Observational Study Report

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A Non-interventional Study of Postoperative or post-Radiation trEatment approaches in locally adVanced prostate cancer patiENTs (high risk) - PREVENT

Sponsor:

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event
ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
Assessment	An observation made on a variable involving a subjective judgement (assessment)
CRF	Case Report Form (electronic/paper)
CRO	Clinical research organisation
EC	Ethics committee, synonymous to Institutional Review board (IRB) and Independent ethics committee (IEC)
FAS	Full Analysis Set
GCP	Good clinical practice
Hb	Hemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
LHRH	Luteinizing hormone-releasing hormone
MedDRA	Medical Dictionary for Regulatory Activities
National Coordinator	The National Coordinator is the main line of contact to coordinate the submissions and responses of the Leading Ethics Committee and of the Ethics Committees related to the other participating sites (Non-Leading Ethics Committees).
NIS	Non-Interventional Study
NISA	Non-Interventional Study Agreement
NISP	Non-Interventional Study Protocol
NISR	Non Interventional Study Report
PCa	Prostate Cancer
PI	Principal Investigator responsible for the conduct of a NIS at a site
PRO	Patient Reported Outcome
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time

Abbreviation or special term	Explanation
RECIST	Response Evaluation Criteria in Solid Tumours
RP	Radical prostatectomy
RT	Radiotherapy
SAE	Serious adverse event
SD	Standard deviation
TRUS	Transrectal Ultrasound
WhoDDE	WHO Drug Dictionary Enhanced

RESPONSIBLE PARTIES

Name	Professional Title	Role in Study	Affiliation	Email Address

STUDY REPORT SUMMARY (ABSTRACT)

A Non-interventional Study of Postoperative or post-Radiation trEatment approaches in locally adVanced prostate cancer patiENTs (high risk) - PREVENT

Background/Rationale:

Background

Prostate cancer is the fourth most common cancer in both sexes combined and the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759 000) occurring in more developed regions. This can be attributed to the fact that the practice of prostate-specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. With an estimated 307 000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths). [3]

27 046 new cases of prostate cancer were diagnosed in Russian Federation in 2012. Stages I-II were diagnosed in 48.4 % of cases, stage III - in 31.8% of cases, stage IV - in 17.8% of cases. Lethality during one year after diagnosis was 10.3%. [1, 2]

The widespread use of the serum prostate-specific antigen (PSA) level measurements for diagnostic purposes has resulted in a 20% increase in the detection of clinically localized PCa. Nonetheless, approximately one-third of newly diagnosed PCa cases are considered locally advanced at the time of diagnosis [9, 10]. A rising PSA after radical prostatectomy / radiotherapy (post-treatment PSA) can be indicative of local recurrence, distant disease, or both. Post-treatment PSA kinetics - doubling time (PSA-DT) and PSA velocity (PSA-V) - can be attractive surrogate end-points for studies in PCa patient population and may allow a more rapid and meaningful evaluation of therapeutic strategies. [12] Biochemical progression is also used for PCa course monitoring in routine clinical practice and are commonly selected as parameters in clinical and non-interventional PCa studies. Biochemical progression is defined as PSA level rise ≥ 0.2 ng/ml after surgery or PSA increase ≥2 ng/ml above nadir after radiation. [15 16].

For some locally advanced PCa cases primary definitive local treatment modalities such as radical prostatectomy or radiation therapy can be used. However, locally advanced PCa encompasses a wide spectrum of tumor phenotypes with differing prognoses and more than 50% of these men are at risk of experiencing tumor recurrence after local therapy. It is,

therefore, important to be able to recognize these high-risk cases in order to apply appropriate primary and / or adjuvant therapy.

Locally advanced PCa with high (T3a or Gleason score = 8-10 or PCA >20 ng/ml) and very high (T3b-T4) risk of recurrence after surgical treatment and radiation are the candidates for androgen deprivation therapy [2].

As soon as androgen plays a role as a growth factor for prostatic carcinoma cells, interference with the androgen-signalling pathway can be clinically beneficial for patients with the locally advanced prostate cancer. The majority of circulating androgen is produced by the testes in the form of testosterone, and the remainder is produced by the adrenal glands. Androgen deprivation is readily achieved through orchiectomy but may also be obtained by hormonal treatments.

Recent large, multi-centre, randomised trials have demonstrated that early androgen deprivation therapy of high-risk localised or locally advanced PCa after radical prostatectomy or radiation therapy can significantly delay disease progression and improve overall survival.[17]

Rationale for conducting this NIS

Currently there is no clear understanding of preferences among oncologists in Russia in decision-making process regarding adjuvant androgen deprivation therapy administration (“go / no go” decision, choosing drugs and their regimens) in patients with locally advanced prostate cancer with high and very high risk of recurrence after prostatectomy or radiotherapy.

Objectives and Hypotheses:

Primary objective

The primary objective of this NIS was to provide accurate and reliable information regarding the adjuvant endocrine treatment of patients with locally advanced prostate cancer with high and very high risk of recurrence after surgery or radiotherapy in the Russian routine clinical practice by evaluation of treatment approaches

Secondary objectives

Secondary objectives of the NIS were:

(1) To describe patient characteristics of Russian patients with locally advanced prostate cancer

(2) To evaluate diagnostic approaches applied prior to surgery in Russian clinical sites

(3) To assess prostate-specific antigen (PSA) levels in patient groups with and without androgen deprivation therapy before, after and during the year after surgery/radiotherapy

(4) To evaluate the proportion of patients with double increase in PSA level during 1 year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation therapy type and duration

(5) To evaluate the proportion of patients free from progression after 1 year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation therapy type and duration

(6) To evaluate the proportion of patients with progression of disease after 1 year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation type and duration

Methods:

This was a multicentre, non-interventional, prospective observational cohort study designed to collect real world clinical data related to the management of high and very high risk of recurrence locally advanced prostate cancer patients following surgery or radiation therapy from within the Russian healthcare system.

No additional procedures besides those already used in the routine clinical practice were to be applied to the patients. Treatment assignment was to be done according to the current routine medical practice.

It was planned to enrol 200 subjects in up to 30 sites in Russian Federation. The average number of patients per site was planned as 6 - 10; there were no restrictions on minimum and maximum number of subjects per site in this study.

Evidence generation, via collection and interpretation of data on current real world clinical approaches relating to the postoperative and post-radiation management of locally advanced prostate cancer patients with high and very high risk of recurrence in Russia was considered as the primary outcome variable in this study.

Information on the routine diagnosis-specific examinations, including PSA measurements before, after and during one year after prostatectomy/radiotherapy, performed by local laboratories, was to be collected.

Accordingly, two study visits – Baseline Visit and Follow-up Visit (in one year after Baseline Visit) were planned for all patients.

Information regarding patient demographics, disease characteristics, management approaches, diagnostic tests performed and medications received by patients was to be taken from the medical records. The paper CRF was to be completed at each study visit.

Results:

A total of 204 males with locally advanced prostate cancer were enrolled in 18 clinical centres and 202 were included in the Full Analysis set. Almost all patients were White with mean age

of 64.9 ± 6.2 years. Median duration of prostate cancer at the time of enrolment was less than 2.7 months, for 75% of patients disease duration did not exceed 7 months.

About 60% of patients had disease stage T3a according to TNM classification, 37.6% had T3b and 2.5% had T4 stage. In 86.1% of patients lymph node metastases were absent and for 13.9% lymph nodes could not be assessed (stage Nx). Primary prostate cancer diagnosis was based on PSA analysis in vast majority of patients (98.5%), finger rectal examination of prostate was carried out in 80.2% of patients, 50.5% of males underwent transrectal ultrasonography, 30.2% were diagnosed with MRI and radioisotope examination was used for 11.9% of patients. Transrectal ultrasound-guided prostate thick needle biopsy (TRUS) and histological examination were in the top of methods for diagnosis confirmation (96.0% and 92.6%, respectively).

Description of prostate cancer cells morphology with Gleason grading system revealed that 39.6% of patients had moderately differentiated adenocarcinoma (Gleason score 7), about one third (29.7%) had poorly differentiated or anaplastic adenocarcinoma (score 8 or more) and approximately the same number (29.2%) of patients had well differentiated adenocarcinoma (score 6 or less).

Among males participated in the study, 64.4% were treated surgically, and 38.6% underwent radiotherapy. 6 patients (4.6%) underwent radical prostatectomy followed by radiotherapy.

Androgen deprivation therapy was carried out for 65.3% of patients (132 males). About one third (31.2%) of patients received both neoadjuvant and adjuvant therapy, 19.8% underwent only neoadjuvant therapy and 14.4%underwent only adjuvant therapy. For two thirds of patients received any ADT (70.5%), duration of treatment was more than 6 months.

Androgen deprivation therapy was received by almost all males underwent radiotherapy without radical prostatectomy (95.8%) and less than half of those underwent radical prostatectomy without radiotherapy (46.8%).

Among all patients underwent any ADT, percentage of males received radical prostatectomy was a little less than those treated with radiotherapy (47.7% vs. 56.1%). Among patients received adjuvant therapy approximately equal number of patients underwent radical prostatectomy or radiotherapy (51.1% and 54.3%, correspondingly). Among patients received neoadjuvant therapy prior to radical treatment 65.0% of patients were treated with radiotherapy and 37.9% of patients were treated with radical prostatectomy.

Castration (including orchidectomy, usage of LHRH analogs, hexestrol) was carried out in more than half of all patients (56.4%). This treatment was conducted in majority cases for both adjuvant and neoadjuvant regimen. Antiandrogens without castration were used by less than 10% of patients (8.9%). 28.2% of patients received treatment with both castration and antiandrogens and the same number of males underwent only castration. Combination of castrations and antiandrogens were used in about half of patients received either adjuvant or neoadjuvant regimen.

Patients' performance status and its dynamics were assessed with ECOG score at Visit 1 and after 1-year follow-up. At first visit ECOG score 0 or 1 was reported for 93.6% of patients, and ECOG score 2 and 3 was reported for 6.4% of patients. At the second visit scores 0 and 1 have been reported for 87.6% of males, and score 2 was registered for 6.9% of patients. Changes in performance status within 1 year was assessed in subgroups of patients by performance of ADT, type of radical treatment, duration of ADT and types of treatment combinations, but there was no significant difference revealed between any subgroups for ECOG status dynamic.

Data on PSA levels after radical treatment and after one year of observation were available for 48 and 169 patients, respectively. Median PSA levels after radical treatment were higher in patients after RT without RP than in those underwent RP without PR: 1.9 vs. 0.1 ng/ml. Similar situation was observed for those received any ADT: median PSA levels were 2.0 ng/ml in patients after RT without RP and 0.2 ng/ml in those underwent RP without PR. After one year there was no notable difference between subgroups of patients, median PSA level was 0.1 ng/ml for all patients with available assessments. Median PSA levels did not exceed 0.7 ng/ml in any subgroup.

50.5% of patients (95%CI: 43.2%; 57.9%), for whom at least two PSA measurements at baseline and after 1 year were available, showed doubling of PSA level after 1 year. Similar situation was observed in subgroups by ADT presence, ADT duration and ADT type: approximately half of males in each subgroups, for whom at least two PSA measurements were available, had two times PSA increasing. Proportion of patients with PSA doubling after one year was greater among males underwent radical prostatectomy without radiotherapy than in group after radiotherapy without radical prostatectomy: 57.5% (CI95%: 47.9%; 66.8%,) vs. 40.0% (CI95%: 28.5%;52.4%), correspondingly. This tendency was presented for all subgroups. But at the same time initial PSA levels after radical treatment were higher in group after radiotherapy than radical prostatectomy.

Disease progression was observed in 8.4% (16 males) of patients with conducted assessment. In most cases biochemical progression was observed without signs of clinical progression. Clinical progression was noted in 4 patients. There were no cases of death due to prostate cancer progression.

Percentage of patients with prostate cancer progression was 9.3% for males after radical prostatectomy without radiotherapy and 7.4% for those underwent radiotherapy without radical prostatectomy.

Disease progression or death was observed more frequent in patients received ADT more than 6 months, although groups were small. It is anticipated, because disease duration in this subgroup was longer, than among males received ADT more short period of time. In subgroups by radical treatment disease progression or death among males received ADT more than 6 months was observed in 18.2% of patients with RP without RT and in 10.7% of patients with RT without RP.

Analysis of time to disease progression conducted for subgroups of patients by radical treatment regimen (radical prostatectomy without any radiotherapy vs. radiotherapy without radical prostatectomy), ADT presence (any ADT vs. no ADT), ADT duration (6 months and less vs. more than 6 months) and ADT type (castration and antiandrogens vs. castration only) did not reveal significant difference in time to disease progression between subgroups.

Conclusion:

The study was conducted to obtain information on current clinical practices in usage of antiandrogen deprivation therapy in patients with locally advanced prostate cancer. Objectives of the study were achieved. Data on prostate cancer diagnostics, radical treatment, androgen deprivation therapy, patients performance status, PSA levels dynamics, cancer progression were obtained.

Data on clinical management strategy in Russia for locally advanced prostate cancer were obtained. Among males participated in the study, more than half were treated surgically, and other underwent radiotherapy. Androgen deprivation therapy was carried out for 65.3% of patients. Androgen deprivation therapy was received by almost all males underwent radiotherapy without radical prostatectomy and less than half of those underwent radical prostatectomy without radiotherapy. Castration (including orchidectomy, usage of LHRH analogs, hexestrol) was carried out in more than half of all patients. Antiandrogens without castration were used by less than 10% of patients. 28.2% of patients received treatment with both castration and antiandrogens and the same number of males underwent only castration.

The results are in alignment with international guidelines and standards and with data of other studies. Received data can help to improve management approaches for treatment of Russian patients with high risk locally advanced prostate cancer.

AMENDMENT HISTORY

Date	Section of study protocol	Amendment or update	Reason
15.05.2014	NIS Protocol	NA	NA
25.07.2014	Protocol Title Protocol Synopsis Section 1. Introduction Section 3. Study Plan and Procedures Section 13. Statistical Methods and Sample Size	Amendment 1	Correct wording in
27.04.2015	Section 9. Safety Reporting Section 11.2 Training of study site personnel Section 11.3 NIS timetable and end of study Section 12.2 Reporting and publication of data APPENDIX C AE reporting form	Amendment 2	Patient's enrolment period extension. Safety Assessment and Training of study site personnel sections Update.
18.01.2018	Section 13.5 Subgroup analysis	Amendment 3	Subgroup analysis section update.

