NEW APPROACHES IN THE ONCOLOGICAL TREATMENT OF METASTATIC PROSTATE CANCER

Ph.D. Thesis

/Short version /

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1. Introduction

The treatment of metastatic prostate cancer can be divided into hormone-sensitive and castration-resistant pathophysiological phases. Until recently, androgen deprivation therapy (ADT) alone surgical or medical castration was the standard-of-care for metastatic hormone-sensitive prostate cancer (mHSPC). Once the disease progresses to castration-resistant prostate cancer (CRPC), currently approved therapeutic options include sipuleucel-T, enzalutamide, abiraterone, docetaxel, cabazitaxel, and Radium-223. Recently, there was a paradigm shift as a result of new data from clinical studies which opened new perspectives and changed the standard-of-care in mHSPC. In the pivotal CHAARTEED and STAMPEDE-Docetaxel studies, the combination of docetaxel and ADT demonstrated a survival benefit over ADT alone among patients with mHSPC. Similarly, early abiraterone therapy was also integrated into the standard-of-care in combination with ADT among patients with newly-diagnosed, high-risk mHSPC due to the favorable results of the multinational, randomized, placebo-controlled phase III LATITUDE clinical trial, and the STAMPEDE-Abiraterone study. In the case of high-volume disease, ADT *and* docetaxel *or* (if Gleason score ≥8) abiraterone, or ADT alone is recommended, while for patients with low-volume disease, ADT monotherapy *or* – in high-risk patients – ADT in combination with abiraterone should be administered. Therefore, in many cases, clinicals are faced with the dilemma of choosing between docetaxel (D) and abiraterone (AA), especially among patients with a high burden of mHSPC.

The identification of biomarkers which are potentially associated with response to therapy and clinical outcomes remains to be a major unmet need both in the hormone-sensitive and castration-resistant phases. During the previous years, several retrospective studies focused on the identification of factors with potential predictive value in prostate cancer with a view to help identify baseline resistance to D or AA and optimize treatment decisions. One of the genetic alterations which have been implicated in the development of taxane-resistance is the overexpression of ERG (ETS-related gene), a member of the ETS transcription factor family, which results from recurrent gene fusions with an androgen-regulated 5' gene partner, TMPRSS2. The *TMPRSS2: ERG* fusion gene is the most common ETS gene rearrangement in

prostate cancer which can be detected in about 50% of patients. Interestingly, Galletti *et al.* demonstrated that ERG overexpression was associated with decreased sensitivity to taxanes in *in vitro* and *in vivo* models of CRPC.

Therefore, the identification of ERG status may allow for a tailored approach and may help predict response to docetaxel chemotherapy (ChT) as well as clinical outcomes. While these studies provide valuable information, which may aid treatment decisions and patient selection for appropriate therapies, most of them focused on the predictive value of the examined factors in the castration-resistant phase. Consequently, it is not yet understood whether the biomarkers implicated in mCRPC might have a predictive value in the hormone-sensitive phase regarding response to early D therapy added to ADT.

Metastatic CRPC (mCRPC) frequently metastasizes to the bone, often resulting in painful skeletal events, reduced quality of life, and reduced survival. Patients with mCRPC and bone metastases often experience skeletal-related events (SREs) such as pathologic fractures and spinal cord compression, which are major causes of mortality and can lead to other comorbidities. However, ongoing research led to the development of targeted therapeutics, such as the radiopharmaceutical Radium-223 dichloride (Radium-223, Xofigo®). Radium-223 is a calcium-mimetic alpha-emitting radiopharmaceutical, which selectively targets bone, specifically the areas of bone metastases, while sparing normal tissue. Alpha particles travel much shorter distances than beta particles, and are therefore less damaging to normal tissue, which explains the fewer side-effects observed with Radium-223 therapy compared to beta-emitting radiopharmaceuticals. Unlike previous radiopharmaceuticals, Radium-223 was found to prolong survival in patients with mCRPC in the pivotal phase III ALSYMPCA trial. Based on the results of this study, Radium-223 was approved by the FDA in May 2013 for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease. Radium-223 has been reimbursed in Hungary since July 2014 on an individual basis.

