# Management of Castration Refractory Prostate Cancer in Senior Adults

Helen Jane Boyle, MD[1] and Jean-Pierre Droz, MD, PhD[1,2]

*1. Consultant, Department of Medical Oncology, Centre Léon-Bérard, Lyon, France;*
*2. Emeritus Professor Medical Oncology, Lyon-Est School of Medicine, Claude-Bernard Lyon 1 University, Lyon, France*

## Abstract

Metastatic prostate cancer is frequent in elderly patients. Initial treatment is based on hormone-deprivation treatment. Resistance however occurs and several treatments have been developed and approved for castration-resistant prostate cancer, such as chemotherapy (docetaxel, cabazitaxel), new hormonal treatments (abiraterone, enzalutamide), and bone-targeting agents. These drugs have been studied in large phase III trials, and seem safe and effective even in older men; however, only fit elderly patients were enrolled in the pivotal trials.

Prostate cancers are a frequently occurring tumor in which incidence increases with age. In 2008, there were around 65,000 new cases in France. Median age at diagnosis is 68 years and 27 % of patients are 75 years of age or more.[1] Most deaths from prostate cancer (70 %) occur in men over 75.

Treatment of metastatic prostate cancer is an oncogeriatric problem,[2] and is palliative, at any age. Initial treatment is based on androgen deprivation. The most frequent method is chemical castration with luteinizing-hormone-releasing hormone (LHRH) agonists or, more recently, LHRH antagonists. Surgical castration is still offered to some patients.[3] Most patients respond initially, however, resistance occurs. Median hormone sensitivity is around 18 to 24 months.

Until 2010, the only drug that had shown an overall survival (OS) benefit in patients with metastatic castration prostate cancer (mCRPC) was docetaxel. Since then, several new drugs have been developed: new hormone therapies (such as abiraterone acetate and enzalutamide), new chemotherapy agents (cabazitaxel), new bone-targeting agents (denosumab, radium-223), and new immunotherapies. In this article, we will review how to evaluate elderly patients with mCRPC, what data are available on the different treatments, and how we can predict toxicity.

## Geriatric Evaluation and Decision-making

The majority of advanced prostate cancer patients are elderly. The trials conducted to determine the effect and toxicity of drugs in the treatment of mCRPC have followed the recommendations generally used for clinical trials: good performance status (PS); no major comorbidities—i.e. everything that is not common in elderly patients. It is therefore warranted to establish recommendations for the management of elderly patients with mCRPC. Few have been published: the National Comprehensive Cancer Network (NCCN) has determined the impact of geriatric characteristics on decision-making process; the International Society for Geriatric Oncology (SIOG) has published extensive guidelines and a shorter version for clinical use both in the setting of localized and advanced prostate cancer.[4,5] Life expectancy is a major determinant of the potential benefit from therapy yet it varies substantially between individuals within a given age group. It applies to a population and represents a useful tool for public health, but is not valid for a given individual due to the heterogeneity of the patient population. Although it is not possible to calculate the exact chance of living for an individual, variables such as the number and severity of comorbidities and nutritional and functional status can be used to predict life expectancy within an age group.

Health status influences patients' survival and may affect patients' ability to tolerate treatment-related side effects. A SIOG working group[6] concluded that screening for geriatric problems, with tools such as Instrumental Activities of Daily Living (IADL), ADL, the geriatric depression scale, and Folstein's mini-mental status, was not sufficient to detect age-related factors that would affect treatment outcomes in senior adults. This screening stage should be followed by a more complete comprehensive geriatric assessment (CGA), which assesses various biologic and clinical correlates of aging on an individual basis and includes diagnostic procedures, specific treatment plans, and geriatric intervention.