MILESTONES

Milestone	Date
First Subject In (FSI)	25 Jul 2014
Last Subject In (LSI)	16 Dec 2015
Last Subject Last Visit (LSLV)	19 Dec 2016
Database Lock	27 Aug 2018
Development of Analytic Datasets	29 Oct 2018
Final Result Tables	12 Nov 2018
Final Report	20 Mar 2019

1. BACKGROUND AND RATIONALE

1.1 Background

Prostate cancer is the fourth most common cancer in both sexes combined and the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. This can be attributed to the fact that the practice of prostate-specific antigen (PSA) testing and subsequent biopsy has become widespread in those regions. With an estimated 307,000 deaths in 2012, prostate cancer is the fifth leading cause of death from cancer in men (6.6% of the total men deaths). [3]

27 046 new cases of prostate cancer were diagnosed in Russian Federation in 2012. Stages I-II were diagnosed in 48.4 % of cases, stage III - in 31.8% of cases, stage IV - in 17.8% of cases. Lethality during one year after diagnosis was 10.3%. [1, 2]

More than 90% cases of prostate cancers belong to acinar adenocarcinoma (atrophic, pseudohyperplastic, foamy, colloid, signet ring, oncocytic and lymphoepithelioma-like carcinomas), the rest – to non-acinar carcinomas (sarcomatoid carcinoma, ductal adenocarcinoma, urothelial carcinoma, squamous and adenosquamous carcinoma, basal cell carcinoma, and neuroendocrine tumours, specifically small-cell carcinoma). [4]

Generally, the incidence of PCa is growing with increasing age: about 6 cases in 10 are diagnosed in men aged 65 or older, and it is rare before age 40. The average age at the time of diagnosis is about 66. [5]

Besides age, other risk factors for PCa are family history and ethnicity (higher risk exists for Black ethnic group, lower risk – for Asian ethnic group). [6, 7]

The widespread use of the serum prostate-specific antigen (PSA) level measurements for diagnostic purposes has resulted in a 20% increase in the detection of clinically localized PCa. Nonetheless, approximately one-third of newly diagnosed PCa cases are considered locally advanced at the time of diagnosis [9, 10]. A rising PSA after radical prostatectomy / radiotherapy (post-treatment PSA) can be indicative of local recurrence, distant disease, or both.

Post-treatment PSA kinetics - doubling time (PSA-DT) and PSA velocity (PSA-V) - can be attractive surrogate end-points for studies in PCa patient population and may allow a more rapid and meaningful evaluation of therapeutic strategies. [12]

Besides PSA assessment, other diagnostic procedures like transrectal ultrasound (TRUS, MRI etc) are used to monitor disease progression in order to initiate appropriate treatment timely. [13,14]

Locally advanced PCa is diagnosed when the tumor has extended beyond the prostatic capsule without evidence of nodal or distant metastatic spread (stage T3-T4, Nx-N0, M0: prostate adenocarcinoma with extracapsular invasion (T3a) or invasion to the seminal vesicles (T3b) or invasion to adjacent structures (T4), but without lymphatic invasion (N0) nor metastasis (M0)) . [11]

For some locally advanced PCa cases primary definitive local treatment modalities such as radical prostatectomy or radiation therapy can be used. However, locally advanced PCa encompasses a wide spectrum of tumor phenotypes with differing prognoses and more than 50% of these men are at risk of experiencing tumor recurrence after local therapy. It is, therefore, important to be able to recognize these high-risk cases in order to apply appropriate primary and / or adjuvant therapy.

Locally advanced PCa with high (T3a or Gleason score = 8-10 or PCA >20 ng/ml) and very high (T3b-T4) risk of recurrence after surgical treatment and radiation are the candidates for androgen deprivation therapy [2].

As soon as androgen plays a role as a growth factor for prostatic carcinoma cells, interference with the androgen-signalling pathway can be clinically beneficial for patients with the locally advanced prostate cancer. The majority of circulating androgen is produced by the testes in the form of testosterone, and the remainder is produced by the adrenal glands. Androgen deprivation is readily achieved through orchiectomy but may also be obtained by hormonal treatments.

Recent large, multi-centre, randomised trials have demonstrated that early androgen deprivation therapy of high-risk localised or locally advanced PCa after radical prostatectomy or radiation therapy can significantly delay disease progression and improve overall survival.[17]

An increasing PSA level is an early sign of prostate cancer recurrence. PSA doubling time and biochemical progression are used for PCa course monitoring in routine clinical practice and are commonly selected as parameters in clinical and non-interventional PCa studies. Biochemical progression is defined as PSA level rise ≥ 0.2 ng/ml after surgery or PSA increase ≥2 ng/ml above nadir after radiation. [15 16].

1.2 Rationale

Currently there is no clear understanding of preferences among oncologists in Russia in decision-making process regarding adjuvant androgen deprivation therapy administration (“go / no go” decision, choosing drugs and their regimens) in patients with locally advanced prostate cancer with high and very high risk of recurrence after prostatectomy or radiotherapy.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective

The primary objective of this NIS was to provide accurate and reliable information regarding the adjuvant endocrine treatment of patients with locally advanced prostate cancer with high and very high risk of recurrence after surgery or radiotherapy in the Russian routine clinical practice by evaluation of treatment approaches.

2.2 Secondary Objectives

Secondary objectives of the NIS were:

(1) To describe patient characteristics of Russian patients with locally advanced prostate cancer.

(2) To evaluate diagnostic approaches applied prior to surgery in Russian clinical sites.

(3) To assess prostate-specific antigen (PSA) levels in patient groups with and without androgen deprivation therapy before, after and during the year after surgery/radiotherapy.

(4) To evaluate the proportion of patients with double increase in PSA level during 1 year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation therapy type and duration.

(5) To evaluate the proportion of patients free from progression after 1-year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation therapy type and duration.

(6) To evaluate the proportion of patients with progression of disease after 1 year follow-up in groups with and without androgen deprivation therapy and by androgen deprivation type and duration.

3. METHODOLOGY

3.1 Study Design – General Aspects

This was a multicentre, non-interventional, prospective observational cohort study designed to collect real world clinical data related to the management of high and very high risk of recurrence locally advanced prostate cancer patients following surgery or radiation therapy from within the Russian healthcare system.

No additional procedures besides those already used in the routine clinical practice were to be applied to the patients. Treatment assignment was to be done according to the current routine medical practice.

Evidence generation, via collections and interpretation of data on current real world clinical approaches relating to the postoperative and post-radiation management of locally advanced prostate cancer patients with high and very high risk of recurrence in Russia was considered as the primary outcome variable in this study.

Information on the routine diagnosis-specific examinations, including PSA measurements before, after and during one year after prostatectomy/radiotherapy, performed by local laboratories, was to be collected.

Accordingly, two study visits – Baseline Visit and Follow-up Visit (in one year after Baseline Visit) were planned for all patients.

Information regarding patient demographics, the disease characteristics, management approaches, diagnostic tests performed and medications received by patients was to be taken from the medical records. The paper CRF was to be completed at each study visit.

Table 3.1 Study Plan

Study procedures	Baseline visit (Visit 1; Day 1)	Observation visit (Visit 2; 12 months)
Informed consent	X	
Patient demographics	X	
Medical history	X	
Inclusion / Exclusion criteria	X	
ECOG	X	X
PSA measurement results*	X	X
Disease information	X	X
Treatment information	X	X
Clinical outcome / patient response		X

* - available PSA levels before and within 1 year after radical PCa treatment were to be recorded into CRF

3.1.1 Data Source

Patients were to be recruited by the specialists working at oncology institutions/departments in which patients with PCa are being treated. The number of participating investigators was to be approx. 40 – 60, which were needed to ensure enrolment of 200 subjects in up to 30 sites. It was planned that each investigator would include 6-10 patients into the study. There were no restrictions on minimum and maximum number of patients per investigator. Each investigator had to invite all patients with locally advanced PCa with high level of recurrence receiving treatment or coming for medical consultation in his/her department to participate in the study if inclusion/exclusion criteria were met.

The Medical Department of company selected the investigators that were qualified by experience and ability to perform the study. The Medical Director reviewed and approved the list of participating Investigators.

3.2 Study Population

It was planned to enrol 200 subjects in up to 30 sites in Russian Federation. The average number of patients per site was planned as 6 - 10; there were no restrictions on minimum and maximum number of subjects per site in this study.

3.3 Inclusion Criteria

The subject population had to fulfil all of the following criteria:

1. The voluntarily given informed consent, confirmed by the Informed Consent Form, properly signed by both the subject and the investigator.

2. Male 18 years age or older.

3. Histologically confirmed diagnosis of prostate adenocarcinoma

4. Prostatectomy or radiotherapy completed within 3 months prior to the study enrolment

5. Locally advanced stage of PCa (stage T3-T4, Nx-N0, M0: prostate adenocarcinoma with extracapsular invasion (T3a) or invasion to the seminal vesicles (T3b), invasion to adjacent structures (T4) but without lymphatic invasion (N0) nor metastasis (M0))

6. High (T3a or Gleason score = 8-10 or PCA >20 ng/ml) and very high (T3b-T4) risk of recurrence

The prescription of the medicinal product was to be clearly separated from the decision to include the subject in the NIS.

3.4 Exclusion Criteria

In the case of presence of at least one of the following criteria a potential subject could not be enrolled in the NIS:

1. Patients participated in clinical trials
2. Any medical condition which on the opinion of the investigator might interfere with the patient's participation in the study, e.g. severe non-malignant concomitant disease which could affect life expectancy
3. Evidence of metastatic disease on imaging studies

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposure

Not applicable for this study. The assignment of a subject to a particular treatment was not decided in advance by a protocol but fell within current practice.

There was no specific medicinal product to be focused on during the study. All treatments received by the patients according to the routine practice were to be collected and analysed.

4.2 Outcomes

4.2.1 Primary variable

Primary variable includes adjuvant endocrine therapy: drugs used for adjuvant androgen deprivation therapy, regimen, dose, duration.

4.2.2 Secondary variables

The secondary variables for this study were defined as:

Patient characteristics:

- Gender – all patients were to be males
- Age
- Race
- Family history of PCa
- Co-morbidities

Disease information/ treatment and diagnostic procedures:

- Date of diagnosis
- Disease stage, TNM classification
- Gleason score, PSA level.
- Testosterone level
- Diagnostic techniques used
- Performance Status (ECOG)
- Neoadjuvant antiandrogen therapy
- Prior prostate cancer treatment – surgery / radiotherapy (dates, types)
- Adjuvant endocrine treatment (medications by groups, orchidectomy)
- Other therapy received during the study

Clinical outcome/Patient response in one year of follow-up (at Visit 2):

- Proportion of patients with double increase in PSA level during 1 year follow-up
- Proportion of progression-free patients after 1 year follow-up
- Proportion of patients with disease progression after 1 year follow-up
- Proportion of patients having biochemical relapse after 1 year follow-up
- Proportion of patients having clinical relapse (local or metastatic) after 1 year follow-up
- Death: disease-related or for other reasons

4.3 Other Variables and Covariates

The following subgroups were to be reported in the study:

4.3.1 Radical Treatment Regimen

- Patients with radical prostatectomy without any radiotherapy
- Patients with radiotherapy without radical prostatectomy.

4.3.2 Androgen Deprivation Therapy Presence

The following subgroups were to be defined:

- Patients with any ADT (including both neoadjuvant and adjuvant regimens);
- Patients with no ADT recorded.

Data were to be reported for these subgroups and overall.

Also, selected summaries will be also produced for the following subgroups:

- Patients with at least one neoadjuvant ADT;
- Patients with at least one adjuvant ADT.

4.3.3 Androgen Deprivation Therapy Duration

Additional subgroup analysis of clinical and biochemical relapse and disease progression as well as PSA levels was to be performed by categorized duration of the androgen deprivation treatment. The following categories were to be defined:

- ADT duration is 6 months and less
- ADT duration is more than 6 months.

ADT duration was to be defined as the sum of both neoadjuvant ADT duration and adjuvant ADT duration, in months.

4.3.3.1 Neoadjuvant ADT Duration

Due to the fact that neoadjuvant ADT duration was collected in weeks the following rules were to be applied to estimate the summary neoadjuvant ADT duration:

- If a patient had an orchidectomy before radical treatment then time since orchidectomy to the date of radical treatment was to be counted as an exposure to the castration neoadjuvant therapy.
- If a patient received only castration therapy (orchidectomy, LHRH analogs and/or hexestrol) then the total duration was the sum of all the separate castration therapy durations because these treatment were not usually administered concurrently.
- If a patient received only antiandrogen treatments (flutamide, bicalutamide, cyproterone acetate) then also the total duration was the sum of all the separate antiandrogen therapy durations.
- In case a patient received both antiandrogen and castration treatments then the total duration was the maximum duration of one of the separate treatment durations.

4.3.3.2 Adjuvant ADT Duration

Adjuvant ADT duration was to be estimated in months as follows:

Duration = (Date of adjuvant ADT stop – Date of adjuvant ADT start + 1)/30.44.

Date of adjuvant ADT start was the earliest date of start of any adjuvant ADT regimen. Date of adjuvant ADT stop was the latest date of stop of any adjuvant ADT regimen. If date of stop was absent then date of Visit 2 was to be used to estimate the adjuvant ADT duration. In case if any date was partial the imputation rule was to be applied as described in section 5.1 General Aspects.

The total ADT duration was to be estimated as follows:

ADT duration = neoadjuvant ADT duration *7/30.44 + adjuvant ADT duration.

If a patient had orchidectomy then the post-orchidectomy period was to be counted as a continuous castration ADT regimen and was to be included into adjuvant ADT duration calculatuion.

Classification between castration and antiandrogen treatments was to be defined manually at the time of data review. Selected analyses were to be repeated for patients who have received any ADT (neoadjuvant and adjuvant regimens combined) for six and less months period and for patients who have received any ADT (neoadjuvant and adjuvant regimens combined) during more than six months. A number and percentage of patients in each duration category were to be tabulated.