Apart from Radium-223, currently available agents for mCRPC in the post-docetaxel setting include cabazitaxel, enzalutamide and abiraterone, while the options for prechemotherapy treatment are enzalutamide and abiraterone. As mentioned before, the indication for abiraterone was recently expanded. Since 2017, abiraterone is also approved for the treatment of newly diagnosed, high-risk mHSPC patients, which led to significant changes in the recommended therapeutic sequences in mCRPC. Consequently, clinicians are faced with the

growing challenge of providing a tailored approach. Ideally, patients should be provided with the benefits of all treatment lines while achieving the best possible quality of life, which requires the appropriate assessment of progression in all disease stages and during all treatment regimens.

In the TAX 327 clinical study with docetaxel, radiographic progression was assessed using WHO criteria, while the cabazitaxel registration trial already applied the RECIST 1.1 criteria. In studies testing abiraterone/enzalutamide in the prechemotherapy setting, progression was evaluated according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations. The most important learning point from the PCWG2 consensus is that PSA progression in itself without radiographic or clinical progression should not be regarded as an indication for treatment discontinuation. Since 2016, newly designed clinical studies routinely apply the PCWG3 criteria. The PCW3G consensus underlines the importance of documenting progression as distinct from the decision to terminate treatment, keeping in mind the biological heterogeneity of individual metastatic lesions. PCWG3 introduced the concept of „no longer clinically benefitting" (NLCB) in order to avoid the premature or undue discontinuation of treatment. The new guidelines highlight the need for documenting the exact time and reason for treatment discontinuation, and allow for individual decisions on treatment continuation in the case of radiographic or biochemical progression if there are perceived additional benefits to slowing progression in patients without clinical progression.

2. Aims

The primary objective of this thesis was to identify management strategies that may improve quality of life and overall survival and facilitate individualized treatment approaches for patients with metastatic prostate cancer.

2.1. Our study aimed to analyze the potential association between clinical parameters and ERG expression and the outcome of docetaxel chemotherapy among patients with mHSPC.

2.2 Our specific aim was to investigate the efficacy and safety of Radium-223, and to assess the changes in pain intensity as a result of Radium-223 therapy.

2.3. To investigate the overall survival (OS) of chemotherapy refractory mCRPC patients who were treated with abiraterone acetate + prednisolone (AA+P) beyond PSA and radiographic progression (PRP) until clinical progression in comparison to patients treated only until PRP.

3. Patients and methods

3.1. ERG Expression Can Predict the Outcome of Docetaxel Combined with Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Potentially eligible cases were identified from a patient database with mHSPC receiving docetaxel ChT for mHSPC between 1 August 2014 and 31 October 2017 at one of the two centers, the National Institute of Oncology, Budapest and the Department of Oncotherapy, University of Szeged. All patients received intravenous docetaxel ChT (docetaxel every 3 weeks at a dose of 75 mg/m^2 in 6 cycles depending on toxicity, without prednisone), starting within 120 days after the initiation of ADT. Physical examination and laboratory tests were carried out every 3 weeks. The severity of AEs was evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. Patients' general condition was assessed using the ECOG scale. Data were collected prospectively starting in August 2014. The assessment of outcomes was carried out before and 8–12 weeks after the completion of chemotherapy and involved clinical examinations, PSA measurements, bone scan, and diagnostic chest-abdomino-pelvic CT examinations. Response to therapy and follow-up were assessed according to the PCWG2 criteria system. Good response was defined as a ≥50% decrease in baseline PSA levels. Relapse-free survival (RFS) and overall survival (OS) were defined as the period from the initiation of ChT to the detection of castration-resistant prostate cancer or death. Early progression was defined as the development of CRPC within 12 months after the initiation of ChT. Before ChT, immunhistochemical (IHC) staining was performed to quantify ERG expression in the biopsy samples.

