Horizon Scanning in Oncology

Abiraterone acetate (Zytiga™) as 2nd-line therapy for the treatment of metastatic castration-resistant prostate cancer after docetaxel therapy

HTA-Zentrum Bremen

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, November 2011

Horizon Scanning in Oncology

Abiraterone acetate (Zytiga™) as 2nd-line therapy for the treatment of metastatic castration-resistant prostate cancer after docetaxel therapy

HTA-Zentrum Bremen

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, November 2011

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft in collaboration with

HTA-Zentrum der Universität Bremen
c/o Institut für Pharmakologie
28177 Bremen, Germany
http:/www.hta.uni-bremen.de

Author(s):	Dr. Anna Nachtnebel, MSc (LBI-HTA Vienna)
	Dr. med. Isabel Püntmann (HTA-Zentrum Bremen)
Internal review:	Prof. Dr. med. Bernd Mühlbauer,
	Dr. med. Hans Wille
	(Institute for Pharmacology,
	Klinikum Bremen Mitte, 28177 Bremen, Germany)
External review:	Dr. med. Jürgen Spehn
	(Consultant for Haemato-Oncology
	Klinikum Links der Weser, 28277 Bremen, Germany)

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 020
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/dsd.html

Abbreviations

95%CI	95% confidence intervall
AA	abiraterone acetate
ADT	androgen deprivation therapy
AE	adverse event
ATC	Anatomical Therapeutic Chemical classification system
BPI-SF	Brief Pain Inventory - Short Form
BRCA1	Breast Cancer 1 susceptibility protein
BRCA2	Breast Cancer 2 susceptibility protein
CRPC	Castration-resistant prostate cancer
CYP17	cytochrome P450 17 enzyme
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
FACT-P	Functional Assessment of Cancer Therapy-Prostate Quality of Life questionnaire
FDA	Food and Drug Administration
HR	hazard ratio
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
mg	milligram
mg/d	milligram per day
n	number
NA	not available
NCI CTCAE v3.0	Common Terminology Criteria for Adverse Events of the National Cancer Institute version 3.0
ng/dL	nanogramm per decilitre
ng/mL	nanogramm per milliilitre
OS	overall survival
PFS	progression-free survival
plac	placebo
pred	prednisone
PSA	prostate-specific antigen
PSAWG	Prostate Specific Antigen Working Group
QoL	quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
TNM system	Tumour/Node/Metastasis stating system of malignant tumours
TTPSA	Time to PSA progression
US	United States of America
vs	versus

1 Drug description

Generic/Brand name/ATC code:

Abiraterone acetate/Zytiga™/L02BX03

Developer/Company:

Ortho Biotech Oncology Research & Development, Unit of Cougar Biotechnology, Inc., marketed Janssen-Cilag

Description:

Proliferation and survival of prostate cancer cells depends on signalling from the activated androgen receptor. Deprivation of gonadal androgen (i.e. androgen produced in the testes), either by surgical or medical castration, is thus an initially effective treatment for metastatic prostate cancer [1]. But prostate cancer becomes inevitably castration-resistant by several mechanisms, for example by overexpression of the cytochrome P450 17 enzyme (CYP17), the 17α-hydroxylase/C17,20-lyase which regulates the androgen biosynthesis in the testes, but also in the adrenal glands and in the prostate [2-4]. By overexpression of CYP17 the androgen-receptor signalling is maintained, but abiraterone acetate (AA), a new molecular entity, inhibits CYP17.

over-expression of the enzyme CPY17 one mechanism for development of castration-resistant prostate cancer

Capsules containing 250 mg AA are available. The recommended dose is 1,000 mg/d orally in combination with 5 mg prednisone administered orally twice daily. Prednisone is administered to avoid side-effects such as hypertension, hypokalaemia, and fluid retention which can occur due to increased mineralocorticoid levels. These side-effects are especially problematic for patients with an underlying heart disease. Dose modifications are necessary for patients with moderate hepatic impairment [5].

abiraterone which as administered orally inhibits CYP17

median survival for patients with metastasised tumours is 1 - 3 years

2 Indication

AA is indicated for patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel containing regimen.

