HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

12 June 2013

ZYTIGA 250 mg, tablet

Bottle of 120 (CIP: 217 497-4)

Applicant: JANSSEN CILAG

INN	abiraterone acetate
ATC Code (year)	L02BX03 (androgen biosynthesis inhibitor)
Reason for the review	**Extension of the indication**
List(s) concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"The treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated."**

Actual Benefit (AB)	The actual benefit is substantial.
Improvement in Actual Benefit (IAB)	ZYTIGA provides a minor improvement in actual benefit (level IV) in terms of efficacy in the treatment of metastatic castration-resistant prostate cancer patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
Therapeutic use	ZYTIGA is a first-line treatment for patients with metastatic castration-resistant prostate cancer, who are asymptomatic or mildly symptomatic (score for most intense pain felt in the last 24 hours $\leq$ 3 on a VAS scale from 0 to 10), after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	5 September 2011 (centralised European procedure); Amendment of 18 December 2012 (extension of the indication to be assessed)
Prescribing and dispensing conditions / special status	Initial annual hospital prescription, restricted to oncologists or doctors with cancer training. Renewal not restricted.

ATC Classification	2012	
	L	Antineoplastic and immunomodulating agents
	L02	Endocrine therapy
	L02B	Hormone antagonists and related agents
	L01BX	Other hormone antagonists and related agents
	L02BX03	abiraterone

02 BACKGROUND

This opinion concerns a request of changing the inclusion conditions for ZYTIGA on the list of medicines reimbursed through National Insurance and on the list of medicines approved for hospital use following an extension of the indication in the treatment of metastatic castration-resistant prostate cancer in patients for whom chemotherapy is not yet clinically indicated.

03 THERAPEUTIC INDICATION(S)

"ZYTIGA is indicated with prednisone or prednisolone for:

- the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1 of the SPC)

- the treatment of metastatic castration-resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen."

04 DOSAGE

"The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see information on the mode of administration). Taking the tablets with food increases systemic exposure to abiraterone (see SPC).

ZYTIGA has to be taken with low dose prednisone or prednisolone. The recommended dose of prednisone or prednisolone is 10 mg daily.

Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see SmPC)."

05 THERAPEUTIC NEED

Castration-resistant prostate cancer is defined as a continued clinical or biological progression despite effective castration. It occurs within 18 to 24 months following the implementation of androgen deprivation therapy in metastatic patients.
Recommendations from the French Association of Urologists (AFU) state the following options at this stage of the disease:
Treatment is governed by the presence of pain associated with bone metastases, as well as the progressive nature of the metastatic lesions.
In symptomatic patients, docetaxel-based chemotherapy is proposed as a first-line treatment. For patients unable to receive docetaxel, mainly due to their age or their general health not enabling the cytotoxic effects to be tolerated (neutropenia in particular), the combination of mitoxantrone and corticosteroids may be proposed.
For asymptomatic patients, there is no evidence to justify chemotherapy, which should be discussed individually and weighed up against simple monitoring.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

Conclusion

There are no comparator medicinal products with a comparable Marketing Authorisation to that of ZYTIGA within the scope of the extension of the indication.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSED	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
European Union countries	Assessment in progress	
United States	yes	Population comparable to that of the Marketing Authorisation in Europe

08 ANALYSIS OF AVAILABLE DATA

The submitted dossier includes the results from a pivotal study, COU-AA-302, which is analysed below.