Orchidectomy was to be considered as both adjuvant and neoadjuvant treatment in case if it was performed before the radical treatment.

4.3.4 Androgen Deprivation Therapy Type

The following ADT classes were to be defined manually at the time of data review for both neoadjuvant and adjuvant regimens:

- Castration and antiandrogens (received at least one castration treatment and at least one antiandrogen treatment during all observational period, in any neoadjuvant and adjuvant regimen)
- Castration only, without antiandrogens
- Antiandrogens only, without castration

Analysis of PSA levels, change in ECOG status and disease outcome data were to be provided for these three subgroups.

4.4 Safety assessment

The active collection of any safety data was not performed due to the non-interventional type of the study. Spontaneous reports of events related to safety were to be reported in accordance with the pharmacovigilance regulatory requirements in the post-marketing period. It was imperative that all investigators participated in the study had to be familiarized with this section of the Protocol. Primary investigator was responsible for training of co-investigators

involved in the study upon the procedures of processing of spontaneously reported safety events, as well as with national pharmacovigilance regulatory requirements in Russia.

4.4.1 Definitions

Adverse Event (AE)

"Adverse Event" or "AE" mined a development of any untoward medical occurrence, or the deterioration of a pre-existing medical condition in a patient or clinical trial subject administered a medicinal product or product with the same MNN and which did not necessarily had a causal relationship with this treatment.

Adverse Event might be an unfavourable symptom (e.g. nausea, chest pain), factor (e.g. tachycardia, enlarged liver) or abnormal research result (e.g. deviation of laboratory rates, alteration of electrocardiogram) temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following information had to be collected and reported to the Patient Safety department of the company: the use of company products during pregnancy (irrespectively of whether the pregnancy termination is known), and/or lactation, lack of efficacy, overdose, abuse, off label use and misuse, medication errors, suicide and attempted suicide, suspected drug interactions.

Serious Adverse Event (SAE)

A SAE was to be an AE, occurred at any dose or study phase that fulfilled one or more of the following:

- Resulted in death.
- Was life-threatening.
- Required in-patient hospitalization or prolongation of existing hospitalization.
- Resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Was a congenital abnormality/birth defect.
- Was an important medical event that might jeopardize the subject or might require medical intervention to prevent one of the outcomes listed above.

- The Term "threat to life" with respect to SAEs mined that there was an immediate risk of lethal outcome in the patient at the time of this event. This definition did not refer to event, which hypothetically could result in lethal outcome, in that case, that if it had occurred at more severe form.

- Medical events that were important, but did not result in lethal outcome, or events that were directly life-threatening or required hospitalization, could also be considered as serious adverse events in those cases when, in accordance with sound clinical or scientific opinions, it was hazardous for the patient (or patient) and when in order to prevent one of the outcomes mentioned above medical or surgical intervention might be required. In this case, the event was considered as serious. Examples of such events were common or malignant tumor, allergic bronchospasm required intensive therapy in the emergency care department or at home, haematological disorders or convulsions that did not result in hospitalization or the development of drug dependency or drug abuse.

Adverse Drug Reactions (ADR)

An ADR was to be the development of an undesirable medical condition or the deterioration of a preexisting medical condition following or during exposure to a medicinal product, suspected to be causally related to the product

4.4.2 Reporting

Reporting of adverse events

The company didn't supply any investigational product (either therapeutic or diagnostic) for this survey. All treatment-associated adverse events were to be reported according to the procedures established by the manufacturers of the prescribed therapies.

Reporting of serious adverse events

From the day the informed consent had been signed until the time the blood sample had been taken, all SAEs had to be reported. All SAEs were to be recorded on a SAE reporting form in accordance with local requirements and company procedures for global pharmacovigilance purposes.

Investigators and other site personnel had to inform appropriate company representatives of any SAE that occurred in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she became aware of it.

The company representative was to work with the investigator to compile all the necessary information and ensure that the appropriate Company Drug Safety Department received a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

The investigator was responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Reporting of spontaneously mentioned adverse drug reactions

With regard to the reporting of Adverse Drug Reactions (ADRs) observed in patients participated in this study, the following guideline applied: ADRs had to be reported by the

investigator for purposes of pharmacovigilance in accordance with applicable local regulations to:

1. Federal Service on Surveillance in Healthcare (Roszdravnadzor) in writing to: 4 Slavyanskaya sq., bld. 1, Moscow, 109074, Russian Federation, using the special form available via the link: www.roszdravnadzor.ru/i/upload/images/2017/4/14/1492156795.32143-1-12824.doc

2. The appropriate pharmaceutical company, i.e., the marketing authorization holder for the product as per local regulatory requirements.

If the subject spontaneously mentioned adverse drug reaction to the product the company, the investigator was to complete the Adverse Event Report Form (in attachment to the protocol) and send it at company adress.

5. STATISTICAL ANALYSIS

5.1 Statistical Methods – General Aspects

Continuous data were to be summarized in terms of the mean, standard deviation (SD), upper quartile, median with 95% confidence interval, if applicable, lower quartile, minimum, maximum and number of observations. The minimum and maximum were to be reported to the same number of decimal places as the raw data recorded in the database. The mean, SD, median, confidence interval, lower quartile and upper quartile were to be reported to one more decimal place than the raw data recorded in the database. In general, the maximum number of decimal places reported were to be four for any summary statistic.

Categorical data were to be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Proportion was to be assessed together with 95% confidence interval, if applicable. Percentages were to be presented to one decimal place. Percentages were not to be presented for zero counts. Percentages were to be calculated using n as the denominator.

95% exact Clopper-Pearson confidence intervals were to be presented to estimate the proportions.

Baseline was to be defined as Visit 1 data, if applicable.

Missing data category were to be reported where applicable.

In case if there is a partial date the following rule was to be applied to impute the data value:

- If year is unknown the date will be set to missing;
- If year is known but no month available the data will be set to missing

- If both month and year are known and the day is unknown then the date will be imputed with 15.

5.2 Study Patients

5.2.1 Analysis Populations

5.2.1.1 All Enrolled Set

All Enrolled Set was to consist of all the subjects who signed informed consent to enter the study. Patient disposition and baseline characteristics and demographic characteristics were to be based on this set.

5.2.1.2 Full Analysis Set

Full Analysis Set was to consist of all patients who had been identified as locally advanced PCa patients with high and very high risk of recurrence. Patients included into FAS had to satisfy all inclusion and exclusion criteria. The population was to be used for the primary and secondary objective reporting.

The number and percentage of patients in each analysis population were to be reported.

5.2.2 Disposition of Patients

The following summaries were to be provided:

- A summary of the number of patients enrolled into the study
- A summary of the patients violated any inclusion/exclusion criterion
- A summary of the number of patients in each analysis set
- A summary of the number of patients attended each visit. Patient was to be considered as attended the visit if the date of visit was available.
- A summary of the number and percentage of patients completed the study and prematurely discontinued from the study, by reason of discontinuation and overall.

By-patient listings of enrolment details, visit dates and withdrawal/study completion details were to be provided.

5.3 Subgroup Analysis

The following subgroups were to be reported in the study:

5.3.1 Radical Treatment Regimen

The following subgroups were to be defined:

- Patients with radical prostatectomy without any radiotherapy
- Patients with radiotherapy without radical prostatectomy.

5.3.2 Androgen Deprivation Therapy Presence

The following subgroups were to be defined:

- Patients with any ADT (including both neoadjuvant and adjuvant regimens);
- Patients with no ADT recorded.

Data were to be reported for these subgroups and overall.

Also, selected summaries were also to be produced for the following subgroups:

- Patients with at least one neoadjuvant ADT;
- Patients with at least one adjuvant ADT.

5.3.3 Androgen Deprivation Therapy Duration

Additional subgroup analysis of clinical and biochemical relapse and disease progression as well as PSA levels were to be performed by categorized duration of the androgen deprivation treatment. The following categories were to be defined:

- ADT duration was 6 months and less
- ADT duration was more than 6 months.

ADT duration was to be defined as the sum of both neoadjuvant ADT duration and adjuvant ADT duration, in months.

5.3.3.1 Neoadjuvant ADT Duration

Due to the fact that neoadjuvant ADT duration was collected in weeks the following rules were to be applied to estimate the summary neoadjuvant ADT duration:

- If a patient had an orchidectomy before radical treatment then time since orchidectomy to the date of radical treatment was to be counted as an exposure to the castration neoadjuvant therapy.

- If a patient received only castration therapy (orchidectomy, LHRH analogs and/or hexestrol) then the total duration was to be the sum of all the separate castration therapy durations because these treatment are not usually administered concurrently.

- If a patient received only antiandrogen treatments (flutamide, bicalutamide, cyproterone acetate) then also the total duration was to be the sum of all the separate antiandrogen therapy durations.

- In case a patient received both antiandrogen and castration treatments then the total duration was to be the maximum duration of one of the separate treatment durations.

5.3.3.2 Adjuvant ADT Duration

Adjuvant ADT duration was to be estimated in months as follows:

Duration = (Date of adjuvant ADT stop – Date of adjuvant ADT start + 1)/30.44.

Date of adjuvant ADT start was the earliest date of start of any adjuvant ADT regimen. Date of adjuvant ADT stop was the latest date of stop of any adjuvant ADT regimen. If date of stop was absent then date of Visit 2 was to be used to estimate the adjuvant ADT duration. In case if any date was partial the imputation rule was to be applied as described in section 5.1 General Aspects.

The total ADT duration was to be estimated as follows:

ADT duration = neoadjuvant ADT duration *7/30.44 + adjuvant ADT duration.

If a patient had orchidectomy then the post-orchidectomy period was to be counted as a continuous castration ADT regimen and was to be included into adjuvant ADT duration calculatuion.

Classification between castration and antiandrogen treatments was to be defined manually at the time of data review. Selected analyses were to be repeated for patients who had received any ADT (neoadjuvant and adjuvant regimens combined) for six and less months period and for patients who had received any ADT (neoadjuvant and adjuvant regimens combined) during more than six months. A number and percentage of patients in each duration category were to be tabulated.

Orchidectomy was to be considered as both adjuvant and neoadjuvant treatment in case if it was performed before the radical treatment.

5.3.4 Androgen Deprivation Therapy Type

The following ADT classes were to be defined manually at the time of data review for both neoadjuvant and adjuvant regimens:

- Castration and antiandrogens (received at least one castration treatment and at least one antiandrogen treatment during all observational period, in any neoadjuvant and adjuvant regimen)
- Castration only, without antiandrogens
- Antiandrogens only, without castration

Analysis of PSA levels, change in ECOG status and disease outcome data were to be provided for these three subgroups.

5.4 Demographic and Other Baseline Characteristics

The following baseline summaries were to be provided:

- A summary of demographic variables (age, race)
- A summary of medical history data, by system organ class and preferred term
- A summary of family PCa history data (presence of any PCa in family history, relation degree and age of a relative when PCa diagnosed, number of relatives diagnosed with PCa, number of relatives diagnosed with PCa before age 55 years)
- A summary of disease history:
    - Time in days from diagnosis till radical treatment;
    - TMN classification (proportions of different T, N and M categories)
    - Diagnostic method
    - Diagnosis confirmation method
    - Number of biopsy cores
    - Proportion of positive biopsy cores
    - Gleason score
- A summary of radical treatment data:
    - Time in days since radical treatment till inclusion
    - Surgery type
    - Any radiation therapy and its type
    - Any adjuvant radiation therapy
- A summary of concomitant therapy by anatomical therapeutic chemical class and preferred term.
- A listing of testosterone level

Age was to be calculated as the number of complete years between a patient's birth date and the date of their screening visit.

Time from diagnosis was to be calculated as follows:

Time (days) = date of radical treatment - date of diagnosis. In case if either the date of diagnosis or the date of radical treatment was partial imputation rule was to be applied as described in section 5.1 General Aspects. In case if date of diagnosis was later than the date of radical treatment the time from diagnosis was to be considered as missing.

Date of radical treatment was to be defined as the date of surgery or the date of the start of radiotherapy whichever comes first.

Medical history data were to be coded using MedDRA dictionary version 19.0. Concomitant and androgen deprivation medications were to be coded using WHO Drug dictionary version as of 1st of December, 2016.

A by-patient listing of demographic data was to be provided.

5.5 Androgen Deprivation Therapy

Androgen deprivation therapy was to be reported by specified subgroups, as discussed at the stage of statistical analysis plan preparation. The following ADT subgroups were to be defined to report adjuvant and neoadjuvant ADT regimen, separately and combined:

- Cyproterone acetate
- Flutamide
- Bicalutamide
- Hexestrol
- Buserelin
- Goserelin
- Leuprorelin
- Triptorelin
- Degarelix
- Orchidectomy
- One or several nonsteroidal antiandrogens (flutamide, bicalutamide)
- One or several antiandrogens (cyproterone acetate, flutamide, bicalutamide)
- One or several LHRH analogs (buserelin, goserelin, leuprorelin, triptorelin, degarelix)
- Castration (orchidectomy, LHRH analogs, hexestrol)

Each subgroup could include both monotherapy and combination regimen, if applicable.

Also, the number and percentage of patients with no ADT, with any neoadjuvant ADT, with any adjuvant ADT, and with any ADT were to be reported.

ADT therapy was to be tabulated by radical treatment subgroup and by patient having neoadjuvant and adjuvant ADT.

5.6 Endpoints Evaluation

5.6.1 ECOG Status

ECOG status was to be tabulated by visit for Full Analysis set population, for patients receiving any ADT, not receiving any ADT and overall.

Also, change in ECOG status from Visit 1 to Visit 2 (during one year of observation) was to be reported as decrease, no change and increase categories together with 95% confidence interval for the percentage by the following subgroups:

- Androgen deprivation therapy (performed / not performed)
- Radical treatment (radical prostatectomy / radiotherapy)
- Androgen deprivation therapy duration (6 months and less/ more than 6 months)
- Treatment combination (castration and antiandrogens / castration only, without antiandrogens)

P-value for Mantel-Haenzel chi-square test was to be reported for the difference between each subgroup.

All ECOG data were to be listed.