The SIOG Prostate Cancer Working Group reviewed recent literature and opinions on prognostic factors that might affect health status and OS. The most important factors to consider for the evaluation of health status in senior adult patients with prostate cancer are the following:

- Comorbidities. The Cumulative Illness Score Rating-Geriatrics (CISR-G) was judged to be the best available tool for assessing the risk for

## Table 1: Summary of Health Groups in International Society for Geriatric Oncology Recommendations

| Group | Healthy/Fit | Vulnerable | Frail | Too Sick |
|---|---|---|---|---|
| ADL | No | No | ≥1 | Dependence |
| | and | and | and | and |
| IADL | No | Yes ≤1 | Yes | Dependence |
| | and | or | or | and |
| Weight loss (%) | <5 | 5–10 | >10 | >10 |
| | and | or | or | and |
| CISR-G (grade) | 0/1/2 | ≤1 grade 3 | ≥2 grade 3 or ≥1 grade 4 | Major comorbidities |
| Geriatric intervention | None | Yes, reversibility | Yes, no reversibility | Palliative management |

*ADL = Activities of Daily Living; CISR-G = Cumulative Illness Rating Scale-Geriatrics; IADL = Instrumental ADL.*

nonprostate cancer death because conversely to the Charlson index, which is principally a prognostic index. It also rates diseases according to their severity and level of control by treatment: Grade 0—no problem; Grade 1—current mild problem or past significant problem; Grade 2—moderate disability or morbidity, requires first-line therapy, controlled; Grade 3—severe/constant significant disability/uncontrollable chronic problems; Grade 4—extremely severe/immediate treatment required/end organ failure/severe impairment in function.[7]

- Dependence status. There is evidence that the level of dependence in daily living activities influences survival in senior adult patients.[8] Dependence may be easily evaluated using the ADL[9] and the IADL scales.[10]

  The ADL scale rates the patient's ability to accomplish basic activities of daily living (bathing, dressing, toileting, transferring, continence, and feeding). One ADL impairment is considered abnormal in senior adult patients with prostate cancer, with the exception of incontinence. ADL impairment may be reversible through specific geriatric intervention.

  The IADL scale rates activities that require a higher level of cognition and judgment. Four items apply to men with prostate cancer: ability to manage money, to manage medications, to use transportation, and to use the telephone. One IADL impairment is considered abnormal. It is unlikely that geriatric intervention would be able to reverse IADL impairment.

- Nutritional status. Malnutrition has also been shown to be associated with increased mortality in senior adult patients.[11] Nutritional status can be estimated simply by the variation of weight during the previous 3 months: good nutritional status: <5 % of weight loss; risk for malnutrition: weight loss between 5 and 10 %; severe malnutrition: weight loss >10 %. Geriatric intervention could be implemented to reverse malnutrition.

Therefore, the SIOG Prostate Cancer Working Group recommended that the decision-making process in senior adult patients with prostate cancer should be based on a systematic evaluation of comorbidities (CISR-G scale), dependence status (IADL and ADL scales), and nutritional status (weight-loss estimation). In case of vulnerability and frailty, additional geriatric interventions, including a CGA, may be required.[4] This allows senior adult patients with prostate cancer to be classified into four health status categories as described by Balducci et al.[12] They are summarized in *Table 1*.

Since 2010, other important studies have been published on the different tools to screen health status in elderly people. These tools have been described for several years and have often been compared with the CGA: the most important are the Groningen Frailty Index (GRI)[13,14] and the Vulnerable Elders Survey (VES-13).[15,16] A large national study (ONCODAGE) was performed in France, which involved 1,600 patients and compared the G8 tool and the VES-13 to a CGA.[17,18] The G8 screening tool comprises eight items. It is performed in a median time of 4.4 minutes. It is used to identify healthy patients ('fit patients' group). The other patients ('unfit' according to the G8) should have some kind of geriatric evaluation to specifically study individual impairment, more precisely, comorbidities, nutritional status, cognitive and thymic functions, and, importantly, physical functions. The objective of this assessment should be to determine whether geriatric intervention could reverse impairment. Patients with reversible impairments ('vulnerable patients' group) should be eligible to standard treatment and those with irreversible impairments ('frail patients' group) should receive adapted treatment. All of these patients would also benefit from geriatric intervention to increase their health conditions. A specific group of experts of the SIOG is working on the objective to determine a practical procedure to help the physician in the decision-making. However, there are only incomplete data to define exactly the criteria that should be used: in many cases the guidelines are based on expert consensus more than on evidence in the field of health status evaluation. The refinement of the decision-making process requires new discussions and consensus.