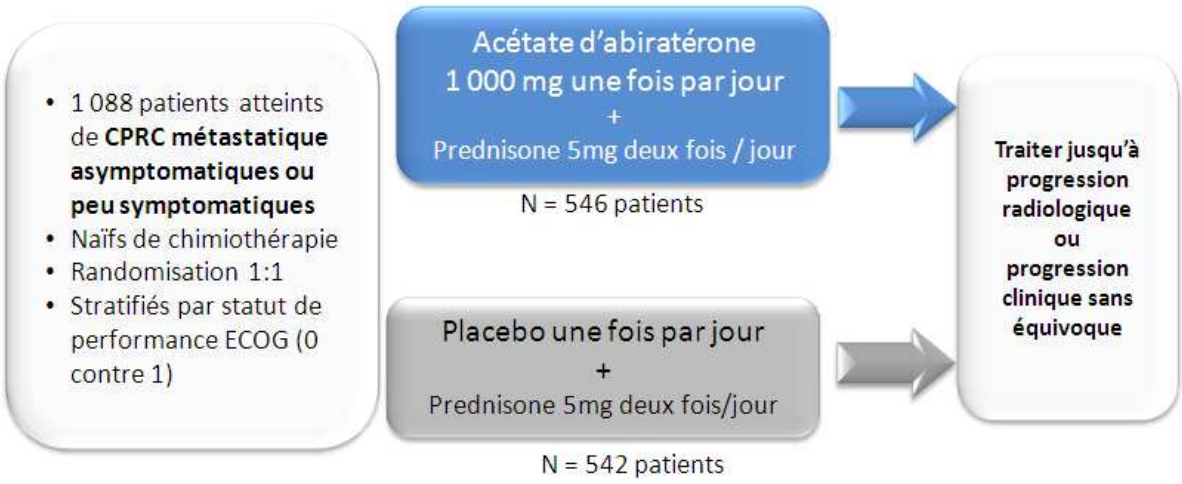
08.1 Efficacy

Study COU-AA-302

A randomised, double-blind phase III study that compared the efficacy and safety of abiraterone acetate (ZYTIGA) to placebo, both combined with prednisone or prednisolone, in asymptomatic or mildly asymptomatic patients with metastatic castration-resistant prostate cancer,[1] and not previously treated with chemotherapy.

Patients were randomised 1:1 into one of the two following groups:
- abiraterone group: patients received 1,000 mg of abiraterone acetate per day (4 x 250 mg tablets/day given as a single dose, orally, 1 hour before or 2 hours after eating) and 5 mg of prednisone or prednisolone 2 times/day, every day of the 28 days "cycles";
- placebo group: patients received 4 tablets of the placebo per day taken at the same time (1 hour before or 2 hours after eating) and 5 mg of prednisone or prednisolone 2 times/day, every day of the 28 days "cycles".
Randomization of patients was stratified at inclusion according to ECOG performance score and PS 0 versus PS 1 performance status.

Figure 1: Study COU-AA-302 – Study design



- 1,088 asymptomatic or mildly asymptomatic patients with metastatic CRPC
- Chemotherapy naïve
- Randomisation 1:1
- Stratified by ECOG performance status (0 or 1)

  1,000 mg abiraterone acetate once daily + 5 mg prednisone twice daily

  Placebo, once daily + 5 mg prednisone twice daily

[1] most intense pain felt in the last 24 hours on a VAS scale from 0 to 10 (asymptomatic = score 0 or 1; mildly symptomatic = score 2 or 3)

Treat until radiological progression or unequivocal clinical progression

Patients had to remain on treatment until confirmed radiological progression was seen. However:

- if the patient showed radiological progression in the absence of unequivocal clinical progression and if no other treatment was indicated, the patient could continue to receive the treatment in progress at the investigator's discretion;
- if the patient showed unequivocal clinical progression without any radiological progression, they could discontinue the study treatment to receive the standard treatment available.

For clarification, unequivocal clinical progression was defined as:

- the presence of cancer pain requiring chronic treatment with morphine (the use of *oral* morphine for more than 3 weeks or parenteral morphine for more than 7 days). The investigator could thus evaluate the need to implement a cytotoxic chemotherapy treatment or not;
- the immediate need to have cytotoxic chemotherapy treatment or radiotherapy, or to perform a surgical procedure due to tumour-related complications (even in cases of an absence of radiological progression);
- deterioration in ECOG performance status of grade PS 3 or above. Patients with an ECOG performance status that deteriorated to a grade PS 2 had to be monitored with regard to their need for chemotherapy.

The two joint primary endpoints were radiological progression-free survival (rPFS) and overall survival.

Radiological progression-free survival was defined as the time between randomisation and radiological progression or death.
Radiological progression was defined[2], according to PCWG2 (bone scintigraphy) or modified RECIST (CT-CAT scan or MRI) criteria, respectively by:

- disease progression observed through scintigraphy, showing new lesions confirmed by a second scintigraph (PCWG2 criteria):
  - if the first scintigraph showed at least 2 new lesions compared with baseline at least 12 weeks since randomisation and was confirmed by a second scintigraph at least 6 weeks later showing at least 2 additional lesions (at least 4 new lesions compared with baseline);
  - if the first scintigraph showed at least 2 new lesions compared with baseline more than 12 weeks after randomisation and was confirmed at least 6 weeks after a second scintigraph showing these same lesions (at least 2 new lesions compared with baseline);
- disease progression into the soft tissue according to modified RECIST[3] criteria confirmed by CT-CAT scan or MRI.

