446':ab,ti	2966
85.	'5, 6 dimethyl 9 oxo 9h xanthene 4 acetic acid':ab,ti OR dmxaa:ab,ti OR 'as 1404':ab,ti OR as1404:ab,ti OR 'asa 404':ab,ti OR asa404:ab,ti OR 'nsc 640488':ab,ti OR nsc640488:ab,ti	205
86.	'imc a12':ab,ti OR 'imc ? a12':ab,ti OR cixutumumab:ab,ti OR 'anti-igf-1r recombinant monoclonal antibody imc-a12':ab,ti	39
87.	patupilone:ab,ti OR 'epo 906':ab,ti OR epo906:ab,ti OR 'epothilon b':ab,ti	111
88.	sunitinib:ab,ti OR 'pha 2909040ad':ab,ti OR pha2909040ad:ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR su011248:ab,ti OR su10398:ab,ti OR su11248:ab,ti OR sutent:ab,ti	3185
89.	'cab':ab,ti OR 'complete androgen blockade':ab,ti	2212
90.	alpharadin OR ‘radium 223’ OR ‘radium-223’	133
91.	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90	1 309 026

#	Search History	Results
92.	#27 AND #35 AND #91	921
93.	#27 AND #35 AND #91 AND [9-6-2011]/sd NOT [28-2-2012]/sd	107
94.	#27 AND #35 AND #90	5
95.	**#93 OR #94**	**108**

Table 17: Embase® and MEDLINE® database (searched on 20/11/2012)

#	Search History	Results
96.	'economics'/de	202,932
97.	'economic aspect'/de	99,955
98.	'cost'/de	50,020
99.	'health care cost'/exp OR 'health care cost'	183,225
100.	'drug cost'/de	52,965
101.	'hospital cost'/de	12,233
102.	'socioeconomics'/de	102,170
103.	'health economics'/de	32,663
104.	'pharmacoeconomics'/de	5,687
105.	'fee'/exp	31,800
106.	'budget'/exp	17 765
107.	'economic evaluation'/exp	190 682
108.	'hospital finance'/de OR 'financial management'/de	99 097
109.	'health care financing'/de	10 914
110.	'health care utilization'/de	34 198
111.	'low cost'	24 319
112.	'high cost'	7 999
113.	health*care NEXT/1 cost* OR 'health care' NEXT/1 cost*	187 943
114.	fiscal OR funding OR financial OR finance	339 612
115.	cost NEXT/1 estimate*	1748
116.	'cost variable'	40
117.	unit NEXT/1 cost*	2079
118.	economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti	200 312
119.	cost* NEAR/3 (treat* OR therap*)	38 108
120.	health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization)	36 037
121.	resource NEXT/1 (utilisation OR utilization OR use)	11 679
122.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1 001 685
123.	'prostate cancer'/exp	109 074
124.	'prostate tumor'/de	26 020
125.	prostat* NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplasm* OR adeno* OR intraepithelial)	149 000
126.	crpc	1226
127.	castrat* NEAR/3 resistant	2936
128.	cancer* OR carcinoma* OR malignan* OR tumo?r* OR neoplas* OR adeno*	4 798 762
129.	#32 AND #33	2931
130.	#28 OR #29 OR #30 OR #31 OR #34	149 036
131.	'2,4-dioxo-5-fluoropyrimidine':ab,ti OR '5-fluoro-2,4(1h, 3h)-pyrimidinedione':ab,ti OR '5-fluorouracil':ab,ti OR '5-fluracil':ab,ti OR '5-fu':ab,ti OR accusite:ab,ti OR 'actino-hermal':ab,ti OR adrucil:ab,ti OR arumel:ab,ti OR cytosafe:ab,ti OR efudex:ab,ti OR efurix:ab,ti OR fiverocil:ab,ti OR 'fluoro uracil':ab,ti OR fluoroplex:ab,ti OR fluorouracil:ab,ti OR fluouracil:ab,ti OR flurablastin:ab,ti OR fluracedyl:ab,ti OR	38 921