3 Current regulatory status

EMA licensed abiraterone in September 2011

The EMA licensed AA in combination with prednisone or prednisolone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen in September 2011 [6].

FDA in April 2011

In the US, the FDA approved Zytiga™ in combination with prednisone for the treatment of patients with mCRPC who have received prior chemotherapy containing docetaxel in April 2011 [5].

4 Burden of disease

prostate cancer most common cancer affecting men

Prostate cancer is the most common cancer in men in developed countries and the second most common cancer-related cause of death [7]. Median age at diagnosis is 72 years. In Austria, about 4,800 men were newly diagnosed with prostate cancer and 1,100 died in 2009 [8]; in Germany, 60,100 men were diagnosed and 11,600 died in 2006 [9]. Due to widespread prostate-specific antigen (PSA) testing, prostate cancer is mostly diagnosed at an early, asymptomatic stage of disease, resulting in less than 5% of patients which were diagnosed after the tumour has spread [8]. About 40% of men will eventually develop metastases [10]. In Austria, disseminated disease was found in about 3.6% of patients, resulting in about 150 patients with metastatic prostate cancer per year [8]. Applying the same numbers to Germany would result in about 2,000 patients with disseminated prostate cancer.

due to PSA screening, diagnosis often at early stage

risk factors: age, ethnicity, family history,..

Risk factors for developing prostate cancer include age, ethnicity, family history, diet and genetic factors such as mutations in BRCA1 and BRCA2 genes [11].

symptoms might include urinary urgency, erectile dysfunction, pain…

Clinical findings include asymmetric areas of induration or frank nodules in the prostate during digital rectal examination, genitourinary symptoms (e.g. urinary urgency, nocturia, erectile dysfunctions) and, in the minority of patients, symptoms of metastatic disease. As prostate cancer mainly metastasises to bones, most common symptoms at this stage are bone pain. To establish diagnosis of prostate cancer, a histologic examination should be performed [11].

Staging is done by using the TNM system which provides information for choosing the initial therapy. Other factors which impact on the choice of initial therapy are life expectancy, comorbidities, therapeutic side-effects and patients' preferences [12].

TNM system, Gleason score and pre-treatment levels to establish prognosis

Besides the TNM system, the Gleason score is used to establish prognosis. This score is a histopathologic grading system which distinguishes well and poorly differentiated prostate tissue [12, 13]. By taking the TNM system, the Gleason score and pre-treatment PSA levels into account, five patient groups with different probabilities of cure can be derived [11].

Prognosis strongly depends on the stage at diagnosis. If the tumour is confined to the prostate gland, a median survival of more than 5 years can be expected. For locally advanced forms of prostate cancer, cure is rarely possi-

ble, but median survival is still about 5 years. Patients with metastasised tumours have a median survival of 1-3 years [13].

Castration-resistant prostate cancer refers to prostate cancer which progresses despite androgen deprivation therapy. Disease progression can either be defined as a rise in serum levels of PSA, as progression of pre-existing disease and/or as the development of new metastases.

5 Current treatment

hormone therapy is standard initial therapy

Metastatic prostate cancer is not curable; therefore the main objective of therapy for this stage is to maintain quality-of-life (QoL) and to control the disease [11]. Therapy includes:

- Androgen deprivation therapy (ADT) (synonym: hormone therapy, castration) is the standard initial therapy for patients with metastatic prostate cancer. Surgical castration (synonym: orchiectomy) or medical castration using a luteinizing hormone-releasing hormone (LHRH) agonist is the optimal ADT. In addition, antiandrogens for at least 7 days should be administered either prior to or simultaneously to LHRH agonists to patients with metastases who are likely to develop symptoms associated with an initial increase in testosterone ("flare") with LHRH-agonists only [7, 13].