Overall survival was defined as the time between randomisation and death from any cause.

The main secondary endpoints were the following:

- time until the need for treatment with opiates, defined as the time between randomisation and the use of an opiate for the treatment of cancer pain;
- time until the start of cytotoxic chemotherapy, defined as the time between randomisation and administration of cytotoxic chemotherapy for the treatment of prostate cancer;
- time until deterioration in ECOG performance status, defined as the time between randomisation and the date when ECOG PS deteriorated by at least 1 point/grade (corresponding to a worsening in performance status compared with baseline). Determination of the time until confirmed deterioration in ECOG performance status (evaluated at the following visit) was the subject of a *post-hoc*[4] analysis;

[2] Scintigraphy or MRI performed at inclusion then cycle 3, 5, 7, 10 then every 3 cycles.
[3] RECIST: Response Evaluation Criteria in Solid Tumours
[4] *Post-hoc* analysis carried out during the second and third interim analysis (20 December 2011 and 22 May 2012).

- time until PSA progression[5] defined as the time between randomisation and PSA progression according to PCWG2 criteria;
- PSA response rate, defined as the proportion of patients showing a reduction in PSA by at least 50% compared with baseline according to PCWG2 criteria;
- objective response rate defined as the proportion of patients showing an objective response (i.e. a complete response [CR[6]] or a partial response [PR[7]]) identified with CT-CAT scan or MRI;
- duration of response, defined as the time between the first response and the appearance of progression identified with CT-CAT scan or MRI;
- time until an increase in the need for analgesics, defined as the time between randomisation and the date of an increase of ≥ 30% in score for analgesics used over a 4 week period;
- quality of life measured using a functional status scale specific to prostate cancer: FACT-P (Functional Assessment of Cancer Therapy – Prostate) and BPI-SF quality of life questionnaire;
- safety.

Statistical analysis

The significance level was set at 5% for the superiority conclusions for abiraterone (+ prednisone/prednisolone) over placebo (+ prednisone/prednisolone), the α risk was shared between the two joint primary efficacy endpoints:

- α = 0.01 for rPFS. Considering a proportional risk model for the two treatment arms, it was estimated that 378 events would be necessary to highlight a difference of two months for the median (4 months in the placebo group and 6 months in the abiraterone group) with a power of 91% and an α risk of 0.01 (HR=0.667);
- α = 0.04 for overall survival. Considering a proportional risk model for the two treatment arms, it was estimated that 773 events would be necessary to highlight a difference of 5.5 months for the median overall survival (22 months in the placebo group and 27.5 months in the abiraterone group) with a power of 85% and an α risk of 0.04 (HR=0.80).
- The significance thresholds should be used for the final analysis of each of the joint primary endpoints.

<u>Statistical analyses planned for in the protocol</u>

The exact timings for carrying out the evaluations for the two joint endpoints were pre-specified and determined as follows:

- a single analysis was planned in the protocol for radiological progression-free survival (rPFS); this analysis was performed with a centralised review by an independent review board (IDMC).
- three interim analyses and one final analysis were scheduled for overall survival (OS):
    - the first analysis for OS was scheduled after the occurrence of 15% of deaths (116 deaths);
    - the second interim analysis for OS was scheduled after the occurrence of 40% of deaths (311 deaths);
    - the third interim analysis for OS was scheduled after 55% of deaths (425 deaths).
    - In order to manage the inflation in α risk, the O'Brien-Fleming method enabled thresholds to be adjusted for the various analyses for overall survival; the significance threshold to be achieved was <0.0001 for the first interim analysis for OS, ≤0.0005 for the second and ≤0.0034 for the third interim analysis. This adjustment enabled the type I risk error to be controlled throughout the interim

[5] Progression is defined as an increase in PSA ≥25% compared with the baseline value and ≥2 ng/ml above nadir confirmed by a second analysis at least 3 weeks later. In the absence of a reduction in PSA compared with baseline, progression is also defined as an increase ≥25% compared with the baseline value and ≥2 ng/ml above nadir at 12 weeks.

[6] Complete response: disappearance of lesions after treatment

[7] Partial response: reduction ≥30% in the total diameter of all lesions (compared with the initial value)

analyses and will enable conclusions to be made regarding efficacy in the final analysis, with a predefined risk of 4%.

