ZYTIGA® (ABIRATERONE ACETATE)

CLINICAL DATA FACT SHEET

ZYTIGA's® full summary of product characteristics is available online at:
www.emea.europa.eu/ema/

What is ZYTIGA?

ZYTIGA® (abiraterone acetate) is a once-daily, oral, androgen biosynthesis inhibitor developed for the treatment of prostate cancer.

ZYTIGA is indicated with prednisone or prednisolone for:[1]

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

- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen

ZYTIGA selectively and irreversibly blocks a key enzyme required for the production of male hormones (androgens), a process known as androgen biosynthesis. Androgen biosynthesis is an important factor in the growth and progression of prostate cancer and occurs in three critical sites: the testes, adrenals glands and in the tumour itself.[2]

Overview of ZYTIGA's efficacy and safety

Two pivotal Phase III studies have supported the current licensed indication for ZYTIGA in the European Union. These have shown, compared to placebo, that abiraterone acetate plus prednisone/prednisolone:

- **In a chemotherapy-naive population**:[3*]
    - Significantly prolongs overall survival with a 19% reduction in risk of death [HR= 0.81; 95% CI: 0.70-0.93]; P = 0.0033]

[*] Abstract #753O states: abiraterone acetate plus prednisone/prednisolone significantly prolonged overall survival versus prednisone alone. Median overall survival was 34.7 versus 30.3 months [HR= 0.80; 95% CI: 0.69-0.93]; P = 0.0027].

        - The median overall survival in the ZYTIGA arm was 34.7 and was 30.3 months in the control arm
    - Significantly increases median radiographic progression-free survival (rPFS) (16.5 vs. 8.3 median months [HR=0.53; 95% CI: 0.45–0.62; p<0·0001])
    - Can significantly impact positively on other factors that influence quality of life, including delaying time to use of opiates for cancer pain

- **In a population who have failed on prior chemotherapy:**[4]
    - Increases median overall survival by 41% (15.8 vs 11.2 months [HR=0.74; 95% CI: 0.64–0.86; p<0.0001])
    - Increases median rPFS by 56% (5.6 vs. 3.6 months [HR=0.66; 95% CI: 0.58–0.76; p<0.0001])

Data on use of ZYTIGA in a chemotherapy-naive population[3]

Study COU-AA-302 is a Phase III, randomised, double-blind, multicentre, placebo-controlled international clinical study, which evaluated ZYTIGA plus prednisone compared to placebo plus prednisone in 1,088 men with mCRPC. Patients included were asymptomatic or mildly symptomatic after failure of androgen deprivation therapy and had not received any prior cytotoxic chemotherapy.

Final analysis[3]

On 28 September 2014, at 11:00am CET, a final analysis of the Phase 3 COU-AA-302 trial is being presented at the European Society for Medical Oncology (ESMO) conference in Madrid, Spain.[3]

These data show that in a median follow-up of more than 4 years (49.2 months) abiraterone acetate plus prednisone significantly prolonged overall survival (OS), with a 19% reduction in risk of death in this study population, compared to an active control of placebo plus prednisone, in men with chemotherapy-naïve mCRPC (median OS, 34.7 vs 30.3 months; HR= 0.81 [95% CI, 0.70-0.93]; p = 0.0033).[3] Abiraterone acetate also significantly reduced the risk of disease progression, delayed the onset of symptoms and demonstrated a significant improvement in median time to opiate use for cancer-related pain compared to placebo plus prednisone. [3] These data include nearly two additional years of follow-up since the third interim analysis was reported in February 2013.

Key findings are shown below:

Assessment	Abiraterone acetate	Control arm	Statistical information
Primary endpoints			
Median overall survival (OS)[3]	34.7 months	30.3 months	HR=0.81; 95% CI: 0.70–0.93; p=0.0033
Radiographic progression-free survival (rPFS)[5]	16.5 median months	8.2 median months	HR=0.52; 95% CI: 0.45–0.61; p=0.0001
Secondary endpoints			
Median time to opiate use (cancer-related pain)[3]	33.4 months	23.4 months	HR=0.72; 95% CI: 0.61−0.85; p=0.0001
Median time to chemotherapy initiation[5]	26.5 months	16.8 months	HR=0.61; 95% CI: 0.51−0.72; p<0·0001
Median time to ECOG PS deterioration[5]	12.3 months	10.9 months	HR=0.83; 95% CI: 0.72−0.94; p=0.005
Median time to PSA progression[5]	11.1 months	5.6 months	HR=0.50; 95% CI: 0.43−0.58; p<0.0001