## Treatment of Metastatic Castration-resistant Prostate Cancer

### Docetaxel—The Backbone of Treatment of Metastatic Castration-resistant Prostate Cancer

Until 2004, mitoxantrone chemotherapy was the standard of care for patients with mCRPC. Compared with prednisone alone it improved symptom control but not OS.[19] The TAX-327 trial compared two schedules of docetaxel (three weekly or weekly) + prednisone to mitoxantrone + prednisone.[20] The median age in the trial was 68 years; 20 % of patients were 75 or older. However, patients had to be fit enough to meet the inclusion criteria (Karnofsky PS ≥60 %, no other serious medical condition, normal cardiac function, and creatinine levels <1.5 upper limit of normal). OS was improved with docetaxel administered every 3 weeks compared with mitoxantrone (median=19.2 months 95 % confidence interval [CI] [17.5–21.3] versus 16.3 months 95 % CI [14.3–17.9], hazard ratio [HR]=0.79 95 % CI [0.67–0.93]; p=0.04). This difference was found in patients older than 68 years. The difference between the weekly schedule and mitoxantrone was not significant (median=17.8 months 95 % CI [16.2–19.2], HR=0.87 95 % CI [0.74-1.02], p=0.086). Patients receiving docetaxel administered every 3 weeks had improved pain control. Patients in both docetaxel groups had better prostate specific antigen (PSA) responses and quality of life (QOL) compared with patients receiving mitoxantrone.

The main side effects of docetaxel are asthenia, diarrhea, nail changes, peripheral edema, sensory neuropathy, and stomatitis. These side effects can affect patients' daily life and can add on to pre-existing conditions, such as arthritis, and further impair patients' dependence level. Patients should be informed of side effects and these should be managed pro-actively.

The standard schedule of docetaxel is 75 mg/m$^2$ every 3 weeks. Weekly docetaxel does not improve survival compared with mitoxantrone. However, compared with prednisolone alone it probably does. In a phase II randomized trial, weekly docetaxel + prednisolone was compared with prednisolone alone.[21] Median age was 70 years (range: 52–84). There again, patients had good PS and adequate renal and liver functions (serum creatinine ≤1.5 upper limit of normal [ULN] and liver functional tests (LFT) ≤2.5 ULN). Docetaxel was associated with higher PSA response rates (at 12 weeks: 63 % versus 59 %) and pain control. Median OS was 27 months (95 % CI 19.8–34.2) with docetaxel plus prednisolone and 18 months (95 % CI 15.2–20.8) with prednisolone alone.

## New Hormone Therapies
### Abiraterone Acetate
Abiraterone acetate is a CYP 17 inhibitor that decreases adrenal, testicular, and intratumoral testosterone synthesis, studied in two large phase III trials in patients with mCRPC, in both the predocetaxel setting (in asymptomatic or mildly symptomatic patients) and in the postdocetaxel setting.[22–24]

In the COU-AA-301 trial, patients with mCRPC who had progressed during or after docetaxel were randomized between receiving abiraterone + prednisone and placebo + prednisone.[22,23] There were several exclusion criteria that are important to consider when treating elderly patients. Patients with abnormal LFTs, with a serum creatinine ≥1.5 x ULN, calculated creatinine clearance <60 ml/minute, chronic liver disease or uncontrolled hypertension, clinically significant heart disease, or using aldactone, spironolactone, and drugs metabolized by the CYP2D6 and 1A2 were excluded. The median age in the trial was 69 years (range: 39–95), more than a quarter of the patients were older than 75.