Main inclusion and exclusion criteria

Inclusion criteria:
- age >18 years
- metastatic stage of prostate adenocarcinoma confirmed histologically or cytologically (apart from hepatic, visceral or cerebral metastases)
- documented tumour progression with a rise in PSA levels (according to PCWG2 criteria) or according to radiological criteria (based on modified RECIST criteria)
- history of anti-androgen treatment and progression following withdrawal of anti-androgen treatment
- ECOG performance status of 0 or 1
- medical or surgical castration with testosterone < 50 ng/dl
- asymptomatic or mildly symptomatic (according to question n°3 of BPI-SF ranging from 0 to 10 [most intense pain felt within the last 24 hour period]): asymptomatic = score 0 or 1; mildly symptomatic = score 2 or 3

Exclusion criteria:
- history of cytotoxic chemotherapy and biological treatment for castration-resistant prostate cancer
- history of treatment with ketoconazole for more than 7 days for prostate cancer
- known cerebral, hepatic or visceral metastases
- use of opiate-based analgesics for cancer pain, in particular codeine and dextropropoxyphene, currently or in the four weeks prior to Day 1 of cycle 1

Results:

A total of 1,088 patients were randomised and formed the ITT population:
- 546 patients in the abiraterone group;
- 542 patients in the placebo group.

Four patients in the abiraterone group and 2 patients in the placebo group did not receive the study treatment and were excluded from the assessable population for safety (safety population N = 1,082 patients; abiraterone n = 542 patients; placebo n = 540 patients).

The median age at inclusion was 70 years; 32% of patients were aged 75 years or above (distribution for over 75 years: 34% in the abiraterone group and 30% in the placebo group).
Twenty-six percent (26%) of patients were initially diagnosed at the metastatic stage and 52% showed a Gleason score of ≥ 8 at inclusion.
More than eighty percent (81.4%) of patients presented with bone metastases; 50% of patients only had bone metastases and 19% of patients only had soft tissue metastases or lymph node involvement. Patients presenting with visceral, hepatic or cerebral metastases were excluded from the study.

Results for the joint primary endpoints

- radiological progression-free survival (rPFS)

During the analysis carried out on December, 20th 2010, the main analysis for rPFS, 27.5% (n=150) of patients in the abiraterone group and 46.3% (n=251) of those in the placebo group had reported an event (radiological progression or death). The median follow-up for patients during this analysis was 8.3 months.
The median radiological progression-free survival was 8.3 months in the placebo group but this was not achieved in the abiraterone group (HR = 0.425 (95% CI: [0.347; 0.522]; p<0.0001).
An analysis carried out within the context of the second analysis of overall survival showed a median radiological progression-free survival of 8.3 months in the placebo group and 16.5 months in the abiraterone group, HR = 0.530 (95% CI: [0.451; 0.623]; p<0.0001).

- overall survival

During the first interim analysis, carried out on December, 20th 2010 in conjunction with the main rPFS analysis, median overall survival had not been achieved in either of the two treatment groups.

During the second interim analysis, carried out one year later on December, 20th 2011, the median overall survival had still not been achieved in the abiraterone group but it was 27.24 months in the placebo group.

No difference was observed between the two groups during the third interim analysis for median overall survival (35.3 months in the abiraterone group versus 30.1 months in the placebo group with a value for p = 0.0151 above the threshold initially set at 0.0034 to conclude superiority).

The third interim analysis was carried out after 434 deaths, which was close to half (56%) of the events planned for the final analysis (773 events). This analysis was carried out after the blind status was removed, a decision made by the independent review board in light of the clinical benefit observed in rPFS and the secondary endpoints during the second interim analysis. On this date, 14.4% of patients in the placebo had already received abiraterone.

Results for the secondary endpoints (second interim analysis)

- The median time to PSA progression, based on PCWG2 criteria, was 11.1 months for patients receiving ZYTIGA and 5.6 months for patients receiving placebo (HR = 0.488; 95% CI: [0.420; 0.568], p < 0.0001).

The proportion of patients with a confirmed response for PSA levels was larger in the ZYTIGA group than in the placebo group (62% versus 24%; p < 0.0001).

- Time to use of opiates for cancer pain: the median time was not achieved for patients receiving ZYTIGA, but was 23.7 months for patients receiving placebo (HR = 0.686; 95% CI: [0.566; 0.833], p = 0.0001).

- Time to start of chemotherapy with a cytotoxic agent: the median time was 25.2 months for patients receiving ZYTIGA and 16.8 months for patients receiving placebo (RR = 0.580; 95% CI: [0.487; 0.691], p < 0.0001)

- Time to deterioration of ECOG performance index ≥ 1 point: the median time was 12.3 months for patients receiving ZYTIGA and 10.9 months for patients receiving placebo (HR = 0.821; 95% CI: [0.714; 0.943], p = 0.0053).