#	Search History	Results
	fluracil:ab,ti OR fluril:ab,ti OR fluroblastin:ab,ti OR flurox:ab,ti OR ribofluor:ab,ti OR 'ro 2-9757':ab,ti OR timazin:ab,ti	
132.	abarelix:ab,ti OR plenaxis:ab,ti OR 'ppi 149':ab,ti OR 'r 3827':ab,ti OR ppi149:ab,ti OR r3827:ab,ti	57
133.	abiraterone:ab,ti OR 'cb 7598':ab,ti OR cb7598:ab,ti OR 'abiraterone acetate':ab,ti OR zytiga:ab,ti	381
134.	aflibercept:ab,ti OR 'ave0005':ab,ti OR 'vascular endothelial growth factor trap':ab,ti OR 'vegf trap r1r2':ab,ti OR 'vegf trap':ab,ti OR 'vasculotropin trap':ab,ti	329
135.	'2-(p-aminophenyl)-2-ethylglutarimide':ab,ti OR '3-(4-aminophenyl)-3-ethyl-2,6-piperidinedione':ab,ti OR 'alpha-(4-aminophenyl)-alpha-ethylglutarimide':ab,ti OR aminoblastin:ab,ti OR aminoglutethimide:ab,ti OR 'ba-16038':ab,ti OR cytadren:ab,ti OR elipten:ab,ti OR mamomit:ab,ti OR orimenten*:ab,ti OR orimeten:ab,ti OR rodazol:ab,ti	1577
136.	'abt 627':ab,ti OR atrasentan:ab,ti OR xinlay:ab,ti OR abt627:ab,ti OR 'a 147627':ab,ti OR a147627:ab,ti OR a1277*:ab,ti OR (a NEXT/1 1277*):ab,ti	422
137.	bevacizumab:ab,ti OR avastin:ab,ti OR 'nsc 704865':ab,ti OR nsc704865:ab,ti OR 'anti-vegf':ab,ti OR 'anti-vegf humanized monoclonal antibody':ab,ti OR 'anti-vegf rhumab':ab,ti OR 'recombinant humanized anti-vegf monoclonal antibody':ab,ti OR 'rhumab-vegf':ab,ti	11 861
138.	bicalutamide:ab,ti OR casodex:ab,ti OR cosudex:ab,ti OR 'ici 176334':ab,ti OR ici176334:ab,ti OR raffolutil:ab,ti	1302
139.	'1-hydroxy-7beta,10beta-dimethoxy-9-oxo-5beta,20-epoxytax-11-ene-2alpha,4,13alpha-triyl 4-acetate 2-benzoate 13-[(2r,3s)-3-{[(tertbutoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate]':ab,ti OR cabazitaxel:ab,ti OR 'rpr 116258a':ab,ti OR 'taxoid xrp6258':ab,ti OR xrp6258:ab,ti OR jevtana:ab,ti	216
140.	'(sp-4-2)-diammine[1,1-cyclobutanedicarboxylato(2--)-o,o]platinum':ab,ti OR '1,1-cyclobutanedicarboxylic acid platinum complex':ab,ti OR blastocarb:ab,ti OR carboplatin:ab,ti OR carboplat*:ab,ti OR carbosin:ab,ti OR carbosol:ab,ti OR carbotec:ab,ti OR cbdca:ab,ti OR 'cis-diammine(1,1-cyclobutanedicarboxylato) platinum(ii)':ab,ti OR displata:ab,ti OR ercar:ab,ti OR 'jm-8':ab,ti OR nealorin:ab,ti OR novoplatinum:ab,ti OR paraplat*:ab,ti OR platinwas:ab,ti OR ribocarbo:ab,ti	13 466
141.	'nsc 81340':ab,ti OR 'nsc 81430':ab,ti OR nsc81340:ab,ti OR nsc81430:ab,ti OR 'sh 714':ab,ti OR sh714:ab,ti OR sinovir:ab,ti OR virilit:ab,ti OR cyproterone:ab,ti	3078
142.	'corticosteroid'/exp	676 657
143.	'antiandrogen'/exp	42 946
144.	'gonadorelin agonist'/exp OR 'lhrh agonist'	10 107
145.	'cancer immunotherapy'/exp	33 680
146.	dasatinib:ab,ti OR 'bms 354825':ab,ti OR bms354825:ab,ti OR sprycel:ab,ti	2220
147.	degarelix:ab,ti OR fe200486:ab,ti OR 'fe 200486':ab,ti	139