3.2. A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary

This was a single-center retrospective study carried out at the National Institute of Oncology, Budapest, Hungary. All mCRPC patients receiving Radium-223 for the treatment of bone metastases between 23rd July 2014 and 23rd February 2016 were included in the analysis.
Patients were administered intravenous Radium-223 at a dose of 50 kBq/kg over one minute every 28 days for up to 6 cycles. Medical records were reviewed for patient demographics and baseline characteristics, laboratory PSA and alkaline phosphatase (ALP) values, treatment outcomes, treatment-emergent adverse events, and changes in pain intensity. The patients'

level of functioning was assessed by the ECOG Scale of Performance Status before Radium-223 treatment. Pain intensity was subjectively assessed, and changes in bone pain were classified as ‘increase’, ‘no change’, ‘decrease’, or ‘complete cessation’.

3.3. Abiraterone+prednisolone treatment beyond prostate specific antigen (PSA) and radiographic progression in metastatic castration-resistant prostate cancer patients (mCRPC): a retrospective observational one-centre study

Unselected cohorts of mCRPC patients treated at the National Institute of Oncology were investigated. The first AA+P treatment started on April 21, 2011 in an early-access protocol trial (NCT01217697). After October 8, 2012 AA became generally available in Hungary. It has been reimbursed based on special request on an individual basis. From April 21, 2011 to November 05, 2014 116 patient received AA+P. All patients progressed during or after docetaxel treatment. AA+P was administered according to the treatment protocol including 1,000 mg AA and 10 mg P daily. All patients had ECOG 0 or 1 performance status. The clinical trial patients (T) (n=56) were treated beyond radiographic progression (PRP) until clinical progression. Definition of clinical progression at the early access protocol (EAP) program was either pain progression (e.g. an opiate was needed for >2 weeks), development of a skeletal-related event (e.g. pathological fracture, spinal-cord compression, or surgery to bone); any increase in dose of prednisolone or a change to a more potent glucocorticoid for prostate cancer-related signs and symptoms; or initiation of new systemic anticancer treatment. In the nonclinical trial group (N) (n=57) the treatment was covered only until PRP. Laboratory parameters and side effects were assessed every 4 weeks, efficacy (CT, bone scan, PSA) at three-month intervals. Treatment outcomes and adverse events were retrospectively evaluated from patient’s charts.

3. Results

4.1. ERG Expression Can Predict the Outcome of Docetaxel Combined with Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Altogether 55 patients were included in the study, with a mean age of 65.6±1.1 years (range: 43–79). Most patients (94.5%) had high-volume disease, defined as the presence of visceral metastases and/or ≥4 bone metastases with at least one outside the vertebral column and pelvis (CHAARTED study definition). Most of the patients also had a Gleason score of ≥8, with a mean value of 8.67±0.14. Performance status was generally good (ECOG 0: 67.3%; ECOG 1: 27.3%), ECOG 2 status was detected in only 3 cases (5.5%). At the time of diagnosis, the mean PSA level of patients was 629.6±161.7 ng/ml. The histological type of prostate cancer was adenocarcinoma in all cases. The mean time between the initiation of ADT and docetaxel ChT was 73.9±3.9 days. The mean number of docetaxel cycles received by patients was 5.69±0.17. Overall, RFS and OS were 10.5±3.2 months and 40.4±8.9 months, respectively. By the time of study completion, 17 patients had died (30.9%), 14 of which due to prostate cancer, 2 due to the development of pneumonia or ileus after ChT, and 1 due to subsequently detected advanced colorectal cancer. Disease progression was mostly detected with increasing PSA levels in 31 patients (56.4%), out of which 19 (34.5%) were bone, 8 (14.5%) were visceral, and 4 (7.3%) were distant lymph node metastases. Castration-resistant prostate cancer developed in 32 patients (58.2%), out of which 23 cases (41.8% of all patients) were detected within 12 months from the initiation of docetaxel ChT. The mean OS after the development of castration-resistant status was 17.2±5.4 months. PSA decrease was detected in 51 cases (92.7%), the mean rate of decrease was 84.7±4.1 ng/ml. The nadir PSA level was 34.0±19.8 ng/ml, a reduction of at least 50% was detected in 44 patients (80%). There was no significant association between RFS/OS and age, Gleason score, initial PSA level, the type of involved organs, or the number of docetaxel cycles. Performance status was significantly associated with clinical outcomes: patients with an ECOG status of 0 had a mean RFS of 17.9±4.6 and a mean OS of 40.43±9.4; those with an ECOG status of 1 had a mean RFS of 8.9±2.1 and a mean OS of 25.7±3.7, while an ECOG status of 2 was associated with a mean RFS of 9.1±6.6 and a mean OS of 10.2±7.5. There were significant differences in RFS