- Objective response: the proportion of patients with an initial measurable disease with an objective response was 36% in the ZYTIGA group and 16% in the placebo group (p < 0.0001).

- Pain: the median time to progression was 26.7 months in the ZYTIGA group and 18.4 months in the placebo group.

- Time to deterioration of FACT-P (total score): treatment with ZYTIGA reduced the risk of deterioration of FACT-P (total score) by 22% compared with placebo (p = 0.0028). The median time to deterioration of FACT-P (total score) was 12.7 months in the ZYTIGA group and 8.3 months in the placebo group.

08.2 Safety/Adverse effects

The frequency of treatment discontinuations due to adverse events was 7.4% in the abiraterone group and 5.4% in the placebo group. Hepatotoxicity was the reason for treatment discontinuation for 2.2% of patients in the abiraterone group versus 0.2% in the placebo group.
The most commonly reported main grade 3 or 4 adverse events (abiraterone group versus placebo group) were: arterial hypertension (4% as opposed to 3%), back pain (3% as opposed to 4%), an increase in alanine aminotransferase (5.4% versus 0.7%) and aspartate aminotransferase (3.0% versus 0.9%).

08.3 Summary & discussion

A randomised, double-blind phase III study compared the efficacy and safety of abiraterone acetate (ZYTIGA) with placebo, both combined with prednisone or prednisolone, in asymptomatic or mildly asymptomatic patients with metastatic castration-resistant prostate cancer, and not previously treated with chemotherapy.
Mildly asymptomatic patients should have a score for the most intense pain felt in the last 24 hours $\leq$ 3 on a VAS from 0 to 10 (asymptomatic = score 0 or 1).
Two joint primary endpoints were defined: radiological progression-free survival (rPFS) and overall survival.
A total of 1,088 patients were randomised (546 patients in the abiraterone group and 542 patients in the placebo group).
The median age at inclusion was 70 years; 32% of patients were aged 75 years or above (distribution for over 75 years was 34% in the abiraterone group and 30% in the placebo group).
Twenty-six percent (26%) of patients were initially diagnosed at the metastatic stage and 52% showed a Gleason score of ≥ 8 at inclusion. More than eighty percent (81.4%) of patients had bone metastases.

With abiraterone compared with placebo:

- the median radiological progression-free survival (joint primary endpoint) during the main analysis, was not achieved vs. 8.3 months (HR = 0.425 (95% CI: [0.347; 0.522]; p<0.0001).
- the median radiological progression-free survival during the second analysis was 16.5 months vs. 8.3 months (HR = 0.530, 95% CI: [0.451; 0.623]; p<0.0001), which is an absolute increase of 8.2 months
- the median overall survival (joint primary endpoint) during the third interim analysis was not different: 35.3 months versus 30.1 months; p = 0.0151 above the threshold initially set at 0.0034 to conclude superiority.
- the median time before starting chemotherapy was 25.2 months vs. 16.8 months (HR = 0.580; 95% CI: [0.487; 0.691], p < 0.0001).
- the median time before using opiates for cancer pain was not achieved vs. 23.7 months (HR = 0.686; 95% CI: [0.566; 0.833], p = 0.0001).