148.	dexamethasone:ab,ti OR 'aeroseb dex':ab,ti OR aflucoson*:ab,ti OR anaflog*:ab,ti OR arcodex*:ab,ti OR azium:ab,ti OR calonat:ab,ti OR cebedex:ab,ti OR colofoam:ab,ti OR cortidron*:ab,ti OR cortisumman:ab,ti OR (dacort* NEAR/1 fue*):ab,ti OR dalalone:ab,ti OR decilone:ab,ti OR decofluor:ab,ti OR dectancyl:ab,ti OR decacort*:ab,ti OR dekacort*:ab,ti OR delladec:ab,ti OR deltafluoren:ab,ti OR dergramin:ab,ti OR deronil:ab,ti OR desadrene:ab,ti OR desalark:ab,ti OR desameto*:ab,ti OR dexinoral:ab,ti OR dexionil:ab,ti OR dexone:ab,ti OR dextelan:ab,ti OR dezone:ab,ti OR d?xamethasone:ab,ti OR esacortene:ab,ti OR 'ex s1':ab,ti OR exadion*:ab,ti OR firmalone:ab,ti OR (fluor* NEAR/1 predniso*):ab,ti OR fluormethylpredniso*:ab,ti OR fluormone:ab,ti OR fluorocort:ab,ti OR fluorodelta:ab,ti OR fortecortin:ab,ti OR gammacorten*:ab,ti OR grosodexon*:ab,ti OR dexa*:ab,ti OR hexadecad*:ab,ti OR hexadiol:ab,ti OR hexadrol:ab,ti OR isnacort:ab,ti OR isopto*:ab,ti OR 'lokalison f':ab,ti OR luxazone:ab,ti OR marvidione:ab,ti OR maxidex:ab,ti OR mediamethasone:ab,ti OR megacortin:ab,ti OR mephameson*:ab,ti OR metasolon*:ab,ti OR methazon*:ab,ti OR 'metisone lafi':ab,ti OR millicorten*:ab,ti OR nisomethasona:ab,ti OR novocort:ab,ti OR opticort*:ab,ti OR oradex*:ab,ti OR orgadrone:ab,ti OR policort:ab,ti OR posurdex:ab,ti OR 'predni f tablinen':ab,ti OR 'prednisolone f':ab,ti OR prodex*:ab,ti OR sanamethasone:ab,ti OR spoloven:ab,ti OR triamcimetil:ab,ti OR visumethazone:ab,ti OR decadeltosona:ab,ti OR decadeltosone:ab,ti OR decadion*:ab,ti OR decadran:ab,ti OR decadron*:ab,ti OR decaesadril:ab,ti OR decamethasone:ab,ti OR decasone:ab,ti OR decaspray:ab,ti OR decasterolone:ab,ti	117 552
149.	'(e)-4,4-(1,2-diethyl-1,2-ethenediyl)bisphenol':ab,ti OR '3, 4-bis(p-hydroxyphenyl)-3-hexene':ab,ti OR acnestrol:ab,ti OR 'alpha,alpha-diethylstilbenediol':ab,ti OR antigestil:ab,ti OR apstil:ab,ti OR boestrol:ab,ti OR bufon:ab,ti OR 'cyren a':ab,ti OR des:ab,ti OR diastyl:ab,ti OR diethylstilbenediol:ab,ti OR diethylstilbestrolum:ab,ti OR diethylstilbestrol:ab,ti OR diethylstilboestrol:ab,ti OR distilbene:ab,ti OR domestrol:ab,ti OR estrobene:ab,ti OR estromenin:ab,ti OR estrosyn:ab,ti OR fonatol:ab,ti OR grafestrol:ab,ti OR makarol:ab,ti OR microest:ab,ti OR milestrol:ab,ti OR 'neo-oestronol i':ab,ti OR oestrogeni*:ab,ti OR oestromenin:ab,ti OR oestromensyl:ab,ti OR oestromon:ab,ti OR sexocretin:ab,ti OR sibol:ab,ti OR stilbestro*:ab,ti OR stilbetin:ab,ti OR stilboefral:ab,ti OR stilboestrol:ab,ti OR stilkap:ab,ti OR synestrin:ab,ti OR synthoestrin:ab,ti OR vagestrol:ab,ti OR hexanestrol:ab,ti OR hexestrofen:ab,ti OR hexital:ab,ti OR hexron:ab,ti OR hexypheen:ab,ti OR 'hi bestrol':ab,ti OR 'hormoestrol':ab,ti OR menostilbene:ab,ti OR 'meso hexestrol':ab,ti OR mesohexestrol:ab,ti OR micrest:ab,ti OR 'neo estranol':ab,ti OR 'nsc 3070':ab,ti OR 'nsc 35752':ab,ti OR 'nsc 9894':ab,ti OR oekolp:ab,ti OR	437 704