and OS between patients with a good PSA response (defined as a ≥50% decrease in PSA level) and those without (RFS: 16.8±2.3vs. 5.9±0.1 months, p<0.001; OS: 40.4±12.2 vs. 11.6±0.8 months, p<0.001). Progression within 12 months from the initiation of docetaxel ChT was associated with poorer OS compared to progression after 12 months (17.97±7.6 months vs 40.4±8.9 months, p<0.001). RFS was 16.8±3.6 months; ERG expression was detected in 21 patients (42%). ERG positivity was significantly associated with better RFS compared to ERG negativity (median RFS: 26.0 vs. 11.4 months, p=0.030). ERG positivity was also significantly associated with a lower frequency of early progression: progression within 12 months was detected in 5 ERG positive patients vs. in 16 ERG negative patients (23.8% vs. 55.2%, p=0.026). Late progression was detected in 16 cases in the ERG positive, and in 13 cases in the ERG negative groups (76.2% vs. 44.8%). There was no statistically significant association between ERG status and OS (p=0.107). Adverse events were detected in 28 patients (50.9%), mostly after the first cycle of docetaxel ChT (23 cases, 41.8%). The most common adverse events were alopecia, anemia and diarrhea. Most adverse events were grade 0–1 and could be managed conservatively. None of the observed adverse events led to the discontinuation of docetaxel ChT.

4.2. A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary.

Between 23rd July 2014 and 23rd February 2016, 41 patients received Radium-223 treatment at our institute. The mean age of the patients was 72.2 years (SD: 7.1, range: 63–85 years). At the beginning of therapy, 23 patients had an ECOG status of 0, and 18 of them had an ECOG status of 1. Ten patients had less than 6 bone metastases, of which only one patient was diagnosed with lymph node metastasis. Of the 31 patients who had at least 6 bone metastases, lymph node metastases were detected in 4 patients. The mean time from the diagnosis of castration resistant prostate cancer to the beginning of Radium-223 treatment was 20.9 months (SD: 16.3). 24 patients received Radium-223 as first-line treatment (58.5%), 7 patients as second-line treatment (17.1%), 3 as third-line therapy (7.3%), 6 as fourth-line treatment (14.6%), and one patient as fifth-line therapy (2.4%). Prior treatments included docetaxel (16 patients), abiraterone (10 patients), mitoxantrone (5 patients), cabazitaxel (3 patients), and enzalutamide (1 patient). The median number of cycles administered was 5.5 (SD: 1.1). Altogether 32 patients received the pre-planned 6 cycles without delay. 9 patients

received a reduced number of cycles due to sudden cardiac death (1 patient), stroke (1 patient), brain metastasis (3 patients), and progression (4 patients, 2 of which due to bone marrow failure).Radium-223 resulted in the complete cessation of bone pain, as a result of which the patient no longer required potent opioid analgesic treatment.The mean PSA level at the beginning of treatment was 307.2 ng/ml (SD: 525.7), which increased to a mean value of 728.5 ng/ml (SD: 1277) by the end of treatment. The mean ALP level before treatment initiation was 521.1 U/L (SD: 728), while at the end of treatment the last measured mean ALP value was 245.1 U/L (SD: 283.5). 13 patients had elevated baseline ALP levels, of which a 30% decrease in ALP levels was detected in 3 patients, a 50% decrease in 6 patients, and altogether 9 patients showed a complete normalization of ALP levels. The most common side effects of Radium-223 treatment were also examined. Adverse events were graded according to the CTCAE version 3.0 (grade 1–4). The most common adverse event was anemia observed in 11 cases (26.8%), 3 of which were classified as grade 1, 2 as grade 2, and 6 as grade 3. Nausea occurred in 9 patients (21.9%), all cases were rated as grade 1. Four patients reported treatment-emergent diarrhea (9.8%), 3 of which were classified as grade 1, and one as grade 2 in severity. Thrombocytopenia developed in 2 patients (4.9%), the severity was grade 2 in both cases. Before the initiation of Radium-223 therapy, 40 patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief. Nearly two thirds of patients were only receiving one type of analgesics (63.4%), most of which were NSAIDS (97.6%). In addition to NSAID treatment, 3 patients were managed with palliative radiotherapy, 5 patients were receiving NSAID + weak opioid, 2 patients were treated with NSAID + weak opioid + radiotherapy, 4 patients were treated with NSAID + major analgesics, one patient with NSAID + major analgesics + radiotherapy, and one patient was only receiving a weak opioid analgesic .Two patients reported an increase in pain intensity (4.8%), 6 patients reported no change (14.6%), 15 patients experienced decreased pain intensity (36.6%), and 18 patients reported a complete cessation of pain by the end of Radium-223 therapy (44%).