In nearly all cases, disease progresses on ADT. If PSA level rises despite castrate levels of testosterone (serum testosterone <20 ng/dL) the cancer is called "castrate-resistant", "hormone-refractory" or "androgen-independent" [11]. Systemic therapy options for men with metastatic prostate cancer are then:

options if disease progresses:

sequential secondary hormone therapy

- Multiple and sequential secondary hormone therapies including withdrawal of ADT, antiandrogen therapy, cytochrome P450 inhibitors, oestrogens and corticosteroids. Even though no improvements in survival have been demonstrated for these therapies, the favourable toxicity profile justifies their use before the administration of chemotherapies [11, 14].
- Chemotherapy:
  - As 1st-line chemotherapy the combination of docetaxel and prednisone showed improved overall survival (OS) and improved QoL in comparison to mitoxantrone and prednisone [11, 15-19]. Therefore docetaxel is the standard of care for the initial chemotherapy in men with castration-resistant prostate cancer [11, 14, 16-20].

docetaxel standard of care for 1st-line chemotherapy

  - Because the combination of mitoxantrone and prednisone compared with prednisone alone achieved pain reduction in patients with bone metastases, mitoxantrone might also be used as 1st -line chemotherapy [11, 12, 14, 19] which is considered appropriate for patients with slowly progressing disease and for those who are intolerant to docetaxel [21].

mitoxantrone has a palliative treatment effect and is de-facto 2nd-line chemotherapy, but impact on survival is unclear

  - 2nd-line chemotherapy needs to be considered after docetaxel therapy has failed. Guidelines are tentative in giving a clear recommendation of what should be applied next. Until recently, mitoxantrone and prednisone were considered *de facto* 2nd-line

chemotherapy, despite its unclear impact on survival [11, 12, 15, 19]. However, this has changed, because cabazitaxel, a new taxane, was licensed in Europe in combination with prednisone or prednisolone for patients with mCRPC who have previously been treated with docetaxel in March 2011 [22]. Regarding OS cabazitaxel+pred was superior to mitoxantrone+pred, probably at the expenses of QoL, which was not investigated.

sipuleucel-T

- Immunotherapy with sipuleucel-T, which is not licensed in Europe, has demonstrated prolonged OS for minimally symptomatic patients with castrate-resistant prostate cancer and is therefore indicated for minimally symptomatic/asymptomatic and chemotherapy-naïve patients [12, 18, 19].
- Symptom palliation for advanced prostate cancer is mainly done by systemic therapy, which includes analgesics, radiation therapy and bisphosphonates for bone metastases [13].

6 Evidence

In addition to a free text search including the websites of the EMA and of the US FDA, an extensive literature search was conducted in Pubmed, Medline, EMBASE and the "Centre for Review and Dissemination Database" on the 4th of July 2011.

Only randomized controlled trials which tested AA in the approved indication (i.e. in men with mCRPC whose disease has progressed on or after a docetaxel-based chemotherapy regimens) were included in the evaluation of efficacy. Additionally, the trials had to investigate patient relevant outcomes. For the evaluation of safety also uncontrolled trials which tested AA in the approved indication regardless of the investigated outcomes were considered.

Overall, one phase III trial, the COU-AA-301 trial [23], met the selection criteria for efficacy evaluation. For safety evaluation one further trial, the phase II COU-AA-004 trial [24], met the criteria.

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title A Phase III, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy [6, 23, 25]			
Study identifier	Study No: COU-AA-301, ClinicalTrials Identifier: NCT00638690; EudraCT No: 2007-005837-13		
Funding	Cougar Biotechnology		
Design	phase III, multinational, randomized (2:1 ratio), double blind, placebo-controlled		
	Duration	Enrolment: May 2008 –July 2009 Median follow-up: 12.8 months Cut-off date: interim analysis: January 2010, Updated analysis: September 2010	
Hypothesis	Superiority		
Treatment groups	Intervention	4 tablets 250 mg AA/d + 5 mg prednisone orally twice daily for 28 days	
	Control	4 tablets placebo/d + 5 mg prednisone orally twice daily for 28 days	
Endpoints and definitions	Overall survival (primary outcome)	OS	time from randomization to death from any cause
	Progression-free survival (pre-specified radiographic criteria)	R-PFS	Per investigator's assessment of progression by soft tissue (according to modified RECIST criteria [26][baseline lymph node ≥2.0 centimetre to be considered target lesion], or progression by bone scans with ≥2 new lesions not consistent with tumour flare.
	PSA response rate (pre-specified PSAWG criteria)	PSA-RESP	PSA decline of ≥50% confirmed by a second PSA decline at least 4 weeks later.
	Time to PSA progression (pre-specified PSAWG criteria)	TTPSA	1) in patients in whom the PSA level had not decreased, PSA progression was defined as a 25% increase over the baseline and an increase in the absolute-value PSA level by at least 5 ng/mL, which was confirmed by a second value; 2) in patients in whom the PSA had decreased but had not reached response criteria [PSA ≤50%], progressive disease would be considered to have occurred when the PSA level increased 25% over the nadir, provided that the increase was a minimum of 5 ng/mL and was confirmed; 3) and if at least a 50% decrease in the PSA level had been achieved, PSA progression would be an increase of 50% above the nadir at a minimum of 5 ng/mL
	Quality of Life by FACT-P score	QOL_FACT-P	Total score and each subscale score from FACT-P (physical well-being, social/family well-being, emotional well-being, functional well-being, and prostate cancer subscale)