Patients receiving abiraterone had better OS (HR=0.74, 95 % CI [0.64–0.86]; p<0.0001). They also had longer biologic progression-free survival (PFS), radiologic PFS, higher biologic and radiologic response rates, and had higher pain-control rates than patients receiving placebo. The survival benefit was seen in all age groups (<65, ≥65, and ≥75 years of age). Toxicity was mild: 33 % developed edema (versus 24 % in the placebo arm), 18 % hypokalemia (versus 9 %), 11 % hypertension (versus 8 %), and 16 % cardiac disorders (versus 12 %).

There are limited data on the use of abiraterone in patients with cardiac comorbidities. This is a frequent problem in elderly patients and may be unbalanced by the mineralocorticoid effect of abiraterone. Data from a monocentric retrospective experience seem to suggest that it is possible to use it.[25] However most of these patients had hypertension only and few patients had other cardiac conditions (arrhythmia, ischemia). More data are needed.

The other phase III trial (COU-AA-302) compared abiraterone + prednisone to placebo + prednisone in patients with mCRPC who were asymptomatic or mildly symptomatic (i.e. who did not require level II or III analgesics) and who were chemo-naïve.[24] Median age in the trial was 71 years (44–95) and nearly one-third of the patients were 75 years of or older. There again, adequate cardiac, renal, and liver function were required.

The trial was stopped after a planned interim analysis showed a clear benefit in radiologic PFS, one of the co-primary endpoints (HR=0.53, 95 % CI 0.45–0.62); p<0.001). Analysis of all the secondary endpoints (biologic and radiologic response rates, median time to opiate use, median time to chemotherapy initiation, and median time to PS decline ≥1) favored abiraterone. However the second co-primary endpoint (OS) did not reach the preplanned statistical significance (HR=0.75, 95 % CI 0.61–0.93; p=0.01). Toxicity was similar to that already reported. Subgroup analysis showed that the benefit seen in radiologic PFS was present in every age group.

Abiraterone has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in both situations (pre- and postchemotherapy). It seems to be efficient in elderly patients and tolerable in fit patients. However, drug interactions should be kept in mind. Kalemia and blood pressure should be closely monitored. Data in patients with comorbidities, as we see in our daily practice are lacking.

### Enzalutamide
Enzalutamide, formerly known as MDV3100, is a novel antiandrogen. It binds to the androgen receptor with higher affinity than the first-generation antiandrogen, bicalutamide. It inhibits nuclear translocation of the androgen receptor and its binding to DNA. It also inhibits coactivator recruitment.

It was developed as abiraterone: first in the postchemotherapy setting, then in mildly or asymptomatic chemo-naïve patients. Only the results from the AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) (postchemotherapy) trial are available.[26] Patients with mCRPC who had progressed during or after docetaxel were eligible for this trial. There again the chosen population was quite selective. Patients needed to have a good PS >3, adequate renal function, no severe comorbidity, no clinically significant cardiac disease, no history of seizures, and not using drugs known to lower the seizure threshold or prolong the QT interval (including insulin, venlaflaxin, and class IA and III antiarrythmics). Median age was 69 years (range: 41–92) and about a quarter of the patients were over 75. Compared with placebo, enzalutamide improved OS (HR=0.631, 95 % CI [0.529–0.752]; p<0.0001). This was true in both age groups (<65 years and ≥65 years). It also improved biologic and radiologic response rates and time to radiologic and biologic progression. Toxicity was mild. The main side effects were fatigue (34 % versus 29 %) and diarrhea (21 % versus 18 %). Seizures occurred in 0.6 % of patients on enzalutuamide. Enzalutamide has now been approved by the FDA and the EMA in the postchemotherapy setting. It appears to be efficient even in older patients. Toxicity is acceptable. However, caution must be taken in case of increased risk for seizures and when combining it with drugs that may prolong the QTc.