4.3. Abiraterone+prednisolone treatment beyond prostate specific antigen (PSA) and radiographic progression in metastatic castration-resistant prostate cancer patients (mCRPC): a retrospective observational one-centre study

The two groups were statistically homogeneous in every aspect, except for the definition of progression and subsequently the duration of AA+P treatment. None of the parameters, but the length of AA+P treatment showed statistical significant difference.

In multivariate analysis (logistic regression) none of the parameters was statistically significant for the cohort type (N or T). After a median follow-up of 39.7 (95% CI 37.4-59.8) months the median OS was significantly longer ($p=8x10^{-7}$) in the T group compared to the N group: 21.9 (95% CI 16.9-25) vs. 12.5 (9.3-14.1) months, respectively. The difference in case of PRP-free survival curves did not reach the level of significance. Median PSA progression-free survivals (PFS) were 4.1 (2.8-7.6) and 4.6 (2.7-5.7) months (p=0.90) in group N and T, respectively. The median radiographic PFS were 5.1 (3-7) and 5.7 (4.9-7.8) months (p=0.29) in group N and T, respectively. The OS in univariate analysis was significantly influenced by the presence of systemic therapy besides of docetaxel, count of white blood cells, neutrophils and lymphocytes, neutrophil to lymphocyte ratio, starting level of AP and LDH, systemic therapy after AA+P and cohort type (N or T) (data not shown). These (significant) variables were included in the multivariate Cox regression analysis of OS. Besides of cohort type the AP level at the start of therapy and systemic therapy after AA+P proved to be independent predictors of OS. The PSA PFS in univariate analysis was significantly influenced by 11 parameters, but out of them only 3 was significant in COX multivariate regression: ≥25% increase in PSA level after 3 month compared to the start or to the first month and LDH level after 1 month compared to the first month (data not shown). The radiographic PFS in univariate survival analysis was significantly influenced by 14 variables and out of them only the ≥25% increase in AP level after 3 month and that of PSA level after 1 months compared to the start proved to be independent factors in Cox multivariate analysis (data not shown). The treatment was well tolerated. In contrast to other studies no drug related adverse events of grade 3-4 were detected among our patient.

5. Discussion

5.1. ERG Expression Can Predict the Outcome of Docetaxel Combined with Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer

In our cohort of mHSPC patients treated with early docetaxel and ADT, we examined the potential relationship between clinical factors as well as ERG expression and response to docetaxel therapy. ERG positivity and good PSA response were strongly associated with better relapse-free survival, and ERG expression was also associated with a lower frequency of early progression. The combined docetaxel + ADT regimen was well-tolerated; no new adverse events were recorded during a mean cycle number of 5.69. Recently, there was a paradigm shift in the management of mHSPC. Until 2014, the only available therapy for these