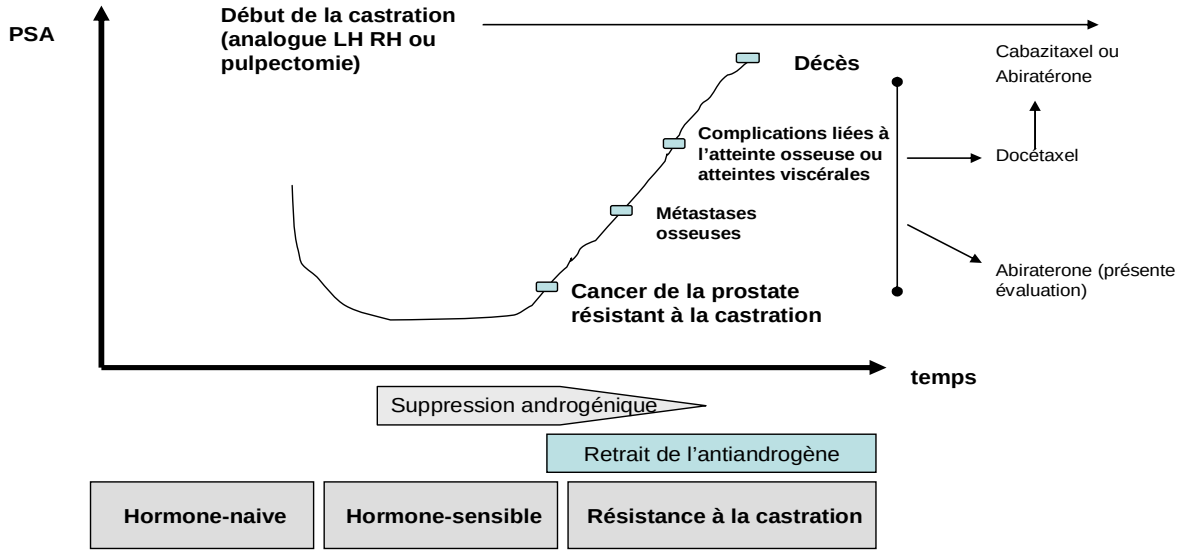
The most commonly reported main grade 3 or 4 adverse events (abiraterone group versus placebo group) were: arterial hypertension (4% as opposed to 3%), back pain (3% as opposed to 4%), an increase in alanine aminotransferase (5.4% versus 0.7%) and aspartate aminotransferase (3.0% versus 0.9%).

09 THERAPEUTIC USE

Castration-resistant prostate cancer (CRPC) is a very heterogenic disease when it comes to survival. Biological progression of CRPC is shown through an elevation in PSA of 50% compared to nadir under treatment, at 2 doses at least 15 days apart. It occurs within 18 to 24 months following the implementation of androgen deprivation therapy in metastatic patients.
In cases of progression following first-line androgen deprivation therapy, guidelines from the French Association of Urologists (AFU)[8] state the following options: 1) complete androgen block, 2) second-line hormone treatments and 3) docetaxel-based chemotherapy for symptomatic patients.
- Complete androgen block:
Addition of an anti-androgen to aLH-RH (or to pulpectomy), which enables a biological response to be obtained in 60% to 80% of cases with a median duration of response of 4 to 6 months.
After progression under complete androgen block, the rule is to investigate a withdrawal syndrome of anti-androgens observed for a third of patients on stopping anti-androgen in the form of a lowering by more than 50% in PSA with a median duration of 4 months.
- Second-line hormone therapies:
- high dose bicalutamide (150 to 200 mg/day) reduces pain and improves subjective symptoms with no objective response in 25% of patients;
- diethylstilbestrol (DES) provides nearly 50% of objective response for PSA and 20% in the subjective improvement of symptoms. The use of low doses (1 mg) reduces the thrombo embolic risk, which remains high, and can be achieved in nearly one third of patients
Inhibition of the adrenal secretion of androgens (ketoconazole, corticosteroids, etc.) is not routinely proposed.
In symptomatic patients, docetaxel-based chemotherapy is proposed as a first-line treatment. For patients unable to receive docetaxel, mainly due to their age or their general health not enabling the cytotoxic adverse effects to be tolerated (neutropenia in particular), the combination of mitoxantrone and corticosteroids may be proposed.
For asymptomatic patients, there is no evidence to justify starting chemotherapy early, which should be discussed individually and weighed up against simple monitoring (abstention of treatment).

ZYTIGA is a first-line treatment for patients with metastatic castration-resistant prostate cancer, who are asymptomatic or mildly symptomatic (score for most intense pain felt in the last 24 hours $\leq$ 3 on a VAS scale from 0 to 10), after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

[8] Salomon L, Azria D, Bastide C, Beuzeboc P, Cormier L, et al, and members of the Oncology Committee of the French Urology Association. Onco-urology guidelines 2010: Prostate cancer. Progrès en Urologie 2010; 20 (Suppl 4): S215-S240.