Results and analysis			
Analysis description	Primary analysis on intention-to-treat One interim analysis and one final analysis were planned after observing 534 and 797 death events, respectively; distributions of time-to-event variables and associated 95%CI were estimated with the use of the Kaplan-Meier product–limit method; stratified log-rank test was used as primary analysis for comparison of treatment groups.		
Analysis population	Characteristics	Median age (range): AA+pred 69 years (42 - 95 years) vs plac+pred 69 years (39 - 90 years) Disease location: Bone AA+pred 89% vs plac+pred 90%; Node AA+pred 45% vs plac+pred 41%; Liver AA+pred 11% vs plac+pred 8% BPI-SF score for pain: AA+pred 3.0 vs plac+pred 3.0 1 previous chemotherapy: AA+pred 70% vs plac+pred 69% 2 previous chemotherapies: AA+pred 30% vs plac+pred 31% ECOG-PS 0 or 1: AA+pred 90% vs plac+pred 89% ECOG-PS 2: AA+pred 10% vs plac+pred 11%: Median PSA range (ng/mL): AA+pred 128.8 vs plac+pred 137.7	
	Inclusion	previously treated with docetaxel, disease progression, ECOG-PS ≤2	
	Exclusion	abnormal aminotransferase levels, serious coexisting non-malignant disease, active or symptomatic viral hepatitis or chronic liver disease, uncontrolled hypertension, a history of pituitary or adrenal dysfunction, clinically significant heart disease, or previous therapy with ketoconazole	
Descriptive statistics and estimated variability	Treatment group	*Intervention (AA+pred)*	*Control (plac+pred)*
	Number of subjects	797	398
	OS, months Interim survival analysis: median (95%CI)[23] Updated survival analysis: median (95%CI) [6]	 14.8 (14.1 – 15.4) 15.8 (14.8 – 17.0)	 10.9 (10.2 – 12.0) 11.2 (10.4 – 13.1)
	Median R-PFS, months [23]	5.6	3.6
	PSA_RESP, % [23]	29.1	5.5
	TTPSA, months [23]	10.2	6.6
	QOL_FACT-P	NA	NA

Effect estimate per comparison	*Comparison groups*		*Intervention vs Control (AA+pred versus plac+pred)*
	OS (primary analysis)	HR	0.65
		95%CI	0.54 to 0.77
		P value	<0.001
	OS (updated analysis)	HR	0.74
		95%CI	0.64 to 0.86
		P value	NA
	R-PFS	HR	0.67
		95%CI	0.58 to 0.78
		P value	<0.001
	PSA_RESP	P value	<0.001
	TTPSA	HR	0.58
		95%CI	0.46 to 0.73
		P value	<0.001
Notes	Pursuant to the independent data and safety monitoring committee recommendation on August 20, 2010, all patients will be unblinded and patients who have received placebo will be offered cross-over therapy with AA [25].		