patients was ADT, and most of the research focused on patients with castration-resistant disease. The introduction of early docetaxel or abiraterone in addition to ADT in the hormone-sensitive phase opened new perspectives in the management of mHSPC by providing similar benefits in terms of OS compared to ADT alone. However, there are certain aspects that need to be taken into consideration when choosing between docetaxel and abiraterone in eligible patients, such as the expected duration of therapy, and treatment costs. However, biomarkers predicting response to docetaxel are needed to identify patients who would benefit from early docetaxel. The role of the *TMPRSS2:ERG* fusion gene as a potential biomarker of response to docetaxel chemotherapy among patients with mHSPC receiving ADT has been suggested by several authors. Rajpar *et al.* analyzed data from the phase III GETUG-12 and GETUG-15 studies, which assessed the role of docetaxel chemotherapy in combination with ADT in the setting of high-risk localized or metastatic HSPC, respectively. In both datasets, docetaxel-based chemotherapy was associated with improved RFS in ERG positive patients, but not in ERG negative patients, suggesting a potential role for ERG as an important biomarker of the effectiveness of docetaxel chemotherapy. In the present study, ERG positivity was also significantly associated with better RFS and a lower frequency of early progression, than ERG negative status among mHSPC patients treated with early docetaxel and ADT. Furthermore, the finding that good PSA response was associated with better RFS is in line with previous observations suggesting a predictive value for PSA progression in terms of survival in metastatic prostate cancer and complements the existing knowledge base with new data from mHSPC patients receiving the early docetaxel + ADT regimen.

5.2. A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary

In our cohort of patients with symptomatic mCRPC, Radium-223 proved to be effective in terms of pain relief, with moderate side effects. No PSA response was detected, while total ALP levels significantly decreased by the end of treatment. Our findings should be interpreted in view of the clinical evidence supporting the use of Radium-223 for the treatment of bone metastases in mCRPC patients. The phase III, double-blind, randomized Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) trial investigated the efficacy and safety of Radium-223 compared to placebo, in addition to the best standard of care, in men with castration-resistant prostate cancer and bone metastases. Radium-223 significantly

prolonged overall survival, the time to first symptomatic skeletal event, and reduced the risks of external beam radiation therapy for bone pain, and spinal cord compression. The most common adverse reactions associated with Radium-223 treatment in the ALSYMPCA trial were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic laboratory abnormalities in the Radium-223 arm were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Our clinical experience is in line with the results of the ALSYMPCA trial in terms of the efficacy and safety of Radium-223 treatment. The majority of patients receiving Radium-223 at our institute experienced a significant reduction of bone pain by the end of treatment Radium-223, as compared with placebo, significantly prolonged the time to an increase in the total ALP levels, and the time to an increase in PSA levels in the ALSYMPCA trial. In our cohort, Radium-223 treatment resulted in a significant reduction of baseline total ALP levels. The majority of patients (70%) having elevated ALP levels at baseline achieved a complete normalization by the end of treatment, and a decrease of at least 50% was observed in 46% of these patients. On the other hand, we found an increase in mean PSA levels by the end of treatment. Nevertheless, it has to be noted that Radium-223 is not supposed to treat prostate cancer itself or slow down disease progression. The primary purpose is to treat bone metastases and reduce bone pain, thus improving quality of life and prolonging survival. Therefore, changes in ALP levels should be preferred over PSA when it comes to monitoring the efficacy of Radium-223 therapy in terms of bone metastases and the reduction of bone pain. Our clinical experience suggests that Radium-223 is a safe and effective treatment option for patients with mCRPC and bone metastases. In our study, Radium-223 therapy was associated with a significant reduction in bone pain intensity, which was accompanied by a decrease in total ALP levels. The majority of reported adverse events were mild or moderate

5.3. Abiraterone+prednisolone treatment beyond prostate specific antigen (PSA) and radiographic progression in metastatic castration-resistant prostate cancer patients (mCRPC): a retrospective observational one-centre study