### New Chemotherapies—Cabazitaxel
Cabazitaxel is a novel tubulin-binding taxane. It was approved in mCRPC based on the results of the TROPIC trial.[27] This phase III trial compared cabazitaxel + prednisone with mitoxantrone + prednisone in patients with mCRPC who had progressed during or after docetaxel. Patients were required to have a good PS and adequate hepatic, renal, and cardiac (left ventricular ejection fraction [LVEF] >50 %) functions and no severe concurrent illness. Median age was 69 years (range=61–73), just less than 20 % were ≥75. Median OS in the cabazitaxel arm was 15.1 months (95 % CI 14.1–16.3) versus 12.7 months (11.6–13.7) in the mitoxantrone arm (HR=0.70, 95 % CI 0.59–0.83; p<0.0001). Subgroup analysis showed a benefit in patients ≥65 years.

Toxicity with cabazitaxel is more of a concern than with the new hormone therapies. Grade 3 neutropenia occurred in 82 % of patients on cabazitaxel and 8 % had febrile neutropenia; 2 % died of neutropenic fever and its clinical consequences/sepsis. Diarrhea occurred in 47 % of patients (6 % grade 3).

More data on the toxicity of cabazitaxel in elderly patients is available from the European expanded-access program.[28] Only patients with a good PS and no uncontrolled severe disease or medical condition were enrolled. Overall, 736 patients with mCRPC were enrolled: 325 were ≥70 years (among which 145 were ≥75 years) and 421 were <70 years. Any grade treatment emergent adverse event (TEAE) occurred in 88.1 % in patients <70 years and in 89.5 % in patients ≥70 years. Grade 3 TEAE were slightly more frequent in patients ≥70 years (52.9 % versus 47 %). TEAE led to treatment discontinuation in 19.1 % patients ≥70 years compared with 13.3 % patients <70 years. Toxic deaths rates were similar around 2–2.5 %. Elderly patients received more-frequent granulocyte-colony stimulating factor (G-CSF) prophylaxis.

Cabazitaxel is an efficient drug—even in fit, elderly patients. However it has side effects that can be quite severe. G-CSF should be used as primary prophylaxis[29] and diarrhea must be managed proactively.

The optimal sequence has not been determined yet. Patients with high-grade Gleason scores, short response to androgen deprivation therapy (ADT), and progression on docetaxel probably should receive cabazitaxel if available and if patients are fit enough. However, the data supporting this sequence over using a new hormonal treatment are limited.[30–35]

## Bone and Prostate Cancer

Bone is the most frequent metastatic site in patients with prostate cancer. Management of bone pain is crucial in treating men with metastatic prostate cancer.

## Treating Bone Metastases

Radium-223 is a radioactive calcium mimetic that has been studied in patients with mCRPC who had symptomatic bone metastases and no visceral disease and no large lymph nodes (>3 cm).[36] It is an alpha-emitting particle that has an ultralow range of action and is eliminated by the digestive system.

In a phase III trial in patients who had progressed on docetaxel or who were unfit for docetaxel, radium-223 + best supportive care was compared with placebo + best supportive care. The primary endpoint was OS. The median age in this trial was 71 years. The updated results of the interim analysis show that median OS was 14.9 months in the radium-223 arm and 11.3 months in the placebo arm (HR=0.70, 95 % CI 0.58–0.83; p<0.001). Median time-to-first symptomatic skeletal-related event (SRE) was also delayed with radium-223: 15.6 months versus 9.8 months (HR=0.66; p<0.001). Tolerance was quite good. Main side effects were bone pain (50 % with radium-223 versus 62 % with placebo), gastrointestinal (GI) toxicity: diarrhea (25 % with radium-223 versus 15 % with placebo), nausea (36 % with radium-223 versus 35 % with placebo), and vomiting (18 % with radium-223 versus 14 % with placebo). There was little hematologic toxicity: anemia was the main hematologic side effect and occurred in 31 % in both arms (with grade 3–4 events in 11 % patients on radium and 12 % on placebo). This could be an interesting drug for elderly patients with bone metastases from hormone-resistant cancer, but there are no specific data in that population.