Table 2: Adverse events with a frequency of ≥25% (regarding all grades), ≥5 (regarding grade 3), ≥1% (regarding grade 4) in either treatment arm

COU-AA-301 trial			
Grade (according to NCI CTCAE v3.0 [27]	**Outcome** number of patients (%)	**Intervention (AA+pred)** (n= 791)	**Control** (plac+pred) (n=394)
All grades	Fatigue	346 (44)	169 (43)
	Fluid retention and oe-dema	241 (31)	88 (22)
	Back pain	233 (30)	129 (33)
	Nausea	233 (30)	124 (32)
	Arthralgia	215 (27)	89 (23)
	Bone pain	195 (25)	110 (28)
	Constipation	106 (26)	120 (31)
	Vomiting	168 (21)	97 (25)
	Anaemia	178 (23)	104 (26)
Grade 3	Fatigue	64 (8)	36 (9)
	Anaemia	51 (6)	23 (6)
	Back pain	44(6)	37 (9)
	Bone pain	42 (5)	25 (6)
	Pain in arm or leg	18 (2)	20 (5)
Grade 4	Anaemia	8 (1)	6 (2)
	Cardiac disorders	7 (1)	2 (<1)
	Bone pain	2 (<1)	4 (1)
Grade 5	AEs leading to death	NA (12)	NA (15)
	Fatal cardiac events	NA (1.1)	NA (1.3)

797 patients with progressive mCRPC after previous docetaxel therapy were randomised to receive AA+pred and 398 were allocated to the plac+ pred group [23]. Patients were stratified according to ECOG-PS, pain level, number of previous chemotherapies and type of evidence of disease progression. The median duration of treatment was 8 months for the AA+pred group and 4 months for the plac+pred group.

AA + prednisone vs placebo + prednisone

At a pre-planned interim analysis after 534 deaths had occurred, median OS, the primary outcome, was statistically improved in patients treated with AA+pred with 14.8 months compared to 10.9 months in the plac+pred group (HR = 0.65, p<0.001) [23]. An updated survival analysis conducted in September 2010 (i.e. after 97% of the planned number of deaths for final analysis had been observed) showed improved outcomes for OS as well (15.8 vs. 11.2 months, HR = 0.74, 95%CI 0.64 to 0.86) [6]. Focussing on OS, subgroup analyses according to randomization strata, predefined and one non-predefined subgroup were conducted of which the results for the strata and some of the predefined subgroups were published [25]. These data showed consistent results favouring the AA+pred group. Only in one of the presented subgroups, i.e. the patients with ECOG-PS 2, no significant difference was found. Yet, no conclusion can be drawn for this subgroups since it was small and no confirmatory interaction test was performed.

improved outcomes for OS and other endpoints in the AA group

consistent results across subgroups

Better results were also found for all secondary outcomes, i.e. PFS, TTPSA and PSA_RESP [23].

Many exploratory endpoints were investigated, of which the results of objective response rate and pain-related outcomes have been published, the latter mainly on abstract basis [23, 26]. All demonstrated results in favour of AA+pred as, for example, the pain intensity palliation rate was 44% in the AA+pred group and 27% in the plac+pred group (p<0.001) [26]. QoL as as exploratory endpoint was assessed with the FACT-P questionnaire [25], but results have not been published yet.

also better results for pain palliation

In terms of adverse events (AEs), the most frequent one was fatigue of any grade, which occurred at similar frequencies in both treatment arms (AA+pred 44% vs plac+pred 43%). Side-effects due to the blockade of CYP17 and thus due to elevated mineralocorticoid levels (e.g. fluid retention + oedema, hypokalaemia, hypertension) were more frequent in the AA+pred group (AA+pred 55% vs. plac+pred 43%, p<0.001). Even though cardiac events were more often observed in patients treated with AA+pred than with plac+pred, this difference was not significant (13% vs. 11%, p=0.22) [23]. Urinary tract infections of any grade occurred more often in the AA+pred group (12%) than in the comparison group (7%) (p=0.02); and were primarily grade 1 or 2 events. Treatment was discontinued in a similar proportion of patients in both arms (AA+pred 19% vs plac+pred 23%, p=0.09) and 12% died in the AA+pred group due to AEs in comparison to 15% in the plac+pred group.

AEs manageable

The independent data and safety monitoring committee recommended unblinding the study in August 2010. Patients were then allowed to cross-over from the plac+pred group to the active therapy AA+pred arm.

6.2 Further studies - safety

one further uncontrolled phase II study…

An uncontrolled phase II study, the COU-AA-004 trial, investigated AA+pred in 58 patients with mCRPC who had progressed under ADT and docetaxel-based chemotherapy [24]. Patients were pre-treated with antiandrogens, estrogens and ketoconazole. Primary endpoint was PSA response. A decline of PSA of ≥50% was confirmed in 36% of patients. No grade 4 AEs were observed and those of grade 3 were infrequent. Most common AEs of grade 1 or 2 were fatigue (16%) and nausea (14%).