#	Search History	Results
	oestrostilben:ab,ti OR oestrosyntal:ab,ti OR orestrol:ab,ti OR ovendosyn:ab,ti OR pabestrol:ab,ti OR pabestrosalve:ab,ti OR palestrol:ab,ti OR proestrin:ab,ti OR serral:ab,ti	
150.	docetaxel:ab,ti OR taxotere:ab,ti	11 409
151.	'(8s-cis)-10-[(3-amino-2,3,6-trideoxy-alpha-l-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroacetyl)-1-methoxy-5,12-naphthacenedione':ab,ti OR '14-hydroxydaunomycin':ab,ti OR doxorubicin:ab,ti OR 'hydroxyl daunorubicin':ab,ti OR adriablastin*:ab,ti OR adriacin:ab,ti OR adriam?cina:ab,ti OR adriamycin:ab,ti OR adriblastin*:ab,ti OR caelyx:ab,ti OR dexorubicin:ab,ti OR 'dox sl':ab,ti OR doxil:ab,ti OR doxorubicin*:ab,ti OR 'fi 106':ab,ti OR lipodox:ab,ti OR 'liposomal doxorubicin':ab,ti OR myocet:ab,ti OR 'nsc 123127':ab,ti OR 'pegylated liposomal doxorubicin':ab,ti OR rastocin:ab,ti OR resmycin:ab,ti OR 'rp 25253':ab,ti OR rubex:ab,ti OR sarcodoxome:ab,ti OR 'tlc d 99':ab,ti	46 002
152.	dutasteride:ab,ti OR 'gg 745':ab,ti OR 'gg745':ab,ti OR avodart:ab,ti OR avolve:ab,ti OR advodart:ab,ti OR duagen:ab,ti OR 'gi 198745':ab,ti OR gi198745*:ab,ti	662
153.	e7389:ab,ti OR 'e 7389':ab,ti OR eribulin:ab,ti OR 'halichondrin b analog':ab,ti	175
154.	estramustine:ab,ti OR 'leo 275':ab,ti OR 'leo 462':ab,ti OR 'nsc 89199':ab,ti OR 'ro 21 8837':ab,ti OR 'ro 22 2296 000':ab,ti OR leo275:ab,ti OR leo462:ab,ti OR nsc89199:ab,ti OR ro218837:ab,ti OR ro222296000:ab,ti	1153
155.	'4-demethylepipodophyllotoxin 9-[4,6-o-ethylidene-beta-d-glucopyranoside':ab,ti OR 'demethyl epipodophyllotoxin ethylidine glucoside':ab,ti OR epeg:ab,ti OR etoposide:ab,ti OR vepesid:ab,ti OR 'vp 16-213':ab,ti OR etomedac:ab,ti OR etopol:ab,ti OR lastet:ab,ti OR 'nk 171':ab,ti OR 'nsc 141540':ab,ti OR toposar:ab,ti OR vepesid*:ab,ti	18 446
156.	'(5alpha,17beta)-n-(1,1-dimethylethyl)-3-oxo-4-azaandrost-1-ene-17-carboxamide':ab,ti OR 'chibro-proscar':ab,ti OR finasteride:ab,ti OR finastid:ab,ti OR 'mk 906':ab,ti OR 'pro-cure':ab,ti OR propecia:ab,ti OR propeshia:ab,ti OR proscar:ab,ti OR prostide:ab,ti OR urprosan:ab,ti OR 'ym 152':ab,ti	2410
157.	flutamide:ab,ti OR apimid:ab,ti OR chimax:ab,ti OR eulexine:ab,ti OR flucinome:ab,ti OR flucinom:ab,ti OR flugerel:ab,ti OR fluken:ab,ti OR flulem:ab,ti OR 'fluta-gry':ab,ti OR flutabene:ab,ti OR flutacan:ab,ti OR flutamex:ab,ti OR flutamin:ab,ti OR flutan:ab,ti OR flutaplex:ab,ti OR flut:ab,ti OR fugerel:ab,ti OR grisetin:ab,ti OR oncosal:ab,ti OR profamid:ab,ti OR prostacur:ab,ti OR prostadirex:ab,ti OR prostica:ab,ti OR prostogenat:ab,ti OR 'sch 13521':ab,ti OR sch13521:ab,ti OR tafenil:ab,ti OR tecnoflut:ab,ti OR testotard:ab,ti OR drogenil:ab,ti OR euflex:ab,ti OR eulexin:ab,ti OR flumid:ab,ti OR niftolid:ab,ti OR niphtholid:ab,ti OR sebatrol:ab,ti	2812
158.	goserelin:ab,ti OR 'ici-118630':ab,ti OR 'ici 118 630':ab,ti OR 'ici 118630':ab,ti OR ici118630:ab,ti OR zoladex:ab,ti	1233