## Prevention of Skeletal-related Events

Prevention of skeletal-related events (SREs), such as fractures and fracture-related cord compression, is of upmost importance in patients with mCRPC. Zoledronic acid was the first bisphosphonate to decrease SRE rates in men with mCRPC.[37] However, it requires dose adjustment to renal function and can cause renal toxicity.

Denosumab is a monoclonal humanized antibody directed against receptor activator of nuclear factor kappa-B ligand (RANKL), which plays a central role in osteoclast formation, function, and survival. Denosumab was compared with zoledronic acid in a noninferiority phase III double-blind randomized trial with double dummy placebos in patients with mCRPC.[38] The primary endpoint was time to first on study skeletal event. Median age in the zoledronic acid arm was 71 years (66–77) and 71 years (64–77) in the denosumab arm. Seventy-seven percent of patients in the zoledronic acid were 65 or older and 73 % in the denosumab arm. Denosumab significantly delayed first SRE by 18 % compared with zoledronic acid, with a difference of 3.6 months. Denosumab also delayed subsequent events. There was no difference in OS. Hypocalcemia occurred in 13 % in the denosumab arm and 6 % in the zoledronic arm with grade ≥3 events in 5 % and 1 % of patients, respectively. Osteonecrosis of the jaw occurred in 2 % of patients on denosumab and 1 % on zoledronic acid. Most cases occurred after dental extraction. One advantage for using denosumab in elderly patients compared with zoledronic acid is the absence of dose adjustment if the renal function is impaired. It is mandatory to perform dental workup before starting the treatment and to give calcium and vitamin D supplementation. Denosumab is also approved for ADT-induced osteoporosis. It increases bone mineral density in the lumbar spine, the hip (total + femur neck) and the radius, and reduces lumbar fractures (1.5 % versus 3.9 % with placebo).[39]

## Predicting Toxicity

Fear of toxicity is one of the reasons elderly patients do not receive adequate treatment. However, prediction of chemotherapy toxicity is not easy. Several predictive models have been developed. In the model by Hurria et al.[40] several factors were associated with an increased risk for grade ≥3 toxicity: age, cancer type (GI and genitourinary [GU]), standard chemotherapy dosing, polychemotherapy, low hemoglobin, creatinine clearance <34 ml/minute (Jelliffe), fair or worse hearing impairment, ≥1 fall in the previous 6 months, limited walking one block's distance, need for assistance in taking medications, and decreased social activities because of physical and emotional health. Karnofsky PS did not improve the model. With this model, patients were classified in three risk groups: patients in the low-risk group had a 30 % risk for severe toxicity versus 52 % in the medium group and 83 % in the high-risk group.

The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) models were developed to predict grade 4 hematologic toxicity and grade 3/4 nonhematologic toxicity. Two subscales comprised the score.[41] The best model for hematologic toxicity included diastolic blood pressure, IADL, and lactate dehydrogenase (LDH) along with chemotox. The best model for nonhematologic toxicity included Eastern Cooperative Oncology Group (ECOG) PS, Mini-Mental Status (MMS), mininutritional assessment (MNA), and chemotox. Chemothox is a derivative of the MAX2 index, which summarizes the overall severe toxicity from a chemotherapy regimen.

Patients fell into four categories with a combined risk for severe toxicity ranging from 60 % in the 'low risk' to over 80 % in the 'high-risk' group. The two models did not find the same criteria. However, geriatric and biologic criteria and chemotherapy characteristics, were found to be predictive in both series. One thing that is noteworthy is that severe toxicity rates are quite high in both series and elderly patients should be monitored closely.