7 Estimated costs

no cost estimates for Austria

No cost estimates for Zytiga™ are available yet in Austria but some hint was found that one bottle containing 120 tablets à 250 mg AA is sold for $ 5,000 (≈ € 3,500) in the US [28] which would also be the monthly treatment costs. Since the median duration of treatment in the phase III trial was 8 months and one cycle was 28 days, the overall treatment costs for AA are thus an estimated € 28,000.

in Germany monthly treatment costs of € 5,000

In Germany the pharmacy retail price for Zytiga™ (N2 package) is € 5,445 [29] which might officially result in approximately € 5,000. Due to the fact that 1,000 mg AA are administered daily, the N2 package (i.e. average sized package), which contains 120 tablets à 250 mg AA, covers the treatment for a month. Since the median duration of treatment in the phase III pivotal trial was 8 months, the overall treatment costs for AA are an estimated € 40,000.

8 On-going research

one on-going phase III trial with chemotherapy-naïve patients

Regarding the investigated indication no further on-going RCT was identified.

In chemotherapy-naïve patients with mCRPC, however, one additional phase III RCT was found on ClinicalTrial.gov.

- NCT00887198 (the COU-AA-302 trial): is currently on-going and investigates AA+pred in comparison to plac+pred in asymptomatic or mildly symptomatic patients with chemotherapy-naïve mCRPC. The estimated study completion date is April 2014, but the final data collection date for the primary outcome measure was April 2011.

Several other phase I and II studies are currently conducted in different stages of prostate cancer (mCRPC, CRPC without metastases, prostate cancer not yet hormone-treated, neo-adjuvant setting). Most of them are performed without a control arm and focus on surrogate endpoints only.

Another indication currently under investigation is breast cancer.

9 Commentary

EMA market authorization in September 2011

The EMA has granted market authorization for Zytiga™ in combination with prednisone for patients with mCRPC after docetaxel based chemotherapy in September 2011 [6]. This decision was based on a pivotal phase III study, the COU-AA-301 study, which demonstrated a difference in OS by 3.9 months for AA+pred in comparison to plac+pred in docetaxel pre-treated patients with mCRPC. Due to the findings of this interim analysis the independent data and safety monitoring committee recommended un-blinding of the study and eligible patients were allowed to cross-over to the active treatment arm. AEs related to AA+pred were acceptable and mostly comparable to those observed in the plac+pred group, although statistically significant differences in favour for the placebo group were found for AEs associated with increased mineralocorticoid levels, but they were mainly of grade 1 or 2 [6]. QoL data were assessed, yet results have not been fully published. Since median follow-up was about 13 months, no data on the long-term usage of AA+pred exist.

cabazitaxel was the 1st and AA is the 2nd drug licensed for mCRPC after docetaxel therapy

favourable risk-profile of AA

Until recently, no therapy with demonstrated benefit of OS after failure of docetaxel therapy of patients with mCRPC existed. This has changed lately, because Zytiga™ is now, besides cabazitaxel, the 2nd regimen for which improvements in OS have been found. For cabazitaxel + prednisone, median OS was 15.1 months in comparison to 12.7 months for mitoxantrone + prednisone, yielding a HR of 0.70 ($p<0.0001$) [30]. For AA+pred, median OS was 14.8 months in comparison to 10.9 months ($p<0.001$) for plac+pred, resulting in a HR of 0.65. Comparing the risk-profiles of these two drugs, foremost haematological side-effects were considerably less frequent in patients treated with AA+pred, as haematological AEs grade ≥3 occurred in up to 97% of patients treated with cabazitaxel+pred and in a maximum of 6% in the AA+pred group. Frequencies of non-haematological AEs grade ≥3 were comparable and were observed in 8% in the AA+pred group and in 6% of patients treated with cabazitaxel+pred.

both drugs already recommended in the U.S.