159.	'(11beta)-11,17,21-trihydroxypregn-4-ene-3,20-dione':ab,ti OR 'aeroseb-hc':ab,ti OR 'barseb hc':ab,ti OR cetacort:ab,ti OR 'cort-dome':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortifan:ab,ti OR cortisol:ab,ti OR cortispray:ab,ti OR cortril:ab,ti OR dermacort:ab,ti OR domolene:ab,ti OR eldecort:ab,ti OR hautosone:ab,ti OR 'heb-cort':ab,ti OR hydrocortisone:ab,ti OR hydrocortone:ab,ti OR hytone:ab,ti OR 'komed-hc':ab,ti OR nutracort:ab,ti OR proctocort:ab,ti OR rectoid:ab,ti OR therapeutic:ab,ti AND hydrocortisone:ab,ti OR alphaderm:ab,ti OR barseb:ab,ti OR cetacort:ab,ti OR cobadex:ab,ti OR 'compound f':ab,ti OR cortef:ab,ti OR cortenema:ab,ti OR cortibel:ab,ti OR cortifan:ab,ti OR cortifoam:ab,ti OR cortiment:ab,ti OR cortiphate:ab,ti OR cortisol*:ab,ti OR cortoderm:ab,ti OR cortril:ab,ti OR dermolate:ab,ti OR dioderm:ab,ti OR duomedihaler:ab,ti OR 'ef cortelan':ab,ti OR efcortelan:ab,ti OR egocort:ab,ti OR eksalb:ab,ti OR eldecort:ab,ti OR ficortril:ab,ti OR hebcort:ab,ti OR hycort:ab,ti OR hydracort:ab,ti OR hydrasson:ab,ti OR 'hydro ricortex':ab,ti OR hydrocort:ab,ti OR hydrocorticosteroid:ab,ti OR hydrocortisate:ab,ti OR hydrocortis*:ab,ti OR hydrocortone:ab,ti OR hydroderm:ab,ti OR hysone:ab,ti OR hytone:ab,ti OR incortin:ab,ti OR medihaler:ab,ti OR mildison:ab,ti OR munitren:ab,ti AND 'neo cortef':ab,ti OR neocortef:ab,ti OR novohydrocort:ab,ti OR 'nsc 10483':ab,ti OR 'nsc 741':ab,ti OR nutracort:ab,ti OR otosone:ab,ti OR penecort:ab,ti OR prepcort:ab,ti OR proctocort:ab,ti OR proctosone:ab,ti OR rectocort:ab,ti OR schericur:ab,ti OR 'scherosone f':ab,ti OR 'solu cortef':ab,ti OR synacort:ab,ti OR vasocort:ab,ti	23
160.	'anti-cytotoxic t-lymphocyte-associated antigen-4 monoclonal antibody':ab,ti OR ipilimumab:ab,ti OR 'mdx-010':ab,ti OR 'mdx-ctla4':ab,ti OR 'bms 734016':ab,ti OR yervoy:ab,ti	575
161.	jm216:ab,ti OR 'jm 216':ab,ti	92
162.	ketoconazole:ab,ti OR fungarest:ab,ti OR fungoral:ab,ti OR ketoderm:ab,ti OR ketoisdin:ab,ti OR nizoral:ab,ti OR orifungal:ab,ti OR panfungol:ab,ti OR xolegel:ab,ti OR anisole:ab,ti OR cetonax:ab,ti OR 'dio 902':ab,ti OR dio902:ab,ti OR 'kw 1414':ab,ti OR kw1414:ab,ti OR micoral:ab,ti OR nisoral:ab,ti OR oxocanazole:ab,ti OR oxoconazole:ab,ti OR 'r 41 400':ab,ti OR r41400:ab,ti OR terzolin:ab,ti	8148
163.	leuprolide:ab,ti OR leuprorelin:ab,ti OR leuplin:ab,ti OR leupro*:ab,ti OR lucrin:ab,ti OR lupride:ab,ti OR lupron:ab,ti OR procrin:ab,ti OR prostap:ab,ti OR tap144:ab,ti OR 'tap 144':ab,ti	2493
164.	mdv3100:ab,ti OR 'mdv3100':ab,ti	129
165.	megastrol:ab,ti	6
166.	mitoxantrone:ab,ti OR dihydroxyanthracenedione:ab,ti OR mito?antrone:ab,ti OR novanthron:ab,ti OR novantron*:ab,ti OR 'now 85 34':ab,ti OR 'now 8534':ab,ti OR now8534:ab,ti OR 'nsc 279836':ab,ti OR	17809