5.6.2 PSA Level Summary

A summary of PSA level was to be provided for two time periods:

1. After radical treatment: this time period started at the date of radical treatment+21 day and ended at the date of radical treatment + 60 days. The PSA assessment which was closest to the middle of the period was to be used in the summary.
2. After one year of observation: the time period started at date of Visit 2 minus 60 days and ended at the date of Visit 2 + 60 days. The PSA assessment which was closest to the middle of the period was to be used in the summary.

If there were two closest assessments the latest was to be used for summary. In case if the date of PSA level assessment was partial or missing the date will be imputed using imputation rules as described in section 5.1 General Aspects. Median value of PSA level and 95% confidence intervals were to be tabulated.

The summary was to be provided for FAS population. It was to be repeated for ADT presence, type and duration subgroups.

All PSA data were to be listed.

5.6.3 Double Increase of PSA

Proportion of patients, who had double increase in PSA level during the observational period was to be reported together with 95% confidence interval. Only patients, who had two and

more PSA level assessments recorded in CRF during the observational period were to be included into this summary.

A patient was to be considered as having a double PSA increase if there was at least one PSA level measurement two times or more greater than any previous PSA level measurement during the observational period. Only PSA levels assessed after radical treatment date were to be considered to estimate the proportion.

The summary was to be provided for FAS population. It was to be repeated for ADT presence, type and duration subgroups.

5.6.4 Disease Outcome

Disease outcome was to be assessed at Visit 2.

Disease outcome was to be classified as either progression or absence of progression. Progression was to be classified as either clinical or biochemical. Clinical progression was to be classified as local recurrence, presence of metastasis to regional lymph nodes, or distant metastasis. Metastasis localization was to be collected.

All the disease outcome data were to be tabulated.

The summary was to be provided for FAS population. It was to be repeated for ADT presence, type and duration subgroups.

5.6.5 Time to Progression Analysis

The analysis was to be performed for the FAS population.

Time to disease outcome assessment was to be calculated in months as follows:

Time to disease outcome (months) = (date of disease outcome – date of radical treatment) / 30,44

In case if either the date of disease outcome or the date of radical treatment was partial the imputation rule was to be applied as shown in section 5.1 General Aspects. Disease progression or death was to be regarded as event; absence of progression was to be regarded as censored observation.

A regression analysis of survival data based on the Cox proportional hazards model was to be implemented. The model was to be repeated with the following factors:

- Radical treatment regimen (see section Radical Treatment Regimen: radical prostatectomy without any radiotherapy, radiotherapy without radical prostatectomy - dichotomous variable)
- ADT presence (see section Androgen Deprivation Therapy Presence: any ADT performed, no ADT - dichotomous variable)

- ADT duration (see section Androgen Deprivation Therapy Duration: 6 months and less, more than 6 months - dichotomous variable)
- ADT type (see section Androgen Deprivation Therapy Type: castration and antiandrogens, castration only, without antiandrogens - dichotomous variable)

Hazard ratio was to be tabulated for explanatory variables together with 95% confidence interval and the corresponding level of significance. Survival curves might be produced for selected set(s) of explanatory variables, if applicable.

Likelihood ratio p-value for the difference between each subgroup was to be reported.

Also, survival curves were to be graphically presented for each model.

5.7 Bias

Not applicable for the study.

5.8 Sample Size and Power Calculations

The primary objective was to obtain accurate and reliable information regarding the adjuvant endocrine treatment habits in Russian patients with locally advanced prostate cancer with high and very high risk of recurrence after surgery or radiotherapy during one year after surgery or radiotherapy. For this purpose sample size had to be large enough to contain essential number of patients with different therapy options.

One of the secondary objectives was to assess the proportion of Prostate-specific antigen doubling time (PSADT) patients of 1 year in the study. Sample size determination was based on the confidence limit approach to ensure adequate estimation precision of the proportion of PSADT patients of 1 year with locally advanced prostate cancer with high and very high risk of recurrence after surgery or radiotherapy. With the assumption that the true proportion of PSADT patients of 1 year is 65% and precision value needed is 7.5%, the sample size of 156 patients was sufficient to receive the estimated proportion in the 95% confidence interval.

It was assumed that there will be around 22% of patients with incomplete PSA data. Therefore we needed to enroll 200 patients with locally advanced PCa with high and very high risk of recurrence to account for incomplete data.

5.9 Data Quality

Before the first subject is recruited into the study, the local Marketing Company (MC) representative or delegate was to:

- Establish the adequacy of the facilities and the investigator’s capability to appropriately select the sample

- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of

Company or its representatives. This was to be documented in a NIS Agreement between company/delegate and the investigator.

During the study the local MC representative or delegate could implement different activities to assure compliance with company standards of quality. These activities could include but were not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s)
- Confirm that the research team was complying with the protocol and that data were being accurately recorded in the case report forms (CRFs)
- Ensure that the subject informed consent forms were signed and stored at the investigator's site
- Ensure that the CRFs were completed properly and with adequate quality.

Monitoring activities for:

- Checking a sample of ICFs
- Checking that subjects exist in medical records (a sample)

The extent and nature of monitoring was to be decided during the study planning based on design, complexity, number of subjects, number of sites, etc. Different signals (e.g., high rejection rate in a site) had to be used as potential identification of low protocol compliance by investigators.

If these, or any other signal would occur or if the local coordinator would suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures had to be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

The originals of completed CRFs were to be sent on a regular basis by the participating physicians to the Contract Research Organization (CRO) authorized by the company. Copies of CRFs, as well as the original signed Informed Consents were to be kept by the physician during the study and after the study completion.

Collected data from the CRFs were to be entered into specially designed study database using double data entry method and undergo electronic verification. The Data Management staff was to check entered data for completeness and accuracy. Obvious errors were to be corrected by the authorized Data Management personnel. Other errors or omissions were to be entered on Data Query Forms, which were to be returned to the participating physician for resolution. The signed and dated resolved Data Query Forms were to be sent to the CRO

authorized by Company for data correction and the copies were to be kept by the participating physician.

Relevant drug therapy and non-pharmacological therapy entered into the database were to be coded based on WhoDDE current version. Medical history/current medical conditions were to be coded using current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Database had to be completed, and then passed appropriate quality check, considered to be full and accurate, and then was to be locked. Any changes after the database lock were to be possible only with written permission of project manager, statistician and data manager. Collected data were to be analyzed.

6. RESULTS

6.1 Study Participation

6.1.1 Patients disposition

Disposition of patients for Full Analysis Set is represented in the Table 1. A total of 204 males were enrolled in the study, 202 were included in the Full Analysis Set (FAS). 2 patients had inclusion/exclusion criteria violation, both of them didn't met inclusion criterion #4 (Prostatectomy or radiotherapy completed within 3 months prior to the study enrolment) (Statistical Table 1.2 in Appendix 7). Among all enrolled patients, 191 (93.6%) patients attended the Visit 2 after 1 year, 12 (5.9%) patients prematurely discontinued from the study and for 1 (0.5%) male data were missed (Statistical Table 1.1 in Appendix 7). Of 12 males with early discontinuation 8 were lost to follow-up, 4 dead and 1 of dead patients had entry criteria violation as well. One patient of 12 had two reasons of discontinuation (entry criteria violation and death)..

Among patients included in FAS, 191 (94.6%) patients attended the Visit 2 after 1 year, 11 (5.4%) patients prematurely discontinued from the study. Of 11 males with early discontinuation, 8 were lost to follow-up and 3 dead. Distribution of patients in subgroups by ADT presence is shown in the Table 1.

Table 1 Patient Disposition (Full Analysis Set)

	Overall	Any androgen deprivation therapy	
	(N=202)	Performed (N=132)	Not performed (N=70)
Full Analysis set	202 (100.0%)	132 (100.0%)	70 (100.0%)
Attended visit 1	202 (100.0%)	132 (100.0%)	70 (100.0%)
Attended visit 2	191 (94.6%)	126 (95.5%)	65 (92.9%)
Completed the study	191 (94.6%)	126 (95.5%)	65 (92.9%)

Prematurely discontinued	11 (5.4%)	6 (4.5%)	5 (7.1%)
Reason for discontinuation (1)			
Lost to follow up	8 (72.7%)	4 (66.7%)	4 (80.0%)
Death	3 (27.3%)	2 (33.3%)	1 (20.0%)

Patient is considered as attended the visit if his date of visit is available.
(1) Percentage is based on the number of patients prematurely discontinued from the study.
Source: Statistical Table 1.1.1 in Appendix 7.

6.2 Main Results

6.2.1 Demography and baseline characteristics

Demographic characteristics of the population are shown in the Table 2. Mean age of males was 64.9 ± 6.2 years with range from 49 to 80. Half of patients were in the range of 61.0-68.0 years. Almost all patients in the study were White, and 3 males were Asian. Distribution of patients in subgroups by ADT presence is shown in the Table 2.

Table 2 Baseline Demographics (Full Analysis Set)

Demographic variable	Overall (N=202)	Any androgen deprivation therapy	
		Performed (N=132)	Not performed (N=70)
Age (years)			
n	202	132	70
Mean (SD)	64.9 (6.2)	65.2 (6.6)	64.4 (5.3)
Min - Max	49 - 80	49 - 80	53 - 75
Median	65	66	65
Q1 - Q3	61.0 - 68.0	61.0 - 69.0	61.0 - 68.0
Race			
White	199 (98.5%)	131 (99.2%)	68 (97.1%)
Black	0	0	0
Asian	3 (1.5%)	1 (0.8%)	2 (2.9%)

Source: Statistical Table 2.1 in Appendix 7.

Family history of prostate cancer was noted only for 3.0% of patients (6 males), 80.7% of patients (163 males) did not have relatives with prostate cancer and for 16.3% (33 males) hereditary status was unknown (Table 3). For all 6 patients with family history of cancer, their father had diagnosis of prostate cancer. Details on family history of cancer are presented in Statistical Table 2.2, in Appendix 7.

Table 3 Family History of Prostate Cancer (Full Analysis Set)

	Overall	Any androgen deprivation therapy	
	(N=202)	Performed (N=132)	Not performed (N=70)
Any family history of PCa			
Yes	6 (3.0%)	5 (3.8%)	1 (1.4%)
No	163 (80.7%)	102 (77.3%)	61 (87.1%)
Unknown	33 (16.3%)	25 (18.9%)	8 (11.4%)
Father (1)	6 (100.0%)	5 (100.0%)	1 (100.0%)
Age of diagnosis < 55 years	0	0	0.00%
Age of diagnosis >= 55 years	5 (83.3%)	4 (80.0%)	1 (100.0%)
Unknown	1 (16.7%)	1 (20.0%)	0.00%

(1) Percentage is based on the number of patients having family history of PCa.
Source: Statistical Table 2.2 in Appendix 7.

6.2.2 Prostate cancer diagnosis

Median duration of prostate cancer at the time of enrolment was 2.7 months or 82 days (Table 4). Maximum duration of the disease was about 7.5 years (2724 days). In 75% of patients, the duration of the disease did not exceed 7 months (214 days). Time from diagnosis to the date of radical treatment was estimated for 198 patients, for approx. 2/3 of them any androgen deprivation therapy was performed, for 1/3 – not performed. Since the number of patients who underwent ADT therapy significantly exceeds the number of patients who did not receive this kind of therapy, it is foreseeable, that median duration of prostate cancer was longer in patients, for whom ADT was performed, than for those, who did not undergo ADT: about 5 months (165 days) vs. 1 month (34 days).

About 60% of patients (59.9%, 121 males) had disease stage T3a in accordance with TNM classification, 37.6% (76 males) had T3b and 2.5% (5 males) had T4 stage. In 86.1% of patients (174 males) lymph node metastases were absent and for 13.9% (28 males) lymph nodes could not be assessed (stage Nx). No patients had distant metastases.

Table 4 Disease Anamnesis (Full Analysis Set)

	Overall	Any androgen deprivation therapy	
	(N=202)	Performed (N=132)	Not performed (N=70)
Time from diagnosis (days) (1)			
n	198	131	67
Mean (SD)	170.0 (SD 283.0)	232.3 (SD 329.2)	48.2 (SD 54.2)
Min - Max	0 - 2724	0 - 2724	0 - 359
Median	82	165	34
Q1 - Q3	32.0 - 214.0	65.0 - 290.0	18.0 - 59.0

Tumour category			
T3a	121 (59.9%)	73 (55.3%)	48 (68.6%)
T3b	76 (37.6%)	55 (41.7%)	21 (30.0%)
T4	5 (2.5%)	4 (3.0%)	1 (1.4%)
Node category			
N0	174 (86.1%)	106 (80.3%)	68 (97.1%)
NX	28 (13.9%)	26 (19.7%)	2 (2.9%)

(1) Time from diagnosis to the date of radical treatment. If the date of radical treatment is later than the date of diagnosis then time from diagnosis is considered to be missing.
Source: Statistical Table 2.4 in Appendix 7.

Table 5 shows data on diagnostic techniques used for primary diagnosis of prostate cancer and for its confirmation. PSA analysis was used for primary diagnosis in vast majority of patients (98.5%, 199 males). 80.2% (162 males) of patients underwent finger rectal examination of prostate. Transrectal ultrasonography was used for primary diagnosis in a half of patients (50.5%, 102 males). In one third of patients (30.2%, 61 males) prostate cancer was diagnosed using magnetic resonance imaging (MRI). Radioisotope examination was used for primary diagnosis in 11.9% (24 males) of patients. Other methods (including X-ray computed tomography, uroflowmetry) were used in less than 10% of cases.

Transrectal ultrasound-guided prostate thick needle biopsy (TRUS) and histological examination were used for diagnosis confirmation in 96.0% (194 males) and 92.6% (187 males), respectively. MRI, radioisotope examination and PSA blood test were used for diagnosis confirmation in 62.4% (126 males), 47.5% (96 males) and 43.6% (88 males), correspondingly. Details are presented in the Table 5.