Both drugs have already been incorporated into international guidelines or are recommended in the US after docetaxel therapy [11, 12]. Even though the optimal sequencing of these drugs still remains unknown, AA+pred might be preferable over cabazitaxel+pred for patients with slowly progressive disease due to fewer AEs [11]. The "National Comprehensive Cancer Care Guidelines" even mention that AA might be used for patients not eligible for docetaxel therapy. Hence, studies investigating AA in this setting and as 1st-line therapy in general are of further interest [12].

several other drugs are currently tested

sequencing unclear

Besides these two agents, several other agents are currently being tested in phase III trials, also assessing patients pre-treated with docetaxel [1, 2, 29]. For example, first results for radium-223 chloride (Alpharadin™) showed improvements in OS in comparison to placebo by 2.8 months (HR = 0.695) with low toxicity [31]. It is also likely that several of these new drugs will be administered sequentially or in combination, foremost, because mCRPC will eventually become resistant to AA [1]. Combination therapies are thus discussed, involving experimental drugs such as MDV3100 or TOK-001 which also inhibit androgen receptor signalling [1]. Efforts are therefore increasingly targeted towards predicting response and resistance to certain therapies in order to identify subgroups most likely to benefit [32]. Clinicians are and will be even more confronted with the challenge of choosing

treatment choice based on QoL impact?

one therapy over the other, without direct evidence of comparative effectiveness since such trials are resource intense and time-consuming and might already be outdated by the time finished. However, one means of selecting the best treatment option is to consider a drug's impact on QoL.

AA might also be used for previous lines of therapy

which would increase costs

A positive side-effect of an increasing number of treatment options is that health care providers might be enabled to negotiate on costs or can choose a therapy by also considering the associated treatment costs. For example, in the US cabazitaxel seems to cost about $ 8,000 every three weeks (i.e. one cycle) in comparison to $ 5,000 for one month therapy with AA [33]. In Germany, however, the expenses for one cycle cabazitaxel is about € 5,000 [34], which is about the same like for AA. Concerning treatment costs, it should also be kept in mind, that, for example, AA+pred is also being investigated for chemotherapy-naïve patients and might thus be used in even earlier lines of therapies [10], a fact which would increase the eligible population and thus the overall costs considerably.

AA more tolerable than cabazitaxel, in addition to relevant gains in OS

In conclusion, the landscape for mCRPC therapy is rapidly evolving and several agents have shown increased OS for mCRPC after docetaxel therapy. The gains of about 4 months in OS, which can be regarded as a relevant improvement, in addition to an acceptable safety profile indicate that AA + pred is currently the most beneficial therapy. In order to ultimately identify the best regimen, reliable data for QoL are needed for all treatment options.