#	Search History	Results
	'nsc 301739':ab,ti OR 'nsc 301739d':ab,ti OR nsc279836:ab,ti OR nsc301739:ab,ti OR nsc301739d:ab,ti	
167.	nilutamide:ab,ti OR anandron:ab,ti OR nilandron:ab,ti OR anadron:ab,ti OR nitulamide:ab,ti OR 'rn 23908':ab,ti OR 'ru 23908':ab,ti OR rn23908:ab,ti OR ru23908:ab,ti	269
168.	'abi 007':ab,ti OR 'abi007':ab,ti OR abraxane:ab,ti OR 'bms 181339':ab,ti OR coroxane:ab,ti OR genexol:ab,ti OR hunxol:ab,ti OR intaxel:ab,ti OR 'nsc 125973':ab,ti OR paxceed:ab,ti OR paclitaxel:ab,ti OR paxene:ab,ti OR taxol:ab,ti OR yewtaxan:ab,ti OR anzatax:ab,ti OR asotax:ab,ti OR bristaxol:ab,ti OR praxel:ab,ti	26 559
169.	'pamidronic acid':ab,ti OR pamidronate:ab,ti OR aredia:ab,ti OR aminomux:ab,ti OR 'gcp-23339a':ab,ti	2520
170.	prednison*:ab,ti OR prednisolon*:ab,ti OR adasone:ab,ti OR cortancyl:ab,ti OR dacortin:ab,ti OR 'de cortin':ab,ti OR decortin:ab,ti OR 'de cortisyl':ab,ti OR decortisyl:ab,ti OR decorton:ab,ti OR 'delta(1)-cortisone':ab,ti OR 'delta-dome':ab,ti OR deltacortene:ab,ti OR deltacortisone:ab,ti OR deltadehydrocortisone:ab,ti OR deltasone:ab,ti OR deltison:ab,ti OR deltra:ab,ti OR econosone:ab,ti OR lisacort:ab,ti OR 'meprosona-f':ab,ti OR ofisolona:ab,ti OR panafcort:ab,ti OR 'panasol-s':ab,ti OR paracort:ab,ti OR predeltin:ab,ti OR predicorten:ab,ti OR predicor:ab,ti OR 'prednicen-m':ab,ti OR prednicort:ab,ti OR prednidib:ab,ti OR prednilonga:ab,ti OR predniment:ab,ti OR prednisone:ab,ti OR prednisonum:ab,ti OR prednitone:ab,ti OR promifen:ab,ti OR servisone:ab,ti OR 'sk-prednisone':ab,ti OR sterapred:ab,ti OR ancortone:ab,ti OR biocortone:ab,ti OR colisone:ab,ti OR cortidelt:ab,ti OR decortancyl:ab,ti OR dekortin:ab,ti OR delitisone:ab,ti OR 'delta cortelan':ab,ti OR 'delta cortisone':ab,ti OR 'delta dome':ab,ti OR 'delta e':ab,ti OR 'delta prenovis':ab,ti OR deltacorten:ab,ti OR deltacortone:ab,ti OR 'di adreson':ab,ti OR diadreson:ab,ti OR encorton*:ab,ti OR enkorton*:ab,ti OR hostacortin:ab,ti OR insone:ab,ti OR meprison:ab,ti OR metacortandracin:ab,ti OR meticorten:ab,ti OR meticortine:ab,ti OR 'nsc 10023':ab,ti OR nsc10023:ab,ti OR orasone:ab,ti OR orisane:ab,ti OR precort:ab,ti OR precortal:ab,ti OR pronison*:ab,ti OR pronizone:ab,ti OR rectodelt:ab,ti OR ultracorten:ab,ti OR urtilone:ab,ti	51 149
171.	samarium:ab,ti	1494