Table 5 Prostate Cancer Diagnostics (Full Analysis Set)

		Any androgen deprivation therapy	
	Overall (N=202)	Performed (N=132)	Not performed (N=70)
Primary diagnostics			
Prostate-specific antigen blood test	199 (98.5%)	130 (98.5%)	69 (98.6%)
Digital (finger) rectal examination	162 (80.2%)	116 (87.9%)	46 (65.7%)
Transrectal ultrasonography	102 (50.5%)	76 (57.6%)	26 (37.1%)
Magnetic resonance imaging (MRI)	61 (30.2%)	44 (33.3%)	17 (24.3%)
X-ray computed tomography	12 (5.9%)	4 (3.0%)	8 (11.4%)
Uroflowmetry	2 (1.0%)	2 (1.5%)	0
Radioisotope examination	24 (11.9%)	22 (16.7%)	2 (2.9%)
Other	2 (1.0%)	1 (0.8%)	1 (1.4%)

Diagnosis confirmation			
Fine needle aspiration biopsy of the prostate gland	2 (1.0%)	2 (1.5%)	0
Cytological examination	4 (2.0%)	3 (2.3%)	1 (1.4%)
Transrectal ultrasound-guided prostate thick needle biopsy (TRUS)	194 (96.0%)	126 (95.5%)	68 (97.1%)
Histological examination	187 (92.6%)	118 (89.4%)	69 (98.6%)
MRI	126 (62.4%)	88 (66.7%)	38 (54.3%)
Radioisotope examination	96 (47.5%)	72 (54.5%)	24 (34.3%)
PCa blood test	88 (43.6%)	59 (44.7%)	29 (41.4%)
Other	2 (1.0%)	1 (0.8%)	1 (1.4%)

Source: Statistical Table 2.5 in Appendix 7.

Results of biopsy are provided in the Table 6. Mean number of cores taken during biopsy procedure was 9.6 (±4.9) with range from 1 to 60. Mean percentage of cancer positive cores was 60.87% (±25.30%), minimal and maximal values varied from 8.3% to 100.0%.

The biopsy was done for 195 patients overall (128 patients with and 67 patients without any androgen deprivation therapy). Histological examination with Gleason score assessment revealed that 39.6% (80 males) of patients had moderately differentiated adenocarcinoma (Gleason score 7), about one third (29.7%, 60 males) had poorly differentiated or anaplastic adenocarcinoma (score 8 or more) and approximately the same number (29.2%, 59 males) of patients had well differentiated adenocarcinoma (score 6 and less). Among patients who received androgen deprivation therapy (ADT) the percentage of patients with poorly differentiated tumours was higher than in patients who didn't receive ADT (35.6% and 18.6% respectively). Details are presented in the Table 6.

Table 6 Prostate Cancer Diagnostics (Full Analysis Set)

		Any androgen deprivation therapy	
	Overall (N=202)	Performed (N=132)	Not performed (N=70)
Gleason score			
6 and less	59 (29.2%)	34 (25.8%)	25 (35.7%)
7	80 (39.6%)	48 (36.4%)	32 (45.7%)
8 and more	60 (29.7%)	47 (35.6%)	13 (18.6%)
Missing	3 (1.5%)	3 (2.3%)	0
If biopsy was done			
Number of biopsy cores taken			
n	195	128	67
Mean (SD)	9.6 (4.9)	9.2 (3.4)	10.4 (6.9)
Min - Max	1 - 60	1 - 16	3 - 60
Median	10	10	10
Q1 - Q3	6.0 - 12.0	6.0 - 12.0	6.0 - 12.0

Percentage of cancer-positive cores			
n	166	108	58
Mean (SD)	60.87 (25.30)	65.38 (24.01)	52.48 (25.69)
Min - Max	8.3 - 100.0	10.0 - 100.0	8.3 - 100.0
Median	60	63.75	50
Q1 - Q3	41.70 - 80.00	50.00 - 83.00	30.00 - 70.00

Source: Statistical Table 2.5 in Appendix 7.

6.2.3 Prostate cancer therapy

64.4% (130 males) of patients were treated surgically, and 38.6% (78 males) underwent radiotherapy. Almost all males who did not receive ADT (95.7%) were treated surgically and only 5.7% received radiotherapy, while in the group of patients treated with ADT only 47.7% of patients underwent surgery and 56.1% of patients received radiotherapy. Orchidectomy was conducted only in 2 patients. Details on cancer therapy are represented in the Table 7.

Table 7 Previous Prostate Cancer Therapy (Full Analysis Set)

	Overall	Any androgen deprivation therapy	
		Performed	Not performed
	(N=202)	(N=132)	(N=70)
Surgery performed	130 (64.4%)	63 (47.7%)	67 (95.7%)
Radical prostatectomy (open access surgery)	108 (83.1%)	53 (84.1%)	55 (82.1%)
Robotic radical prostatectomy	5 (3.8%)	3 (4.8%)	2 (3.0%)
Nerve-sparing radical prostatectomy	5 (3.8%)	5 (7.9%)	0
Laparoscopic radical prostatectomy	12 (9.2%)	2 (3.2%)	10 (14.9%)
Extended pelvic lymph nodes dissection	28 (21.5%)	19 (30.2%)	9 (13.4%)
Other	2 (1.5%)	2 (3.2%)	0
Radiotherapy performed	78 (38.6%)	74 (56.1%)	4 (5.7%)
Three-dimensional (3D) conformal radiation therapy	53 (67.9%)	49 (66.2%)	4 (100.0%)
Intensity-modulated radiation therapy	12 (15.4%)	12 (16.2%)	0
Low-dose-rate brachytherapy	0	0	0
High-dose-rate brachytherapy	2 (2.6%)	2 (2.7%)	0
Other	14 (17.9%)	14 (18.9%)	0
Adjuvant radiotherapy (after prostatectomy)	13 (6.4%)	11 (8.3%)	2 (2.9%)
Orchidectomy	2 (1.0%)	2 (1.5%)	0

Source: Statistical Table 3.1 in Appendix 7.

Details on androgen deprivation therapy are presented in the Table 8. Androgen deprivation therapy was prescribed to 65.3% (132 males of 202) of patients. 31.2% (63 males) of patients received both neoadjuvant and adjuvant therapy, 19.8% (40 males) underwent only neoadjuvant therapy and 14.4% (29 males) underwent only adjuvant therapy. 34.7% of patients (70 males) did not receive any ADT, vast majority of them underwent radical

prostatectomy without radiotherapy. Androgen deprivation therapy was used in majority of patients treated with radiotherapy without radical prostatectomy (95.8%, 69 males of 72), almost all of them received either neoadjuvant or both neoadjuvant and adjuvant therapy (64 males of 72). Androgen deprivation therapy was used in less than half of patients treated with radical prostatectomy without radiotherapy (46.8%, 58 males of 124).

For two thirds of patients received any ADT (70.5%, 93 males of 132), duration of treatment was more than 6 months. 28.8% of patients (38 males of 132) received ADT 6 months or less.

Table 8 Neoadjuvant and Adjuvant Androgen Deprivation Therapy Presence, by Radical Treatment Regimen (Full Analysis Set)

Androgen deprivation therapy	Total (N=202)	RP without RT (N=124)	RT without RP (N=72)
Any androgen deprivation therapy	132 (65.3%)	58 (46.8%)	69 (95.8%)
Only neoadjuvant	40 (19.8%)	16 (12.9%)	24 (33.3%)
Only adjuvant	29 (14.4%)	22 (17.7%)	5 (6.9%)
Both neoadjuvant and adjuvant	63 (31.2%)	20 (16.1%)	40 (55.6%)
No androgen deprivation therapy	70 (34.7%)	66 (53.2%)	3 (4.2%)
Duration of ADT (1, 2)			
6 months and less	38 (28.8%)	25 (43.1%)	13 (18.8%)
More than 6 months	93 (70.5%)	33 (56.9%)	56 (81.2%)
Missing	1 (0.8%)	0	0

RT = radiotherapy; RP = radical prostatectomy; ADT = androgen deprivation therapy.
Each medication subgroup can include both monotherapy and combination therapy. Patients with neoadjuvant orchidectomy are also counted as having an adjuvant orchidectomy.
(1) Duration of both neoadjuvant and adjuvant regimen is counted.
(2) Percentage is based on is the number of patients having any ADT.
Source: Statistical Table 3.3.1 in Appendix 7.

Therapy of prostate cancer described by radical treatment regimen and by ADT type is presented in the Table 9. Only 6 males (3.0% of 202 subjects) were treated with radiotherapy followed the surgery, and majority (124 males, 61.4% of 202 subjects) underwent prostatectomy without radiotherapy. Radiotherapy was conducted in 38.6% of patients (78 males), for 35.6% (72 males) it was the only radical treatment.

Among 132 patients underwent any ADT, number of males received surgical treatment with radical prostatectomy was a little less than those treated with radiotherapy (63 patients, 47.7%, vs. 74 patients, 56.1%, correspondingly). Among 70 patients did not received any ADT, majority of males underwent radical prostatectomy (67 patients, 95.7%) and only 4 patients (5.7%) received radiotherapy. Approximately equal number of patients underwent radical prostatectomy and radiotherapy among 92 patients received adjuvant therapy (47 males, 51.1% and 50 males, 54.3%, correspondingly). Among 103 patients received neoadjuvant therapy prior to radical treatment, 65.0% of patients (67 males of 103) were treated with radiotherapy and 37.9% of patients (39 males of 103) were treated with radical prostatectomy.

Table 9 Previous Prostate Cancer Therapy, by Radical Treatment Regimen (Full Analysis Set)

Treatment combination	Overall (N=202)	Neoadjuvant ADT (N=103)	Adjuvant ADT (N=92)	Any ADT (N=132)	No ADT (N=70)
Radical prostatectomy	130 (64.4%)	39 (37.9%)	47 (51.1%)	63 (47.7%)	67 (95.7%)
Radical prostatectomy without radiotherapy	124 (61.4%)	36 (35.0%)	42 (45.7%)	58 (43.9%)	66 (94.3%)
Radical prostatectomy followed by radiotherapy	6 (3.0%)	3 (2.9%)	5 (5.4%)	5 (3.8%)	1 (1.4%)
Radiotherapy	78 (38.6%)	67 (65.0%)	50 (54.3%)	74 (56.1%)	4 (5.7%)
Radiotherapy without radical prostatectomy	72 (35.6%)	64 (62.1%)	45 (48.9%)	69 (52.3%)	3 (4.3%)
Radiotherapy followed by radical prostatectomy	0	0	0	0	0

Note: Three patients had received brachytherapy (one patient received low-dose brachytherapy and two patients both received high-dose brachytherapy and intensity-modulated radiation therapy).
ADT = androgen deprivation therapy.
Source: Statistical Table 3.2 in Appendix 7.

Table 10 describes groups of drugs used for adjuvant and neoadjuvant androgen deprivation therapy. 56.4% of patients (114 males of 202) underwent castration (including orchidectomy, usage of LHRH analogs, hexestrol), 28.2% of patients (57 males of 202) received treatment with both castration and antiandrogens and the same number of males underwent only castration. 8.9% of patients (18 males of 202) received only antiandrogens without castration. More than half of patients (55.9%, 113 patients of 202) received LHRH analogues, antiandrogens (both steroidal and nonsteroidal) were used in 37.1% of males (75 patients of 202).

Majority of patients were treated with castration (including orchidectomy, LHRH analogs, hexestrol) in both adjuvant and neoadjuvant regimens: 92.4% of patients received adjuvant therapy (85 males of 92) and 86.4% of patients received neoadjuvant therapy (89 males of 103) underwent castration. Treatment with LHRH analogues received 84.5% of males underwent neoadjuvant ADT (87 patients of 103) and 88.0% of males patients underwent adjuvant ADT (81 patients of 92). Antiandrogens were prescribed to more than half of patients received neoadjuvant therapy (56.3%, 58 males of 103) and to one third of patients received adjuvant therapy (34.8%, 32 males of 92). Details on using of certain drugs are presented in the Table 10.

Table 10 Neoadjuvant and Adjuvant Androgen Deprivation Therapy Groups (Full Analysis Set)

Androgen deprivation therapy	Total (N=202)	RP without RT (N=124)	RT without RP (N=72)	Neoadjuvant ADT (N=103)	Adjuvant ADT (N=92)
Cyproterone acetate	6 (3.0%)	3 (2.4%)	3 (4.2%)	4 (3.9%)	2 (2.2%)
Flutamide	34 (16.8%)	18 (14.5%)	14 (19.4%)	26 (25.2%)	12 (13.0%)
Bicalutamide	43 (21.3%)	17 (13.7%)	26 (36.1%)	29 (28.2%)	22 (23.9%)
Hexestrol	1 (0.5%)	0	1 (1.4%)	1 (1.0%)	0
Buserelin	46 (22.8%)	25 (20.2%)	19 (26.4%)	30 (29.1%)	32 (34.8%)
Goserelin	65 (32.2%)	22 (17.7%)	39 (54.2%)	44 (42.7%)	47 (51.1%)
Leuprorelin	20 (9.9%)	5 (4.0%)	15 (20.8%)	10 (9.7%)	12 (13.0%)
Triptorelin	13 (6.4%)	6 (4.8%)	7 (9.7%)	6 (5.8%)	7 (7.6%)
Degarelix	4 (2.0%)	4 (3.2%)	0	3 (2.9%)	1 (1.1%)
Orchidectomy	2 (1.0%)	0	2 (2.8%)	2 (1.9%)	2 (2.2%)
One or several nonsteroidal antiandrogens (flutamide, bicalutamide)	70 (34.7%)	33 (26.6%)	35 (48.6%)	55 (53.4%)	30 (32.6%)
One or several antiandrogens (cyproterone acetate, flutamide, bicalutamide)	75 (37.1%)	36 (29.0%)	37 (51.4%)	58 (56.3%)	32 (34.8%)
One or several LHRH analogs (buserelin, goserelin, leuprorelin, triptorelin, degarelix)	113 (55.9%)	47 (37.9%)	61 (84.7%)	87 (84.5%)	81 (88.0%)
Castration (orchidectomy, LHRH analogs, hexestrol)	114 (56.4%)	47 (37.9%)	62 (86.1%)	89 (86.4%)	85 (92.4%)
Castration and antiandrogens	57 (28.2%)	25 (20.2%)	30 (41.7%)	48 (46.6%)	42 (45.7%)
Castration only, without antiandrogens	57 (28.2%)	22 (17.7%)	32 (44.4%)	41 (39.8%)	43 (46.7%)
Antiandrogens only, without castration	18 (8.9%)	11 (8.9%)	7 (9.7%)	14 (13.6%)	7 (7.6%)

RT = radiotherapy; RP = radical prostatectomy.
Each medication subgroup can include both monotherapy and combination therapy. Patients with neoadjuvant orchidectomy also counted as having an adjuvant orchidectomy
Medication data is coded with WHO Drug dictionary version dated as of 1st of December, 2016.
Source: Statistical Table 3.3.2 in Appendix 7.