Safety findings[3]

In the final analysis no new safety concerns were identified with longer treatment with ZYTIGA compared to previously-reported findings with the drug in mCRPC patients who had received prior chemotherapy *(please see the Safety paragraph in the next section for information on the patient population who had failed on prior chemotherapy)*. Fatigue, fluid retention, low blood potassium, hypertension, cardiac disorders and elevated liver transaminase enzymes were adverse events (AEs) reported more frequently in the ZYTIGA arm compared to the control arm. Patients in the ZYTIGA arm of the study experienced more grade 3 and grade 4 AEs than those in the control arm. Grade 3 or 4 AEs classified as liver toxicity, consisting primarily of reversible elevations in liver transaminase enzymes, were reported in more patients in the ZYTIGA arm than in the control arm.

Data on the use of ZYTIGA in a population who have failed on prior chemotherapy[4]

A Phase III randomised, double-blind, placebo-controlled clinical trial, COU-AA-301, was conducted across 147 centres in 13 countries. It investigated the efficacy of abiraterone acetate, in combination with prednisone or prednisolone, in adult patients with metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed following

chemotherapy. The primary endpoint was overall survival. The secondary end points included PSA response rate, time to PSA progression, and progression-free survival (PFS) on the basis of radiographic findings.

Results

In September 2012, data from the final analysis of this study, at a median follow-up of 20.2 months, were published in *The Lancet.*[4] These showed that treatment with abiraterone acetate, in combination with prednisone or prednisolone, significantly improved overall survival and all secondary endpoints, compared to placebo. Key findings from this study are shown below:

Assessment	Abiraterone acetate	Control arm	Statistical information
Primary endpoint			
Median overall survival (OS)*	15.8 months [95% CI: 14.8–17.0]	11.2 months [95% CI:10.4–13.1]	HR=0.74; 95% CI: 0.64–0.86; p<0.0001
Secondary endpoints			
Median time to PSA progression	8.5 months [95% CI 8.3–11.1]	6.6 months [95% CI:5.6–8.3]	HR=0.63; 95% CI: 0.52−0.78; p<0.0001
Median radiologic progression-free survival (rPFS)	5.6 months [95% CI: 5.6–6.5]	3.6 months [95% CI: 2.9–5.5]	HR=0.66; 95% CI: 0.58−0.76; p<0.0001
Proportion of patients who had a PSA response	235 of 797 [29.5%]	22 of 398 [5.5%]	p<0.0001

*The effect of abiraterone acetate and prednisone on overall survival was consistent across all subgroups

Pain relief[4,2]

The number of patients in the study who reported pain relief from their disease was higher in the abiraterone acetate group than in the placebo group (44% versus 27%, p=0.002)

- Pain relief was defined as at least a 30% reduction from baseline in the Brief Pain Inventory-Short Form [BPI-SF] worst pain intensity score over 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart
- Data is from the 2nd interim analysis taken at 12.8 months, which analysed the number of patients in the study who reported high pain from their disease (a baseline pain score of 4 or more using the BPI-SF scale of 0 to 10)

In addition, data showed a lower proportion of patients receiving abiraterone acetate had skeletal related events compared with those given placebo:[6]

- 18% versus 28% at six months,
- 30% versus 40% at 12 months and
- 35% versus 40% at 18 months
- In the overall population, median time to occurrence of first skeletal-related event was significantly longer with abiraterone acetate and prednisone than with prednisone only (25.0 months [95% CI 25.0—not estimable] vs 20.3 months [16.9—not estimable]; p=0.0001).
- A skeletal related event was defined as a pathological fracture (a broken bone caused by disease weakening the bone), spinal cord compression, palliative radiation to bone (used to lessen bone pain), or surgery to bone

Safety[4,2]

The most common grade 3–4 adverse events from the COU-AA-301 study were fatigue (72 [9%] of 791 patients in the abiraterone group vs 41 [10%] of 394 in the placebo group), anaemia (62 [8%] vs 32 [8%]), back pain (56 [7%] vs 40 [10%]), and bone pain (51 [6%] vs 31 [8%]).