172.	sipuleucelt:ab,ti OR 'apc8015 vaccine':ab,ti OR 'apc8015':ab,ti OR 'pa2024 (pap/gm-csf)-loaded dendritic cell vaccine':ab,ti OR provenge:ab,ti OR 'sipuleucel-t':ab,ti OR 'apc 8015':ab,ti	342
173.	strontium:ab,ti	6566
174.	'tak-700':ab,ti OR 'tak 700':ab,ti OR 'tak700':ab,ti	29
175.	triptorelin:ab,ti OR '6-d-tryptophan-lh-rh':ab,ti OR '6-d-tryptophanluteinizing hormone-releasing factor':ab,ti OR 'ay-25650':ab,ti OR 'cl-118,532':ab,ti OR 'decapeptyl':ab,ti OR detryptoreline:ab,ti OR '[d trp 6] lhrh':ab,ti OR 'arvekap':ab,ti OR 'ay 25650':ab,ti OR 'ay25650':ab,ti OR 'd trp 6 lhrh':ab,ti OR 'd trp 6 luteinizing hormone releasing hormone':ab,ti OR 'gonadorelin [6 dextro tryptophan]':ab,ti OR 'gonadotropin releasing hormone [6 dextro tryptophan]':ab,ti OR 'lhrh (d trp 6)':ab,ti OR 'lhrh [6 dextro tryptophan]':ab,ti OR 'luteinizing hormone releasing hormone [6 dextro tryptophan]':ab,ti OR trelstar:ab,ti OR 'trelstar la':ab,ti OR tryptorelin:ab,ti	1058
176.	'le 29060':ab,ti OR 'le29060':ab,ti OR 'leukoblastin':ab,ti OR rozevin:ab,ti OR 'vin blastine':ab,ti OR vinblastin*:ab,ti OR vincaleucoblastin*:ab,ti OR vincaleukoblastin*:ab,ti OR vincoblastin*:ab,ti OR vincoleucoblastin*:ab,ti OR vincoleukoblastin*:ab,ti OR vinleucoblastine:ab,ti OR vlb:ab,ti	9743
177.	navelbine:ab,ti OR vinorelbine:ab,ti OR '3,4-didehydro-4-deoxy-c-norvincaleukoblastine':ab,ti OR '5-nor-anhydrovinblastine':ab,ti OR dihydroxydeoxynorvinkaleukoblastine:ab,ti OR 'nor-5-anhydrovinblastine':ab,ti	3842
178.	zd4054:ab,ti OR 'zd 4054':ab,ti OR zibotentan:ab,ti OR 'n (3 methoxy 5 methylpyrazin 2 yl) 2 [4 (1, 3, 4 oxadiazol 2 yl) phenyl] pyridine 3 sulfonamide':ab,ti	75
179.	'zoledronic acid':ab,ti OR zoledronate:ab,ti OR zometa:ab,ti OR reclast:ab,ti OR 'zol 446':ab,ti OR 'cgp 42446':ab,ti	3463
180.	'5, 6 dimethyl 9 oxo 9h xanthene 4 acetic acid':ab,ti OR dmxaa:ab,ti OR 'as 1404':ab,ti OR as1404:ab,ti OR 'asa 404':ab,ti OR asa404:ab,ti OR 'nsc 640488':ab,ti OR nsc640488:ab,ti	217
181.	'imc a12':ab,ti OR 'imc ? a12':ab,ti OR cixutumumab:ab,ti OR 'anti-igf-1r recombinant monoclonal antibody imc-a12':ab,ti	57
182.	patupilone:ab,ti OR 'epo 906':ab,ti OR epo906:ab,ti OR 'epothilon b':ab,ti	125
183.	sunitinib:ab,ti OR 'pha 2909040ad':ab,ti OR pha2909040ad:ab,ti OR 'su 010398':ab,ti OR 'su 011248':ab,ti OR 'su 10398':ab,ti OR 'su 11248':ab,ti OR su010398:ab,ti OR su011248:ab,ti OR su10398:ab,ti OR su11248:ab,ti OR sutent:ab,ti	3940
184.	'cab':ab,ti OR 'complete androgen blockade':ab,ti	2357