References

1. Seruga, B., A. Ocana, and I.F. Tannock, *Drug resistance in metastatic castration-resistant prostate cancer.* Nature Reviews Clinical Oncology, 2011. **8**(1): p. 12-23.
2. Lassi, K. and N.A. Dawson, *Drug development for metastatic castration-resistant prostate cancer: Current status and future perspectives.* Future Oncology, 2011. **7**(4): p. 551-558.
3. Schrijvers, D., P. Van Erps, and J. Cortvriend, *Castration-refractory prostate cancer: New drugs in the pipeline.* Advances in Therapy, 2010. **27**(5): p. 285-296.
4. Antonarakis, E.S. and M.A. Eisenberger, *Expanding treatment options for metastatic prostate cancer.* N Engl J Med, 2011. **364**(21): p. 2055-8.
5. FDA - U.S. Food and Drug Administration. *Zytiga, Label and Approval History.* 2011 [cited 2011 08. July].
6. European Medicines Agency. *European public assessment reports.* 2011 [cited 2011 03. October]; Available from: http://www.ema.europa.eu.
7. Höltl, W., et al., *Prostatakarzinom – Leitlinien des AUO 2010.* J Urol Urogynäkol, 2010. **17**(3): p. 14-20.
8. Statistik Austria, *Krebserkrankungen - Prostata.* 2011.
9. Husmann, G., et al., *Krebs in Deutschland 2005/2006 - Häufigkeiten und Trends.* 2010, Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V.: Berlin.
10. Beltran, H., et al., *New therapies for castration-resistant prostate cancer: efficacy and safety.* Eur Urol, 2011. **60**(2): p. 279-90.
11. UpToDate Online 19.2. *Prostate Cancer.* 2011 [cited 2011 27.August.].
12. National Comprehensive Cancer Care Network, *Clinical Practice Guidelines - Prostate Cancer V.4.2011.* 2011.
13. National Cancer Institute, *Prostate Cancer Treatment* 2011.
14. Wirth, M., et al., *Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms.* 2009, Deutsche Gesellschaft für Urologie e. V.
15. Hotte, S.J. and F. Saad, *Current management of castrate-resistant prostate cancer.* Current Oncology, 2010. **17**(SUPPL. 2): p. s72-s79.
16. Lee, P. and J.B. Aragon-Ching, *Cytotoxic compounds in the treatment of castration-resistant prostate cancer.* Anti-Cancer Agents in Medicinal Chemistry, 2009. **9**(10): p. 1040-1045.
17. Bianchini, D., et al., *Horizon scanning for novel therapeutics for the treatment of prostate cancer.* Annals of Oncology. **21**(SUPPL. 7): p. vii43-vii55.
18. Wirth, M., et al., *Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms Version 1.03 – März 2011.* 2011, Deutsche Gesellschaft für Urologie e. V.: Düsseldorf.
19. Heidenreich, A., et al., *Guidelines on Prostate Cancer.* 2011, European Association of Urology.
20. Fujimoto, N., et al., *Novel therapeutic strategies following docetaxel-based chemotherapy in castration-resistant prostate cancer.* Expert Review of Clinical Pharmacology, 2010. **3**(6): p. 785-795.
21. Berthold, D.R., C.N. Sternberg, and I.F. Tannock, *Management of advanced prostate cancer after first-line chemotherapy.* J Clin Oncol, 2005. **23**(32): p. 8247-52.

22. European Medicines Agency. *European public assessment reports: Jevtana.* 2011 [cited 2011 13. July]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&murl=menus%2Fmedicines%2Fmedicines.jsp&mid=WC0b01ac058001d124&searchTab=&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&startLetter=J&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=generics.
23. De Bono, J.S., et al., *Abiraterone and increased survival in metastatic prostate cancer.* New England Journal of Medicine, 2011. **364**(21): p. 1995-2005.
24. Danila, D.C., et al., *Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer.* J Clin Oncol, 2010. **28**(9): p. 1496-501.
25. de Bono, J., L. CJ., and M. A., *Protocol for: Abiraterone and increased survival in metastatic prostate cancer.* New England Journal of Medicine, 2011. **364**: p. 1995-2005.
26. Therasse, P., et al., *New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada.* J Natl Cancer Inst, 2000. **92**(3): p. 205-16.
27. Cancer Therapy Evaluation Program, *Common Terminology Criteria for Adverse Events v3.0 (CTCAE).* 2006.
28. Harvard Medical School + Harvard health Publications. *Prostate Knowledge - FDA approves abiraterone for advanced prostate cancer.* 2011 [cited 2011 14. July]; Available from: http://www.harvardprostateknowledge.org/fda-approves-abiraterone-for-advanced-prostate-cancer.
29. Gelbe Liste Pharmindex. 2011 [cited 2011 14. October]; Available from: http://www.gelbe-liste.de/.
30. de Bono, J.S., et al., *Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial.* Lancet, 2010. **376**(9747): p. 1147-54.
31. Parker, C., et al., *Overall Survival Benefit of Raduim-223 Chloride (AlpharadinTM) in the treatment of Patients with Symptomatic Bone Metastases in Castration-resistant Prostate Cancer (CRPC): a Phase III Randomized Trial (ALSYMPCA).* Eur J Cancer 2011. **47** (Suppl 2): p. 3 (Abstract #1LBA).
32. Pal, S.K. and O. Sartor, *Phase III data for abiraterone in an evolving landscape for castration-resistant prostate cancer.* Maturitas, 2011. **68**(2): p. 103-5.
33. Pollack, A., *New Drugs Fight Prostate Cancer, but at High Cost.* 2011, New York Times.
34. Arzneimittelinformationen für Deutschland - Rote Liste. 2011 [cited 2011 14. October]; Available from: http://www.rote-liste.de/.