6.2.4 Concomitant therapy

Concomitant therapy during prostate cancer treatment was received by less than 10% of patients (8.9%, 18 males of 202). 5.0% of patients (10 males) used alpha-adrenoreceptor antagonists (Tamsulosin). Other medications were used by less than 3% of patients per drugs group. Details are presented in the Table 11.

Table 11 Other Concomitant Medications (Full Analysis Set)

		Any androgen deprivation therapy	
System organ class Preferred term	Overall (N=202)	Performed (N=132)	Not performed (N=70)
Any other concomitant medication	18 (8.9%)	14 (10.6%)	4 (5.7%)
ALPHA-ADRENORECEPTOR ANTAGONISTS	10 (5.0%)	9 (6.8%)	1 (1.4%)
TAMSULOSIN HYDROCHLORIDE	9 (4.5%)	8 (6.1%)	1 (1.4%)
TAMSULOSIN	1 (0.5%)	1 (0.8%)	0
ACE INHIBITORS, PLAIN	4 (2.0%)	3 (2.3%)	1 (1.4%)
ENALAPRIL	2 (1.0%)	2 (1.5%)	0
PERINDOPRIL	2 (1.0%)	1 (0.8%)	1 (1.4%)
BETA BLOCKING AGENTS, SELECTIVE	4 (2.0%)	2 (1.5%)	2 (2.9%)
BISOPROLOL	2 (1.0%)	2 (1.5%)	0
BISOPROLOL FUMARATE	2 (1.0%)	0	2 (2.9%)
ANTIARRHYTHMICS, CLASS III	2 (1.0%)	1 (0.8%)	1 (1.4%)
AMIODARONE HYDROCHLORIDE	2 (1.0%)	1 (0.8%)	1 (1.4%)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	2 (1.0%)	1 (0.8%)	1 (1.4%)
FORMOTEROL FUMARATE	2 (1.0%)	1 (0.8%)	1 (1.4%)
SULFONAMIDES, PLAIN	2 (1.0%)	2 (1.5%)	0
INDAPAMIDE	2 (1.0%)	2 (1.5%)	0

Medication data is coded with WHO Drug dictionary version dated as of 1st of December, 2016.
Source: Statistical Table 3.4 in Appendix 7.

6.2.5 Medical History

As shown in the Table 12, about a half of patients (49.5%, 100 males) had concomitant diseases at the time of enrolment. The most common pathology of the systemic and organ class was vascular disorders: more than one third of patients (33.7%, 68 males) had at least one disease from this group. Hypertension was presented in about one third of patients (32.7%, 66 males). Cardiac disorders were occurred in 28.2% of patients (57 males), in vast majority cases (26.2%, 53 males) it was myocardial ischemia. 7.9% of patients (16 males) had

diseases of gastrointestinal system and 5.4% of patients (11 males) had respiratory, thoracic and mediastinal disorders. Rest of diseases were represented in less than 5% of study population. 6 patients (3.0%) had neoplastic diseases.

Data regarding medical history of patients are presented in Statistical Table 2.3 in Appendix 7.

Table 12 Medical History (Full Analysis Set)

System organ class Preferred term	Overall (N=202)	Any androgen deprivation therapy Performed (N=132)	 Not performed (N=70)
Any medical history event	100 (49.5%)	59 (44.7%)	41 (58.6%)
VASCULAR DISORDERS	68 (33.7%)	42 (31.8%)	26 (37.1%)
ESSENTIAL HYPERTENSION	46 (22.8%)	26 (19.7%)	20 (28.6%)
HYPERTENSION	20 (9.9%)	16 (12.1%)	4 (5.7%)
ARTERIOSCLEROSIS	3 (1.5%)	2 (1.5%)	1 (1.4%)
VARICOSE VEIN	2 (1.0%)	0	2 (2.9%)
PERIPHERAL VENOUS DISEASE	1 (0.5%)	0.00%	1 (1.4%)
CARDIAC DISORDERS	57 (28.2%)	40 (30.3%)	17 (24.3%)
MYOCARDIAL ISCHAEMIA	53 (26.2%)	37 (28.0%)	16 (22.9%)
CARDIAC FAILURE CHRONIC	6 (3.0%)	6 (4.5%)	0
ATRIAL FIBRILLATION	5 (2.5%)	5 (3.8%)	0
EXTRASYSTOLES	2 (1.0%)	1 (0.8%)	1 (1.4%)
ANGINA PECTORIS	1 (0.5%)	0	1 (1.4%)
ARRHYTHMIA	1 (0.5%)	1 (0.8%)	0
CARDIAC FAILURE	1 (0.5%)	1 (0.8%)	0
SUPRAVENTRICULAR EXTRASYSTOLES	1 (0.5%)	0	1 (1.4%)
GASTROINTESTINAL DISORDERS	16 (7.9%)	4 (3.0%)	12 (17.1%)
GASTRIC ULCER	4 (2.0%)	2 (1.5%)	2 (2.9%)
CHRONIC GASTRITIS	3 (1.5%)	1 (0.8%)	2 (2.9%)
DUODENAL ULCER	3 (1.5%)	0	3 (4.3%)
GASTRITIS	3 (1.5%)	0	3 (4.3%)
PANCREATITIS CHRONIC	3 (1.5%)	0	3 (4.3%)
INGUINAL HERNIA	1 (0.5%)	1 (0.8%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	11 (5.4%)	7 (5.3%)	4 (5.7%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	5 (2.5%)	3 (2.3%)	2 (2.9%)
BRONCHITIS CHRONIC	4 (2.0%)	2 (1.5%)	2 (2.9%)
BRONCHIECTASIS	1 (0.5%)	1 (0.8%)	0
NASAL CYST	1 (0.5%)	0	1 (1.4%)
PULMONARY FIBROSIS	1 (0.5%)	1 (0.8%)	0
NEOPLASMS BENIGN, MALIGNANT AND	6 (3.0%)	2 (1.5%)	4 (5.7%)

UNSPECIFIED (INCL CYSTS AND POLYPS)			
BASAL CELL CARCINOMA	1 (0.5%)	1 (0.8%)	0
BLADDER CANCER	1 (0.5%)	0	1 (1.4%)
BREAST CANCER STAGE II	1 (0.5%)	1 (0.8%)	0
HODGKIN'S DISEASE	1 (0.5%)	0	1 (1.4%)
RENAL CANCER	1 (0.5%)	0	1 (1.4%)
THYROID CANCER	1 (0.5%)	0	1 (1.4%)

Medical history data are coded by MedDRA dictionary version 19.0.
Source: Statistical Table 2.3 in Appendix 7.

6.2.6 ECOG status assessment

Patients' performance status assessed with ECOG score at Visit 1 and after 1-year follow-up is presented in the Table 13. At first visit ECOG score 0 was reported for 38.6% of patients that means they were able to perform normal activities. More than half of patients in the study had ECOG score 1 (111 males, 55.0%). ECOG score 2 and 3 was reported for 6.4% of patients (13 males), all of them except 1 underwent androgen deprivation therapy. At the second visit scores 0 and 1 have been reported for 42.6% (86 patient) and 45.0% (91 patient) of males, respectively. Score 2 was registered for 6.9% of males (14 patients), 13 of these patients experienced androgen deprivation therapy.

Performance status for males in subgroups by androgen deprivation therapy performance is shown in the Table 13.

Table 13 ECOG Score Summary (Full Analysis Set)

		Overall	Any androgen deprivation therapy	
Visit	ECOG score	(N=202)	Performed (N=132)	Not performed (N=70)
Visit 1	0	78 (38.6%)	51 (38.6%)	27 (38.6%)
	1	111 (55.0%)	69 (52.3%)	42 (60.0%)
	2	12 (5.9%)	12 (9.1%)	0
	3	1 (0.5%)	0	1 (1.4%)
	4	0	0	0
Visit 2	0	86 (42.6%)	57 (43.2%)	29 (41.4%)
	1	91 (45.0%)	56 (42.4%)	35 (50.0%)
	2	14 (6.9%)	13 (9.8%)	1 (1.4%)
	3	0	0	0
	4	0	0	0
	Missing	11 (5.4%)	6 (4.5%)	5 (7.1%)

Source: Statistical Table 4.1 in Appendix 7.

Changes in performance status within 1 year was assessed in subgroups of patients by performance of ADT, type of radical treatment, duration of ADT and types of treatment combinations (Table 14, Table 15, Table 16, Table 17). There was no significant difference

revealed between any subgroups for ECOG status dynamics. For majority of patients (at average from 72% to 86% in each subgroup) ECOG score was not changed after 1-year follow-up. Percentage of patients showed ECOG score decreasing varied between 11% and 18% for each subgroup. Increasing of ECOG score was observed for less than 11% of males in each group.

Table 14 Change in ECOG Score, by Radical Treatment Regimen (Full Analysis Set)

Change in ECOG score to Visit 2	Radical treatment regimen		
	RP without RT (N=118)	RT without RP (N=68)	p-value (1)
ECOG score increased	6 (5.1%) [1.9%, 10.7%]	6 (8.8%) [3.3%, 18.2%]	0.865
No changes	98 (83.1%) [75.0%, 89.3%]	50 (73.5%) [61.4%, 83.5%]	
ECOG score decreased	14 (11.9%) [6.6%, 19.1%]	12 (17.6%) [9.5%, 28.8%]	

RT = radiotherapy; RP = radical prostatectomy.
95% confidence interval for the percentage is presented in squared parentheses.
(1) p-value is for Mantel-Haenzel chi-square test for the difference between radical treatment regimens
Source: Statistical Table 4.2.1 in Appendix 7.

Table 15 Change in ECOG Score, by ADT Presence (Full Analysis Set)

Change in ECOG score to Visit 2	Any androgen deprivation therapy		
	Performed (N=126)	Not performed (N=65)	p-value (1)
ECOG score increased	11 (8.7%) [4.4%, 15.1%]	2 (3.1%) [0.4%, 10.7%]	0.737
No changes	96 (76.2%) [67.8%, 83.3%]	55 (84.6%) [73.5%, 92.4%]	
ECOG score decreased	19 (15.1%) [9.3%, 22.5%]	8 (12.3%) [5.5%, 22.8%]	

ADT = androgen deprivation therapy.
95% confidence interval for the percentage is presented in squared parentheses.
(1) p-value is for Mantel-Haenzel chi-square test for the difference between between ADT absence/presence.
Source: Statistical Table 4.2.2 in Appendix 7.

Table 16 Change in ECOG Score, by ADT Duration (Full Analysis Set)

Change in ECOG score to Visit 2	Androgen deprivation therapy duration		
	6 months and less (N=35)	More than 6 months (N=91)	p-value (1)
ECOG score increased	1 (2.9%) [0.1%, 14.9%]	10 (11.0%) [5.4%, 19.3%]	0.838

No changes	30 (85.7%) [69.7%, 95.2%]	66 (72.5%) [62.2%, 81.4%]
ECOG score decreased	4 (11.4%) [3.2%, 26.7%]	15 (16.5%) [9.5%, 25.7%]

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
95% confidence interval for the percentage is presented in squared parentheses.
(1) p-value is for Mantel-Haenzel chi-square test for the difference between ADT duration subgroups.
Source: Statistical Table 4.2.3 in Appendix 7.

Table 17 Change in ECOG Score, by ADT Type (Full Analysis Set)

Change in ECOG score to Visit 2	Treatment combination		
	Castration and antiandrogens (N=55)	Castration only, without antiandrogens (N=55)	p-value (1)
ECOG score increased	4 (7.3%) [2.0%, 17.6%]	6 (10.9%) [4.1%, 22.2%]	0.690
No changes	43 (78.2%) [65.0%, 88.2%]	42 (76.4%) [63.0%, 86.8%]	
ECOG score decreased	8 (14.5%) [6.5%, 26.7%]	7 (12.7%) [5.3%, 24.5%]	

ADT = androgen deprivation therapy.
95% confidence interval for the percentage is presented in squared parentheses.
(1) p-value is for Mantel-Haenzel chi-square test for the difference between different treatment combinations.
Source: Statistical Table 4.2.4 in Appendix 7.

6.2.7 PSA levels assessment

Data on PSA levels after radical treatment (defined by SAP as time period starts at the date of radical treatment +21 day and ends at the date of radical treatment + 60 days) were available for 48 patients (Table 18). Median PSA level was 0.4 ng/ml, for 50% of these patients PSA level after radical treatment varied from 0.1 to 2.0 ng/ml. Median PSA levels were higher in patients after RT without RP than those underwent RP without PR: 1.9 vs. 0.1 ng/ml. Males underwent any type of ADT had higher median levels of PSA (1.0 ng/ml, Q1 - Q3 0.1 - 4.0 ng/ml), than in those for whom ADT was not conducted (0.1 ng/ml, Q1 - Q3 0.1 - 0.2 ng/ml). The difference can be explained by that all patients (except one) did not receive the any ADT were treated with radical prostatectomy. Among males received any ADT median PSA level was higher in those underwent RT without RP than RP without PR: 2.0 vs. 0.2 ng/ml. Median PSA levels were higher in patients with ADT duration more than 6 months: 1.6 ng/ml (Q1 - Q3 0.5 - 4.3 ng/ml) vs. 0.0 (Q1 - Q3 0.0 - 0.3 ng/ml). Among 28 males with ADT duration more than 6 months PSA levels were higher in patients treated with radiotherapy than radical prostatectomy: 2.1 vs. 0.5 ng/ml. Data on PSA levels after radical treatment in subgroups by ADT type are presented in the Table 18.