## Conclusion

Prostate cancer is frequent in elderly patients. The landscape of mCRPC treatment is changing. The data for the use of the new drugs in the general elderly population are quite scarce. Despite seemingly favourable toxicity profiles of the new hormone therapies, drug interactions, and comorbidity should be assessed and patients closely monitored for side effects and treatment benefit. Applying the therapeutic changes to elderly patients with mCRPC requires developing tools that can easily assess the general status of patients and predict toxicity. It also requires having large datasets on the drug in less-fit elderly patients. The ideal situation would be having specific prospective trials that would integrate geriatric evaluation, prospective evaluation of toxicity scores, and evaluation of new drugs. ■

1. Ferlay J, Shin HR, Bray F, et al., GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer, 2010.
2. SEER data 2008, http://seer.cancer.gov/data (accessed July 15, 2013).
3. Mottet N, Bellmunt J, Bolla M, et al., EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer, Eur Urol, 2011;59(4):572–83.
4. Droz JP, Balducci L, Bolla M, et al., Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology, BJU Int, 2010;106(4):462–9.
5. Droz JP, Balducci L, Bolla M, et al., Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults, Crit Rev Oncol Hematol, 2010;73(1):68–91.
6. Extermann M, Aapro M, Bernabei R, et al., Task Force on CGA of the International Society of Geriatric Oncology. Use of comprehensive geriatric assessment in older cancer patients: recommendations from the task force on CGA of the International Society of Geriatric Oncology (SIOG), Crit Rev Oncol Hematol, 2005;55(3):241–52.
7. Linn BS, Linn MW, Gurel L, Cumulative illness rating scale, J Am Geriatr Soc, 1968;16(5):622–6.
8. Rockwood K, Stadnyk K, MacKnight C, et al., A brief clinical instrument to classify frailty in elderly people, Lancet, 1999;353(9148):205–6.
9. Katz S, Ford AB, Moskowitz RW, et al., Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function, JAMA, 1963;185:914–19.
10. Lawton MP, Brody EM, Assessment of older people: self-maintaining and instrumental activities of daily living, Gerontologist, 1969;9(3):179–86.
11. Blanc-Bisson C, Fonck M, Rainfray M, et al., Undernutrition in elderly patients with cancer: target for diagnosis and intervention, Crit Rev Oncol Hematol, 2008;67(3):243–54.
12. Balducci L, Extermann M, Management of cancer in the older person: a practical approach, Oncologist, 2000;5(3):224–37.
13. Drubbel I, Bleijenberg N, Kranenburg G, et al., Identifying frailty: do the Frailty Index and Groningen Frailty Indicator cover different clinical perspectives? A cross-sectional study, BMC FamPract, 2013;14:64.
14. Hoogendijk EO, van Hout HP, Investigating measurement properties of the Groningen Frailty Indicator: a more systematic approach is needed, J Am Med Dir Assoc, 2012;13(8):757, author reply 757–8.
15. Luciani A, Ascione G, Bertuzzi C, et al., Detecting disabilities in older patients with cancer: comparison between comprehensive geriatric assessment and vulnerable elders survey-13, J Clin Oncol, 2010;28(12):2046–50.
16. Mohile SG, Bylow K, Dale W, et al., A pilot study of the vulnerable elders survey-13 compared with thecomprehensive