Start of castration (LHRH analogue or pulpectomy)
Death
Complications linked to bone or visceral involvement
Bone metastases
Castration-resistant prostate cancer
Cabazitaxel or Abiraterone
Docetaxel
Abiraterone (this evaluation)
time
Androgen suppression
Withdrawal of anti-androgen
Hormone-naïve
Hormone-sensitive
Castration-resistant

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above data and information, and following the debate and vote, the committee's opinion is as follows:

010.1 Actual benefit

- Prostate cancer is a life-threatening disease.
- This proprietary medicinal product is a specific curative treatment for prostate cancer.
- The efficacy/adverse effects ratio is high.
- There are no alternative medicinal products with a comparable Marketing Authorisation to that of ZYTIGA within the scope of this extension of the indication.
- Public health benefit:

  In France, the incidence of prostate cancer is estimated as being approximately 71,000 new cases per year (InVS projections 2011[9]). It is the most common of all cancers, representing 34% of all male incident cancers[10] alone. Its incidence is very low in those under the age of 50 years, but increases progressively with age. Thus, nearly 70% of prostate cancer cases occur after the age of 65 years. The mean age of diagnosis was not available for 2011. It was 71 years in 2005. During these last ten years, the incidence of prostate cancer has risen sharply, due to the combined effect of an aging population, improvements in diagnostic techniques and the spread of individual screening through analysis of prostate specific androgens (PSA)[11], despite the absence of satisfactory evidence justifying a systematic screening strategy in the general population[12] or for at risk patients[13].

  In 2002, the real prevalence, i.e. the number of men with prostate cancer receiving initial treatment or in relapse (number of true prevalent cases apart from prevalent cases in remission), was estimated as being approximately 115,000[14].

  In terms of mortality, prostate cancer is the third most common cause of cancer-related deaths in men and represents 10% of all male deaths from cancer[2]. The mortality rate (standardised worldwide) from prostate cancer has seen a notable reduction, going from 16.4 to 12.6 per 100,000 between the periods 1994-98 and 2004-08, which is a reduction of 23%.

  Relative survival at 5 years varies depending on the stage of the disease at diagnosis. According to American data, the survival rate at 5 years for patients diagnosed between 1999 and 2005 was 100% for the localised or regional stage (lymph node involvement), whereas it was 30.6% for diagnosis at the metastatic stage[15]. In France, the relative survival at 5 years from incident prostate cancer declared in Ile-de-France for Health Insurance based on LTC admissions for a malignant tumour during the period 1994-1999 was estimated as being 100% for stage I, 92% for stage II, 74% for stage III and 60% for stage IV[16,17].

  In France, the public health burden of prostate cancer is therefore considerable (approximately 380,000 DALYs Zone Euro A, 2004). Despite the small number of patients diagnosed or progressing towards a metastatic stage, the burden of the sub-population of patients with metastatic castration-resistant prostate cancer and likely to receive ZYTIGA remains moderate due to the higher associated mortality.

[9] Lyon civil hospices / Health Monitoring Institute / National Cancer Institute / Francim / National Institute of Health and Medical Research. Projections of the incidence and mortality from cancer in France in 2011. Technical report. June 2011. http://www.invs.sante.fr/surveillance/cancers [Accessed 16 04 21013].
[10] Inca. Situation and understanding. The cancer situation in France in 2012.
[11] Belot et al. 2008. National estimation of incidence and mortality from cancer in France between 1980 and 2005
[12] Haute Autorité de Santé. Orientation report. Prostate cancer screening: Critical analysis of articles from ERSPC and PLCO studies published in March 2009. June 2010.
[13] Haute Autorité de Santé. Orientation report. Prostate cancer: identification of risk factors and relevance of screening through analysis of prostate specific antigens (PSA) in high risk male populations? February 2012.
[14] Francim Network. Estimation of the partial prevalence of cancer in France in 2002 and the true prevalence for breast, bowel, prostate and kidney cancer. Study report. October 2007. 36 p
[15] Horner MJ, and al. SEER cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER website, 2009
[16] Regional Health Observatory for Ile-de-France. Epidemiology of cancer in Ile-de-France. June 2006.
[17] InCa. Expected survival of patients with cancer in France: the situation, April 2010.