Table 18 PSA Levels by Radical Treatment Regimen (Full Analysis Set)

Time period: After radical treatment

	Total (N=202) n, median (Q1 - Q3)	Radical treatment regimen	
		RP without RT (N=132) n, median (Q1 - Q3)	RT without RP (N=70) n, median (Q1 - Q3)
Overall	48, 0.4 (0.1 - 2.0)	27, 0.1 (0.0 - 0.4)	21, 1.9 (1.0 - 5.3)
Any androgen deprivation therapy	39, 1.0 (0.1 - 4.0)	19, 0.2 (0.0 - 0.8)	20, 2.0 (1.1 - 6.0)
Only neoadjuvant	9, 0.2 (0.0 - 0.4)	6, 0.0 (0.0 - 0.2)	3, 1.9 (0.3 - 2.1)
Only adjuvant	5, 1.3 (0.3 - 4.0)	4, 0.8 (0.2 - 2.7)	1, 8.1 (8.1 - 8.1)
Both neoadjuvant and adjuvant	25, 1.3 (0.4 - 4.2)	9, 0.4 (0.1 - 0.8)	16, 2.0 (1.1 - 6.0)
No androgen deprivation therapy	9, 0.1 (0.1 - 0.2)	8, 0.1 (0.0 - 0.1)	1, 0.2 (0.2 - 0.2)
Duration of ADT (1)			
6 months and less	11, 0.0 (0.0 - 0.3)	8, 0.0 (0.0 - 0.2)	3, 0.3 (0.0 - 1.9)
More than 6 months	28, 1.6 (0.5 - 4.3)	11, 0.5 (0.1 - 1.5)	17, 2.1 (1.3 - 6.6)
ADT type			
Castration and antiandrogens	21, 1.5 (0.2 - 4.1)	9, 0.1 (0.0 - 0.5)	12, 2.0 (1.5 - 4.8)
Castration only, without antiandrogens	12, 1.2 (0.2 - 3.1)	5, 0.4 (0.3 - 1.3)	7, 1.3 (0.1 - 6.6)
Antiandrogens only, without castration	6, 0.2 (0.0 - 0.8)	5, 0.0 (0.0 - 0.4)	1, 8.5 (8.5 - 8.5)

Number of patients, median and quariles of PSA are reported.
RT = radiotherapy; RP = radical prostatectomy; ADT = androgen deprivation therapy.
(1) Duration of both neoadjuvant and adjuvant regimen.
Source: Statistical Table 5.1 in Appendix 7.

Data on PSA levels after one year of observation (defined by SAP as time period starts at date of Visit 2 minus 60 days and ends at the date of Visit 2 + 60 days) were available for 169 patients (Table 19). Median PSA level was 0.1 ng/ml, for 50% of these patients PSA level after one year of observation varied from 0.0 to 0.2 ng/ml. There was no notable difference observed between subgroups by ADT duration and ADT type. Details are presented in the Table 19.

Table 19 PSA Levels by Radical Treatment Regimen (Full Analysis Set)

Time period: After one year of observation

	Total (N=202) n, median (Q1 - Q3)	Radical treatment regimen	
		RP without RT (N=132) n, median (Q1 - Q3)	RT without RP (N=70) n, median (Q1 - Q3)
Overall	169, 0.1 (0.0 - 0.4)	106, 0.1 (0.0 - 0.2)	59, 0.4 (0.1 - 0.8)
Any androgen deprivation therapy	111, 0.2 (0.0 - 0.5)	52, 0.1 (0.0 - 0.2)	56, 0.3 (0.1 - 0.9)
Only neoadjuvant	33, 0.2 (0.1 - 0.4)	14, 0.1 (0.0 - 0.2)	19, 0.3 (0.2 - 0.9)

Only adjuvant	23, 0.0 (0.0 - 0.3)	19, 0.0 (0.0 - 0.1)	4, 0.7 (0.4 - 1.0)
Both neoadjuvant and adjuvant	55, 0.1 (0.0 - 0.6)	19, 0.1 (0.0 - 0.2)	33, 0.3 (0.0 - 0.7)
No androgen deprivation therapy	58, 0.1 (0.0 - 0.2)	54, 0.1 (0.0 - 0.1)	3, 0.6 (0.0 - 0.8)
Duration of ADT (1)			
6 months and less	31, 0.2 (0.0 - 0.4)	22, 0.1 (0.0 - 0.2)	9, 0.3 (0.2 - 0.8)
More than 6 months	80, 0.1 (0.0 - 0.6)	30, 0.0 (0.0 - 0.2)	47, 0.4 (0.1 - 0.9)
ADT type			
Castration and antiandrogens	45, 0.2 (0.1 - 0.8)	20, 0.0 (0.0 - 0.2)	24, 0.7 (0.2 - 1.0)
Castration only, without antiandrogens	51, 0.1 (0.0 - 0.3)	22, 0.1 (0.0 - 0.2)	27, 0.3 (0.0 - 0.5)
Antiandrogens only, without castration	15, 0.2 (0.0 - 0.5)	10, 0.1 (0.0 - 0.2)	5, 0.5 (0.3 - 0.5)

Number of patients, median and quariles of PSA are reported.
RT = radiotherapy; RP = radical prostatectomy; ADT = androgen deprivation therapy.
(1) Duration of both neoadjuvant and adjuvant regimen.
Source: Statistical Table 5.1 in Appendix 7.

Half of patients (50.5% 95%CI: 43.2%; 57.9%, 95 males of 188), for whom at least two PSA measurements at baseline and after 1 year were available, showed doubling of PSA level after 1 year (Table 20). Presence of androgen deprivation therapy did not influence on doubling of PSA level after one year. Approximately half of males showed two times increasing of PSA in both groups with and without ADT (50.4%, 64 patients of those with at least two PSA measurements, and 50.8%, 31 patients of those with at least two PSA measurements, correspondingly). Half of patients in both subgroups received ADT more than 6 month and 6 month or less showed PSA doubling. Two times PSA increasing was observed in 50.9% of patients received castration and antiandrogens, in 48.1% of those received castration only and in 56.3% of patients treated with antiandrogens only.

Proportion of patients with PSA doubling after one year was greater among males underwent radical prostatectomy without radiotherapy than in group after radiotherapy without radical prostatectomy: 57.5% (CI95%: 47.9%; 66.8%) vs. 40.0% (CI95%: 28.5%;52.4%), correspondingly. This tendency was present in all subgroups.

Data on doubled PSA levels in patients are presented in the Table 20.

Table 20 Patients with Doubled PSA Level after One Year of Observation by Radical Treatment Regimen (Full Analysis Set)

	Total (N=202)	Radical treatment regimen	
		RP without RT (N=124)	RT without RP (N=72)
Patients who have at least two PSA assessments recorded	188 (93.1%)	113 (91.1%)	70 (97.2%)
Overall	95 (50.5%)	65 (57.5%)	28 (40.0%)
	[43.2%, 57.9%]	[47.9%, 66.8%]	[28.5%, 52.4%]
Any androgen deprivation therapy	64 (50.4%)	34 (60.7%)	28 (41.8%)
	[41.4%, 59.4%]	[46.8%, 73.5%]	[29.8%, 54.5%]
Only neoadjuvant	17 (45.9%)	11 (73.3%)	6 (27.3%)
	[29.5%, 63.1%]	[44.9%, 92.2%]	[10.7%, 50.2%]
Only adjuvant	12 (42.9%)	8 (36.4%)	4 (80.0%)
	[24.5%, 62.8%]	[17.2%, 59.3%]	[28.4%, 99.5%]
Both neoadjuvant and adjuvant	35 (56.5%)	15 (78.9%)	18 (45.0%)
	[43.3%, 69.0%]	[54.4%, 93.9%]	[29.3%, 61.5%]
No androgen deprivation therapy	31 (50.8%)	31 (54.4%)	0
	[37.7%, 63.9%]	[40.7%, 67.6%]	[0.0%, 70.8%]
Duration of ADT (1, 2)			
6 months and less	18 (50.0%)	15 (62.5%)	3 (25.0%)
	[32.9%, 67.1%]	[40.6%, 81.2%]	[5.5%, 57.2%]
More than 6 months	46 (50.5%)	19 (59.4%)	25 (45.5%)
	[39.9%, 61.2%]	[40.6%, 76.3%]	[32.0%, 59.4%]
ADT type (2)			
Castration and antiandrogens	29 (50.9%)	16 (64.0%)	13 (43.3%)
	[37.3%, 64.4%]	[42.5%, 82.0%]	[25.5%, 62.6%]
Castration only	26 (48.1%)	11 (52.4%)	13 (41.9%)
	[34.3%, 62.2%]	[29.8%, 74.3%]	[24.5%, 60.9%]
Antiandrogens only	9 (56.3%)	7 (70.0%)	2 (33.3%)
	[29.9%, 80.2%]	[34.8%, 93.3%]	[4.3%, 77.7%]

Patients who have double increase in PSA level during one year of observation are reported. 95% confidence interval for the percentage is presented in squared parentheses. Percentage is based on the number of patients with at least two PSA assessments recorded.
RT = radiotherapy; RP = radical prostatectomy; ADT = androgen deprivation therapy.
(1) Duration of both neoadjuvant and adjuvant regimen.
(2) Percentage is based on the number of patients having any ADT.
Source: Statistical Table 5.2 in Appendix 7.

6.2.8 Disease progression assessment

Disease progression after 1 year of observation was assessed in 191 patients of 202 (94.6%) (Table 21). 16 males showed presence of progression (8.4% of 191 patients). Biochemical progression was registered in 14 cases and clinical progression in 4 cases (2 patients showed both types). 3 patients died due to reasons not related to prostate cancer progression.

Details on disease progression or death among patients are presented in the Table 21.

Table 21 Patients with Disease Progression or Death from Any Cause in One Year by Androgen Deprivation Treatment (Full Analysis Set)

Overall

	Overall (N=202)		
	N	n (%)	95% confidence interval
Disease progression assessed	202	191 (94.6%)	90.5%, 97.3%
Disease progression (1)	191	16 (8.4%)	4.9%, 13.2%
Biochemical	16	14 (87.5%)	61.7%, 98.4%
Clinical	16	4 (25.0%)	7.3%, 52.4%
Clinical progression (2)	4	4 (100.0%)	39.8%, 100.0%
Local recurrence	4	2 (50.0%)	6.8%, 93.2%
Metastasis to regional lymph nodes	4	1 (25.0%)	0.6%, 80.6%
Distant metastasis	4	2 (50.0%)	6.8%, 93.2%
Death	202	3 (1.5%)	0.3%, 4.3%
Cause of death (3)			
Progression of prostate cancer	3	0	0.0%, 70.8%
Other cause	3	3 (100.0%)	29.2%, 100.0%
Unknown	3	0	0.0%, 70.8%
Disease progression or death from any cause	202	19 (9.4%)	5.8%, 14.3%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.3 in Appendix 7.

Disease progression after 1 year of follow-up was assessed in subgroups of patients with RP without RT and with RT without RP. Data in these groups were comparable.

Among 124 patients underwent radical prostatectomy without any radiotherapy, disease progression was assessed after one year of observation in 118 males (95.2%) (Table 22). Progression was observed in 11 males of 118 (9.3%, CI95%: 4.7%;16.1%). Among 11

patients with progression 10 showed biochemical progression and 3 clinical (two patients had both types). There were no deaths caused by prostate cancer progression. 1 patient was dead due to other reasons.

Details on disease progression or death among patients with radical prostatectomy without any radiotherapy are presented in the Table 22.

Table 22 Patients with Disease Progression or Death from Any Cause in One Year by Radical Treatment Regimen (Full Analysis Set)

Patients with radical prostatectomy without any radiotherapy

	Overall (N=124)		
	N	n (%)	95% confidence interval
Disease progression assessed	124	118 (95.2%)	89.8%, 98.2%
Disease progression (1)	118	11 (9.3%)	4.7%, 16.1%
Biochemical	11	10 (90.9%)	58.7%, 99.8%
Clinical	11	3 (27.3%)	6.0%, 61.0%
Clinical progression (2)	3	3 (100.0%)	29.2%, 100.0%
Local recurrence	3	2 (66.7%)	9.4%, 99.2%
Metastasis to regional lymph nodes	3	1 (33.3%)	0.8%, 90.6%
Distant metastasis	3	1 (33.3%)	0.8%, 90.6%
Death	124	1 (0.8%)	0.0%, 4.4%
Cause of death (3)			
Progression of prostate cancer	1	0	0.0%, 97.5%
Other cause	1	1 (100.0%)	2.5%, 100.0%
Unknown	1	0	0.0%, 97.5%
Disease progression or death from any cause	124	12 (9.7%)	5.1%, 16.3%

(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.1 in Appendix 7.

Among 72 patients underwent radiotherapy without radical prostatectomy, disease progression was assessed after one year of observation in 68 males (94.4%) (Table 23). Prostate cancer progression was confirmed for 5 males (7.4%, CI95%: 2.4%;16.3%): 4 patients had biochemical progression and 1 clinical (distant metastases were observed for this patient). 2 patients died from causes other than prostate cancer progression.

Details on disease progression or death among patients with radiotherapy without radical prostatectomy are presented in the Table 23.

Table 23 Patients with Disease Progression or Death from Any Cause in One Year by Radical Treatment Regimen (Full Analysis Set)

Patients with radiotherapy without radical prostatectomy

		Overall (N=72)	
	N	n (%)	95% confidence interval
Disease progression assessed	72	68 (94.4%)	86.4%, 98.5%
Disease progression (1)	68	5 (7.4%)	2.4%, 16.3%
Biochemical	5	4 (80.0%)	28.4%, 99.5%
Clinical	5	1 (20.0%)	0.5%, 71.6%
Clinical progression (2)	1	1 (100.0%)	2.5%, 100.0%
Local recurrence	1	0	0.0%, 97.5%
Metastasis to regional lymph nodes	1	0	0.0%, 97.5%
Distant metastasis	1	1 (100.0%)	2.5%, 100.0%
Death	72	2 (2.8%)	0.3%, 9.7%
Cause of death (3)			
Progression of prostate cancer	2	0	0.0%, 84.2%
Other cause	2	2 (100.0%)	15.8%, 100.0%
Unknown	2	0	0.0%, 84.2%
Disease progression or death from any cause	72	7 (9.7%)	4.0%, 19.0%

(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.1 in Appendix 7.

Disease progression after 1 year follow-up was assessed in groups with and without androgen deprivation therapy and by androgen deprivation therapy type and duration.