The safety profile observed in the group of patients who received abiraterone acetate was similar to that observed in earlier clinical studies. Side effects were predominantly mild or moderate with a low rate of drug discontinuation or dose reduction, largely based on the mode of action of abiraterone acetate. The most common adverse events were fatigue, nausea, back pain, arthralgia, constipation and bone pain in addition to fluid retention.

- ENDS –

APPENDIX

Interim results on use of ZYTIGA in a chemotherapy-naive population [7]

In February 2013, data from the study's 3rd interim analysis[7] of COU-AA-302 (conducted after 55% of events (deaths) had occurred), were presented at the American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU). Key findings are shown below:

Assessment	Abiraterone acetate arm	Control arm	Reduction	Statistical information
Primary endpoint				
Median overall survival (OS)*	35.3 months	30.1 months	21% reduction in risk of death in the abiraterone acetate arm	HR=0.79; 95% CI: 0.66-0.96, P=0.0151. At the time the pre-specified p-value for statistical significance was not met.
Median radiologic progression-free survival (rPFS)	16.5 months	8.3 months	47% reduction in risk of radiographic progression in the abiraterone acetate arm	HR=0.53; 95% CI: 0.45-0.62; p<0.0001.
Secondary endpoints				
Time to initiation of cytotoxic chemotherapy	26.5 months	16.8 months	39% decrease in risk of initiation in the abiraterone acetate arm	HR=0.61; 95% CI: 0.51-0.72; P<0.0001.
Time to opiate use for cancer pain	Median time not reached	23.7 months	29% decrease in risk of use in the abiraterone acetate arm	HR=0.71; 95% CI: 0.59-0.85; P=0.0002.

Interim analyses

Data from three interim analyses of the COU-AA-302 study were used to support submissions to regulatory authorities to extend the use of ZYTIGA to patients who had not yet received cytotoxic chemotherapy. A summary of these analyses, showing when they were presented and published is shown below:

Interim analysis*	Data presented	Data published
1st interim analysis (after 13% OS events)	rPFS data included within presentation of 2nd interim analysis, presented in June 2012	Data included within publication of 2nd interim analysis, published in the *New England Journal of Medicine*, 2013
2nd interim analysis (after 43% OS events)	American Society of Clinical Oncology annual meeting, June 2012	*New England Journal of Medicine*, 2013
3rd interim analysis (after 56% OS events)	American Society of Clinical Oncology 2013 Annual Meeting, February 2013 and Genitourinary Cancers Symposium (ASCO GU), May 2013	*European Urology*, 2014

*Interim analyses were conducted after the noted number of events (deaths) had occurred

In March 2012, Janssen announced that an Independent Data Monitoring Committee (IDMC) had unanimously recommended unblinding this Phase III study after an early interim analysis found a statistically significant difference in rPFS and a trend in the difference in OS. Based on these results, the IDMC also recommended that patients in the control arm be offered treatment with abiraterone acetate.[8]

References

[1] ZYTIGA® European Summary of Product Characteristics. Date: October 2013. Last accessed September 2014.
[2] de Bono J et al. Abiraterone and Increased Survival in Metastatic Prostate Cancer. N Engl J Med 2011; 364(21): p1995-2005.
[3] Ryan C.J et al. Final overall survival (OS) analysis of COU-AA-302, a randomized phase 3 study of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy. Abstract presented at the European Society for Medical Oncology 2014 Congress, September 26-30, Madrid, Spain. Oral Presentation. ESMO abstract #753O. Available at: https://www.webges.com/cslide/library/esmo/browse/search/eor#9f9k02Lm. Last accessed September 2014.
[4] Fizazi K et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012;13(10): p983-92.
[5] Rathkopf D et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Mestastatic Castration-resistant Prostate Cancer Without Prior Chemotherapy (COU-AA-302). *Euro Urol* 2014; 5570: p1-11.
[6] Logothetis C et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. *Lancet Oncol* 2012; 13(12): p1210-1217.
[7] Rathkopf D et al. Updated interim analysis (IA) of COU-AA-302 and randomised phase 3 study of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) without prior chemotherapy. J Clin Oncol. 2013;31 (suppl 6, abstr 5).
[8] Study Unblinded: ZYTIGA® (abiraterone acetate) Plus Prednisone for Asymptomatic or Mildly Symptomatic Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer. Janssen press release issued March 8 2012. Available at: http://www.investor.jnj.com/releasedetail.cfm?ReleaseID=655519. Last accessed September 2014.