#	Search History	Results
185.	alpharadin OR ‘radium 223’ OR ‘radium-223’	195
186.	#36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90	1 361 079
187.	#27 AND #35 AND #91	1040
188.	**#27 AND #35 AND #91 AND [1-3-2012]/sd NOT [20-11-2012]/sd**	125

A3. **Priority Question**: Please provide the following data for the subgroup of people who received docetaxel following AAP or PP in each treatment arm respectively:

- rPFS results as reported in table 19
- OS results as reported in table 20
- Iterative parameter estimate and Rank preserving failure model HRs as reported in table 22.
- Time on docetaxel treatment

Janssen would like to reiterate the following: the data requested is a *post-hoc* analysis of patients in the COU-AA-302 trial who subsequently receive docetaxel. This group of patients progressed more quickly, and therefore moved onto docetaxel treatment earlier than the other patients in the trial. This *post-hoc* analysis violates the principles of randomisation, and in effect, selects for the patients with the worst prognosis (ie those that progress quickly and move onto chemotherapy), which renders any interpretation of these results meaningless. However, we have agreed to release the data requested, as follows (please note the answers to this question must remain **commercial-in-confidence**):

[redacted]

[redacted]

rPFS : AA vs Placebo, stratified by subsequent Docetaxel treatment

[redacted]

Time on treatment : AA vs Placebo, stratified by subsequent Docetaxel treatment

[redacted]

[redacted]

[redacted]

[redacted]