Improvement in the quality of the treatment care management and the quality of life of patients with cancer is a public health need that is already an established priority (Objective 49 of the Law of 9 August 2004 on public health policy, Cancer Plan 2009-2013, Plan to improve the quality of life of patients with chronic diseases 2007-2011).
In view of the available results from the placebo-controlled phase III study on radiological progression-free survival (absolute increase of 8.2 months at the second interim analysis), abiraterone acetate may be expected to provide a moderate impact in terms of a reduction in morbidity. Nevertheless, the expected impact on the reduction in mortality remains difficult to determine, given that the median overall survival was not achieved at the time of the second interim analysis and with no statistical significance (HR= 0.752; 95% CI [0.606; 0.934], p=0.0097 greater than the established limit of 0.00008) and given the third interim analysis was carried out with permitted permutations of treatment for patients presenting with documented disease progression.
The results for time to progression of the disease, deterioration in ECOG performance status and deterioration in quality of life (absolute increase of 4.4 months at the second interim analysis) are comparable and confirm the likely impact of ZYTIGA in slowing down progression of the disease and preserving quality of life, albeit, without enabling clinical relevance to be determined.
Furthermore, the transferability of the results presented to clinical practice appears to be acceptable; the population included appears representative of patients seen in current medical practice, despite the small number of French patients included in the study (n=53).
Finally, the oral method of administration of this medicinal product and its effect on delaying the start of cytotoxic chemotherapy (absolute increase of 8.4 months at the second interim analysis) and therefore admission to hospital could have a positive impact on the organisation of care.
ZYTIGA is therefore likely to provide a response to an identified public health need.
Consequently, the inherent limits and uncertainties of all the public health data presented mean that, at this stage, the public health benefit of ZYTIGA is only small.

◗ This medicinal product is a first-line treatment after failure of castration.

Taking into account of these points, the Committee considers that the actual benefit of ZYTIGA is substantial in the treatment of metastatic castration-resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

The Committee recommends the inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for hospital use in this extension of the indication and at the dosage in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

ZYTIGA provides a minor improvement in actual benefit (level IV) in terms of efficacy in the treatment of metastatic castration-resistant prostate cancer patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

010.3 Target population

The target population of ZYTIGA is represented by patients with metastatic castration-resistant prostate cancer, who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

Estimation of the target population of ZYTIGA in this extension of the indication can therefore be made based on the following steps.

The population of patients with metastatic prostate cancer corresponds to two sub-groups:

- patients initially diagnosed at the metastatic stage;
- patients initially diagnosed at the localised or locally advanced stage and who subsequently progressed towards a metastatic stage.

Patients diagnosed at the metastatic stage:
In 2010 in France, the incidence of prostate cancer was estimated as being 71,577 new cases per year.
According to a study provided by the French Parliamentary Office for Health Policy Evaluation (OPEPS) on prostate cancer, distribution based on stage of diagnosis is estimated as being:

- 84% for localised stages;
- 3% for locally advanced stages;
- 10% for metastatic stages.

The number of patients with prostate cancer initially diagnosed at the metastatic stage can therefore be estimated as being 7,160 patients.

Patients diagnosed at the localised stage, progressing towards the metastatic stage:
For these patients, the percentage progression towards a metastatic state at five years is 5% at the prostate-localised stage (T1 clinical stage in the TNM classification), and is between 22% and 32% at the capsular invasion stage (T2 clinical stage)[18]. Based on the distribution of clinical stages at diagnosis, T1 (27%) and T2 (58%) reported in the OPEPS study, the percentage of progression from the localised stage to the metastatic stage can be put at approximately 20%.
The number of prostate cancer patients diagnosed at the localised stage and progressing towards a metastatic stage can therefore be estimated as being 12,030 patients.

Patients diagnosed at a locally advanced stage progressing towards a metastatic stage:
Locally advanced tumours have a rate of progression towards a metastatic stage of the order of 40% at five years[19]. The number of prostate cancer patients diagnosed at the locally advanced stage and progressing towards the metastatic stage is estimated at 860 patients.
In summary, the number of patients at the metastatic stage is estimated as being 20,050 patients per year (7,160 + 12,030 + 860).

Metastatic castration-resistant patients:
Ninety-six per cent (96%) of patients with metastatic prostate cancer are treated with hormone therapy, that is 19,250 patients treated for their metastatic prostate cancer. Of those patients, 48% will become castration-resistant, that is 9,240[20] metastatic castration-resistant patients.

[18] Avancès C. Prostate cancer: localised disease. Nuclear Medicine. 2008; 32: 46-50.
[19] Soulié M et al. Role of surgery in high risk prostate tumours. Cancer/Radiotherapy. 2010; 14: 493-499.
[20] CT opinion on JEVTANA 2011

Asymptomatic or mildly symptomatic metastatic castration-resistant patients:

Of the patients with metastatic castration-resistant prostate cancer and who are chemotherapy naive, 78% of patients are asymptomatic or mildly symptomatic[21], that is 7,200 patients.
Consequently, the target population for ZYTIGA in its new indication is estimated as being 7,200 patients per year.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

It is appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.

◗ Proposed reimbursement rate: 100%

[21] KANTAR Health study (unpublished study carried out by the company). Treatment of patients with castration-resistant metastatic prostate cancer by urologists and oncologists. Study report. October 2012.