In this retrospective study the treatment with AA+P beyond PSA and radiographic progression significantly improves survival. To our knowledge this phenomenon connected to AA+P treatment is new in the literature. The dissimilarity between the two subgroups was only the definition of progression, otherwise they were homogeneous. In this analysis predictive factors of OS were also investigated, therefore, all variables, which significantly

influenced OS in the univariate analysis, were included in the multivariate Cox regression analysis. Besides of cohort type (T or N) the ALP level at the start of therapy and systemic treatment after AA+P proved to be independent predictors of OS. During the chemotherapy era the treatment of patients just until progression was a fundamental postulate. It seems that with novel treatment options the situation is changing. Some evidence suggests that, in certain circumstances, continuing a therapy beyond disease progression can be successful. In mCRPC androgen deprivation therapy is a life-long treatment irrespectively of disease progression. This is based on the hypothesis that cessation of androgen suppression, with the recovery of androgen production, might allow accelerated tumor growth. Progression during AA+P treatment or resistance may be explained by the generation of constitutively active androgen receptor (AR) splice variants. It was indicated that DDX39B (also known as UAP56, a member of RNA-helicases) may be associated with malignant progression of prostate cancer through promoting splice variant AR generation. It was also shown, that UAP56 can be down regulated by inhibition of the PI3K pathway. An inhibitor of PI3K, PX-866, a derivative of wortmannin, was investigated in a trial of mCRPC patients receiving AA+prednisone, but the addition of PX-866 to AA+prednisone in unselected patients progressing on AA+prednisone showed no evidence of antitumor effects. The authors conclude that strategies to combine PI3K inhibition with AR targeted therapies should consider initiation earlier in the disease course and/or recruiting a selected population.We can agree with their conclusion as the glucocorticoids increases the PTEN expression, which acts as the catalytic antagonist of PI3K , thus during the prednisone treatment further decrease in expression of AR splice variants by using PX-866 is unlikely (it would be interesting to use PX-866 along AA in glucocorticoid-naïve mCRPC patients). The above data indicate that only by the presence of AR splice variants the antitumor effect of AA beyond progression can not be explained. It can be rather supposed that besides of AA-sensitive cancer cells during AA treatment enhanced proliferation of AA-resistant subclones is favored and subsequently progression is manifested. At this stage withdrawal of AA may lead to uncontrolled proliferation of both clones (AA-resistant and AA-sensitive), while the continuous AA treatment let only the AA-resistant subclone to proliferate. Based on our result we can hypothesize that longer treatment with AA+P - at least until clinical progression - results in better survival. It is important to note that the whole clinical picture – and not just response criteria – should be taken into account when deciding which patients to treat beyond first progression.

6. Summary, Conclusions

6.1. ERG expression may have a potential predictive value with respect to the effectiveness of docetaxel chemotherapy combined with ADT.

6.2. Radium-223 proved to be efficient in terms of pain relief, with moderate side effects. No PSA response was detected, while alkaline phosphatase levels significantly decreased.

6.3. Low levels of AP at the start of treatment, systemic therapy applied after AA+P and treatment beyond PRP proved to be independent factors of longer OS.

List of full papers that served as the basis of the Ph.D. thesis

I. Küronya Z, Sükösd F, Varga L, Bíró K, Gyergyay F, Géczi L, Nagyiványi K, Jorgo K, Szarvas T, Kovács Á, Varga Z, Pepó J, Maráz A

ERG Expression Can Predict the Outcome of Docetaxel Combined with Androgen Deprivation Therapy in Metastatic Hormone-Sensitive Prostate Cancer

Urol Oncol. 2018; In press **IF: 3.397**

II. Küronya Z, Sinkovics I, Ágoston P, Bíró K, Bodrogi I, Böde I, Dank M, Gyergyay F, Vajdics T, Kolonics Z, Nagyiványi K, Rúzsa Á, Géczi L

A Retrospective Analysis of the First 41 mCRPC Patients with Bone Pain Treated with Radium-223 at the National Institute of Oncology in Hungary.

Pathol Oncol Res. 2017 Oct;23(4):777-783. **IF: 1.935**

III. Biró K, Budai B, Szőnyi M, **Küronya Z**, Gyergyay F, Nagyiványi K, Géczi L.

Abiraterone acetate + prednisolone treatment beyond prostate specific antigen and radiographic progression in metastatic castration-resistant prostate cancer patients.

Urol Oncol. 2018 Feb;36(2):81.e1-81.e7. **IF: 3.397**

IV. Küronya Z, Bíró K, Géczi L, Maráz A.

Modern treatment of metastatic hormone-sensitive prostate cancer

Orv Hetil. 2018 Oct;159(41):1664-1671. **IF:0.322**