geriatric assessment for identifying disability in older patientswith prostate cancer who receive androgen ablation, Cancer, 2007;109(4):802–10.
17. Soubeyran P, Bellera C, Goyard J, et al., Validation of the G8 screening tool in geriatric oncology: The ONCODAGE project, J Clin Oncol, 2011;29(Suppl., abstract 9001).
18. Bellera CA, Rainfray M, Mathoulin-Pélissier S, et al., Screening older cancer patients: first evaluation of the G-8 geriatric screening tool, Ann Oncol, 2012;23(8):2166–72
19. Tannock IF, Osoba D, Stockler MR, et al., Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points, J Clin Oncol, 1996;14(6):1756–64.
20. Tannock IF, de Wit R, Berry WR, et al., TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer, N Engl J Med, 2004;351(15):1502–12
21. Fosså 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;52(6):1691–8.
22. de Bono JS, Logothetis CJ, Molina A, et al., COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer, N Engl J Med, 2011;364(21):1995–2005.
23. Fizazi K, Scher HI, Molina A, et al., COU-AA-301 Investigators. 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):983–92.
24. Ryan CJ, Smith MR, de Bono JS, et al., COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy, N Engl J Med, 2013;368(2):138–48.
25. Procopio G, Verzoni E, Testa I, et al., Safety of Abiraterone Acetate (AA) in patients with castration resistant prostate cancer (CRPC) and concomitant cardiac risk factors, Ann Oncol, 2012;23(Suppl. 9):926.
26. Scher HI, Fizazi K, Saad F, et al., AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy, N Engl J Med, 2012;367(13):1187–97.
27. de Bono JS, Oudard S, Ozguroglu M, et al., TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastaticcastration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial, Lancet, 2010;376(9747):1147–54
28. Heidenreich A, Bracarda S, Mason M, et al., Tolerability of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer (mCRPC) in Europe, Ann Oncol, 2012;23(Suppl. 9):932
29. Aapro MS, Bohlius J, Cameron DA, et al., European Organisation for Research and Treatment of Cancer. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced

febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours, Eur J Cancer, 2011;47(1):8–32.
30. Azria D, Massard C, Tosi D, et al., An ambispective observational study in the safety and efficacy of abiraterone acetate in the French temporary authorizations for use (ATU): Predictive parameters of response, JCO, 2012;30(Suppl. 5):abs 149.
31. Loriot Y, Massard C, Albiges L, et al., Personalizing treatment in patients with castrate-resistant prostate cancer: A study of predictive factors for secondary endocrine therapies activity, JCO, 2012;30(Suppl. 5):abs 213.
32. Mukherji D, Pezaro C, Bianchini D, et al., Response to abiraterone acetate in the postchemotherapy setting in patients with castration-resistant prostate cancer whose disease progresses early on docetaxel, JCO, 2012;30 (Suppl. 5):abs 17.
33. Oudard S, De Bono JS, Ozguroglu M, Impact of cabazitaxel (cbz) + prednisone (p; cbzp) on overall survival (OS) at 2 yrs and in patients (pts) with aggressive disease: post-hoc analyses of tropic trial, Ann Oncol, 2012;23(Suppl. 9):933.
34. De Bono JS, Oudard S, Ozguroglu M, et al., A subgroup analysis of the TROPIC trial exploring reason for discontinuation of prior docetaxel and survival outcome of cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC), J Clin Oncol, 2011;29:(Suppl.; abstract 4526).
35. Oudard S, Mercier F, Flechon A, et al., Efficacy of cabazitaxel and its relationship with predictors of poor response to second hormonal therapies in metastatic castration-resistant prostate cancer (mCRPC), J Clin Oncol, 2013;31:(Suppl. 6; abstract 137).
36. Parker C, Nilsson S, Heinrich D, et al., ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer, N Engl J Med, 2013;369(3):213–23.
37. Saad F, Gleason DM, Murray R, et al., Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma, J Natl Cancer Inst, 2002;94(19):1458–68.
38. Fizazi K, Carducci M, Smith M, et al., Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study, Lancet, 2011;377(9768):813–22.
39. Smith MR, Egerdie B, Hernández Toriz N, et al., Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer, N Engl J Med, 2009;361(8):745–55.
40. Hurria A, Togawa K, Mohile SG et al Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study, J Clin Oncol, 2011;29(25):3457–65.
41. Extermann M, Boler I, Reich RR, et al., Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score, Cancer, 2012;118(13):3377–86.