In group of 124 patients with radical prostatectomy without any radiotherapy (Table 24), 58 males received any ADT and 66 did not. Disease progression or death was observed in 8 males (13.8% [CI95%: 6.1%;25.4%] of 58 patients who received any ADT, and in 4 males (6.1% [CI95%: 1.7%;14.8%] of 66 patients) who did not receive ADT. 6 cases of disease progression or death occurred in patients with treatment duration more than 6 months (18.2% of 33 males with ADT duration more than 6 months) and 2 cases in those with ADT duration 6 months and less (8.0% of 25 males with ADT duration 6 months and less). 4 cases of disease progression or death were registered in males underwent treatment with castration and antiandrogens (16.0% of 25 patients), and by two cases among males treated with only castration (9.1% of 22 patients) and with only antiandrogens (18.2% of 11 patients).

Details on disease progression or death among patients with radical prostatectomy without any radiotherapy are presented in the Table 24.

Table 24 Patients with Disease Progression or Death from Any Cause in One Year by ADT Duration and Type (Full Analysis Set)

Patients with radical prostatectomy without any radiotherapy

	Overall (N=124)		
Disease progression or death from any cause	N	n (%)	95% confidence interval
Androgen deprivation therapy	124		
Yes	58	8 (13.8%)	6.1%, 25.4%
No	66	4 (6.1%)	1.7%, 14.8%
Duration of ADT (1, 2)	58		
6 months and less	25	2 (8.0%)	1.0%, 26.0%
More than 6 months	33	6 (18.2%)	7.0%, 35.5%
ADT type (2)	58		
Castration and antiandrogens	25	4 (16.0%)	4.5%, 36.1%
Castration only, without antiandrogens	22	2 (9.1%)	1.1%, 29.2%
Antiandrogens only, without castration	11	2 (18.2%)	2.3%, 51.8%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Duration of both neoadjuvant and adjuvant regimen.
(2) Percentage is based on the number of patients having any ADT.
Source: Statistical Table 6.2 in Appendix 7.

Results of disease progression registered for patients received radiotherapy without radical prostatectomy were comparable with the data for males with radical prostatectomy without any radiotherapy (Table 25). Disease progression or death was observed in 7 males (10.1% [CI95%: 4.2%;19.8%] of 69 patients) received any ADT and in none among those who did not receive ADT (0 [CI95%: 0.0%;70.8%]). 6 cases of disease progression or death occurred in patients with treatment duration more than 6 months (10.7% [CI95%: 4.0%;21.9%] of 56 males) and 1 case in those with ADT duration 6 months and less (7.7% [CI95%: 0.2%;36.0%] of 13 males with ADT duration 6 months and less). 4 cases of disease progression or death were registered in males underwent treatment with castration and antiandrogens (13.3% of 30 patients), 2 cases among males treated with only castration (6.3% of 32 patients) and 1 case among males treated with only antiandrogens (14.3% of 7 patients).

Details on disease progression or death among patients with radical prostatectomy without any radiotherapy are presented in the Table 25.

Table 25 Patients with Disease Progression or Death from Any Cause in One Year by ADT Duration and Type (Full Analysis Set)

Patients with radiotherapy without radical prostatectomy

		Overall (N=72)	
Disease progression or death from any cause	N	n (%)	95% confidence interval
Androgen deprivation therapy	72		
Yes	69	7 (10.1%)	4.2%, 19.8%
No	3	0	0.0%, 70.8%
Duration of ADT (1, 2)	69		
6 months and less	13	1 (7.7%)	0.2%, 36.0%
More than 6 months	56	6 (10.7%)	4.0%, 21.9%
ADT type (2)	69		
Castration and antiandrogens	30	4 (13.3%)	3.8%, 30.7%
Castration only, without antiandrogens	32	2(6.3%)	0.8%, 20.8%
Antiandrogens only, without castration	7	1 (14.3%)	0.4%, 57.9%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Duration of both neoadjuvant and adjuvant regimen.
(2) Percentage is based on the number of patients having any ADT.
Source: Statistical Table 6.2 in Appendix 7.

Percentage of patients with disease progression was higher among males underwent any ADT (13 patients, 10.3% [CI95%: 5.6%;17.0%] of 126 subjects) than among those without ADT (3 patients, 4.6% [CI95%: 1.0%;12.9%] of 65 subjects) (Table 26). In the group underwent ADT biochemical progression was registered in 12 cases and clinical progression in 2 cases (1 patient showed both types). In the group without any ADT biochemical progression was occurred in 2 cases and clinical progression in 2 cases as well (1 patient showed both types).

Details on disease progression among patients with and without ADT therapy are presented in the Table 26 and in Statistical Table 6.3 in Appendix 7.

Table 26 Patients with Disease Progression or Death from Any Cause in One Year by Androgen Deprivation Treatment (Full Analysis Set)

	With any ADT therapy			Without any ADT therapy		
		Overall (N=132)			Overall (N=70)	
	N	n (%)	95% confidence interval	N	n (%)	95% confidence interval
Disease progression assessed	132	126 (95.5%)	90.4%, 98.3%	70	65 (92.9%)	84.1%, 97.6%
Disease progression (1)	126	13 (10.3%)	5.6%, 17.0%	65	3 (4.6%)	1.0%, 12.9%

Biochemical	13	12 (92.3%)	64.0%, 99.8%	3	2 (66.7%)	9.4%, 99.2%
Clinical	13	2 (15.4%)	1.9%, 45.4%	3	2 (66.7%)	9.4%, 99.2%
Clinical progression (2)	2	2 (100.0%)	15.8%, 100.0%	2	2 (100.0%)	15.8%, 100.0%
Local recurrence	2	0	0.0%, 84.2%	2	2 (100.0%)	15.8%, 100.0%
Metastasis to regional lymph nodes	2	0	0.0%, 84.2%	2	1 (50.0%)	1.3%, 98.7%
Distant metastasis	2	2 (100.0%)	15.8%, 100.0%	2	0	0.0%, 84.2%
Death	132	2 (1.5%)	0.2%, 5.4%	70	1 (1.4%)	0.0%, 7.7%
Cause of death (3)						
Progression of prostate cancer	2	0	0.0%, 84.2%	1	0	0.0%, 97.5%
Other cause	2	2 (100.0%)	15.8%, 100.0%	1	1 (100.0%)	2.5%, 100.0%
Unknown	2	0	0.0%, 84.2%	1	0	0.0%, 97.5%
Disease progression or death from any cause	132	15 (11.4%)	6.5%, 18.0%	70	4 (5.7%)	1.6%, 14.0%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.3 in Appendix 7.

Disease progression after 1 year of observation was observed in 12.1% (CI95%: 6.2%;20.6%, 11 males of 91) of patients with ADT duration more than 6 months and in 5.7% (CI95%: 0.7%;19.2%, 2 males of 35) of patients with ADT duration 6 months or less (Table 27).

Details on disease progression among patients depending on ADT therapy duration are presented in Statistical Table 6.3 in Appendix 7.

Table 27 Patients with Disease Progression or Death from Any Cause in One Year by Androgen Deprivation Treatment (Full Analysis Set)

	ADT duration is 6 months or less			ADT duration is more than 6 months		
	Overall (N=38)			Overall (N=93)		
	N	n (%)	95% confidence interval	N	n (%)	95% confidence interval
Disease progression assessed	38	35 (92.1%)	78.6%, 98.3%	93	91 (97.8%)	92.4%, 99.7%
Disease progression (1)	35	2 (5.7%)	0.7%, 19.2%	91	11 (12.1%)	6.2%, 20.6%
Biochemical	2	2 (100.0%)	15.8%, 100.0%	11	10 (90.9%)	58.7%, 99.8%
Clinical	2	0	0.0%, 84.2%	11	2 (18.2%)	2.3%, 51.8%
Clinical progression (2)	0			2	2 (100.0%)	15.8%, 100.0%
Local recurrence				2	0	0.0%, 84.2%
Metastasis to regional lymph nodes				2	0	0.0%, 84.2%

Distant metastasis				2	2 (100.0%)	15.8%, 100.0%
Death	38	1 (2.6%)	0.1%, 13.8%	93	1 (1.1%)	0.0%, 5.8%
Cause of death (3)						
Progression of prostate cancer	1	0	0.0%, 97.5%		0	0.0%, 97.5%
Other cause	1	1 (100.0%)	2.5%, 100.0%		1 (100.0%)	2.5%, 100.0%
Unknown	1	0	0.0%, 97.5%		0	0.0%, 97.5%
Disease progression or death from any cause	38	3 (7.9%)	1.7%, 21.4%	93	12 (12.9%)	6.8%, 21.5%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.3 in Appendix 7.

As shown in the Table 28 disease progression after 1 year of observation was observed in 12.7% (CI95%: 5.3%;24.5%, 7 of 55 males) of patients underwent both castration and treatment with antiandrogens, in 5.5% (CI95%: 1.1%;15.1%, 3 of 55 males) of patients treated only with castration and in 18.8% (CI95%: 4.0%;45.6%, 3 of 16 males) of patients treated only with antiandrogens.

Details on disease progression among patients by ADT therapy are presented in Statistical Table 6.3 in Appendix 7.

Table 28 Patients with Disease Progression or Death from Any Cause in One Year by Androgen Deprivation Treatment (Full Analysis Set)

	Castration and antiandrogens			Castration only, without antiandrogens			Antiandrogens only, without castration		
	Overall (N=57)			Overall (N=57)			Overall (N=18)		
	N	n (%)	95% confidence interval	N	n (%)	95% confidence interval	N	n (%)	95% confidence interval
Disease progression assessed	57	55 (96.5%)	87.9%, 99.6%	57	55 (96.5%)	87.9%, 99.6%	18	16 (88.9%)	65.3%, 98.6%
Disease progression (1)	55	7 (12.7%)	5.3%, 24.5%	55	3 (5.5%)	1.1%, 15.1%	16	3 (18.8%)	4.0%, 45.6%
Biochemical	7	7 (100.0%)	59.0%, 100.0%	3	3 (100.0%)	29.2%, 100.0%	3	2 (66.7%)	9.4%, 99.2%
Clinical	7	0	0.0%, 41.0%	3	1 (33.3%)	0.8%, 90.6%	3	1 (33.3%)	0.8%, 90.6%
Clinical progression (2)	0			1	1 (100.0%)	2.5%, 100.0%	1	1 (100.0%)	2.5%, 100.0%
Local recurrence				1	0	0.0%, 97.5%	1	0	0.0%, 97.5%
Metastasis to regional lymph nodes				1	0	0.0%, 97.5%	1	0	0.0%, 97.5%

Distant metastasis				1	1 (100.0%)	2.5%, 100.0%	1	1 (100.0%)	2.5%, 100.0%
Death	57	1 (1.8%)	0.0%, 9.4%	57	1 (1.8%)	0.0%, 9.4%	18	0	0.0%, 18.5%
Cause of death (3)									
Progression of prostate cancer	1	0	0.0%, 97.5%	1	0	0.0%, 97.5%			
Other cause	1	1(100.0%)	2.5%, 100.0%	1	1(100.0%)	2.5%, 100.0%			
Unknown	1	0	0.0%, 97.5%	1	0	0.0%, 97.5%			
Disease progression or death from any cause	57	8 (14.0%)	6.3%, 25.8%	57	4 (7.0%)	1.9%, 17.0%	18	3 (16.7%)	3.6%, 41.4%

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
(1) Percentage for n is based on the number of patients with assessed disease progression.
(2) Percentage for n is based on the number of patients having clinical progression.
(3) Percentage for n is based on the number of deaths.
Source: Statistical Table 6.3 in Appendix 7.

Analysis of time to disease progression was conducted for subgroups of patients by radical treatment regimen (radical prostatectomy without any radiotherapy vs. radiotherapy without radical prostatectomy), ADT presence (any ADT vs. no ADT), ADT duration (6 months and less vs. more than 6 months) and ADT type (castration and antiandrogens vs. castration only) (Table 29, Table 30, Table 31, Table 32). There was no significant difference in time to disease progression between subgroups. Survival curves, hazard ratios with 95% confidence interval and the corresponding level of significance are presented below (Figure 1-Figure 4).

Table 29 Analysis of Time to Disease Progression or Death from Any Cause, by Radical Treatment Regimen (Full Analysis Set)

Parameter/ Contrast	Total (N=202)	Cox hazard ratio	95% confidence interval	Likelihood ratio p-value
Number of patients in the analysis	196			
Radical prostatectomy without radiotherapy	124 (63.3%)			
Number of events	12 (9.7%)			
Number of censored events	112 (90.3%)			
Radiotherapy without radical prostatectomy	72 (36.7%)			
Number of events	7 (9.7%)			
Number of censored events	65 (90.3%)			
Radical prostatectomy vs Radiotherapy		1.022	0.402, 2.599	0.963

Percentage is based on the number of patients in the model.
p-value is for chi square test of significance.
Source: Statistical Table 7.1 in Appendix 7.

Table 30 Analysis of Time to Disease Progression or Death from Any Cause, by ADT Presence (Full Analysis Set)

Parameter/ Contrast	Total (N=202)	Cox hazard ratio	95% confidence interval	Likelihood ratio p-value
Number of patients in the analysis	202			
Patients having any ADT	132 (65.3%)			
Number of events	15 (11.4%)			
Number of censored events	117 (88.6%)			
Patients without ADT	70 (34.7%)			
Number of events	4 (5.7%)			
Number of censored events	66 (94.3%)			
Having ADT vs No ADT		1.967	0.652, 5.930	0.230

ADT = androgen deprivation therapy. Percentage is based on the number of patients in the model.
p-value is for chi square test of significance.
Source: Statistical Table 7.2 in Appendix 7.

Table 31 Analysis of Time to Disease Progression or Death from Any Cause, by ADT Duration (Full Analysis Set)

Parameter/ Contrast	Total (N=202)	Cox hazard ratio	95% confidence interval	Likelihood ratio p-value
Number of patients in the analysis	131			
ADT duration is 6 months or less	38 (29.0%)			
Number of events	3 (7.9%)			
Number of censored events	35 (92.1%)			
ADT duration is more than 6 months	93 (71.0%)			
Number of events	12 (12.9%)			
Number of censored events	81 (87.1%)			
ADT duration <= 6 months vs ADT duration > 6 months		0.634	0.179, 2.250	0.481

ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.
Percentage is based on the number of patients in the model.

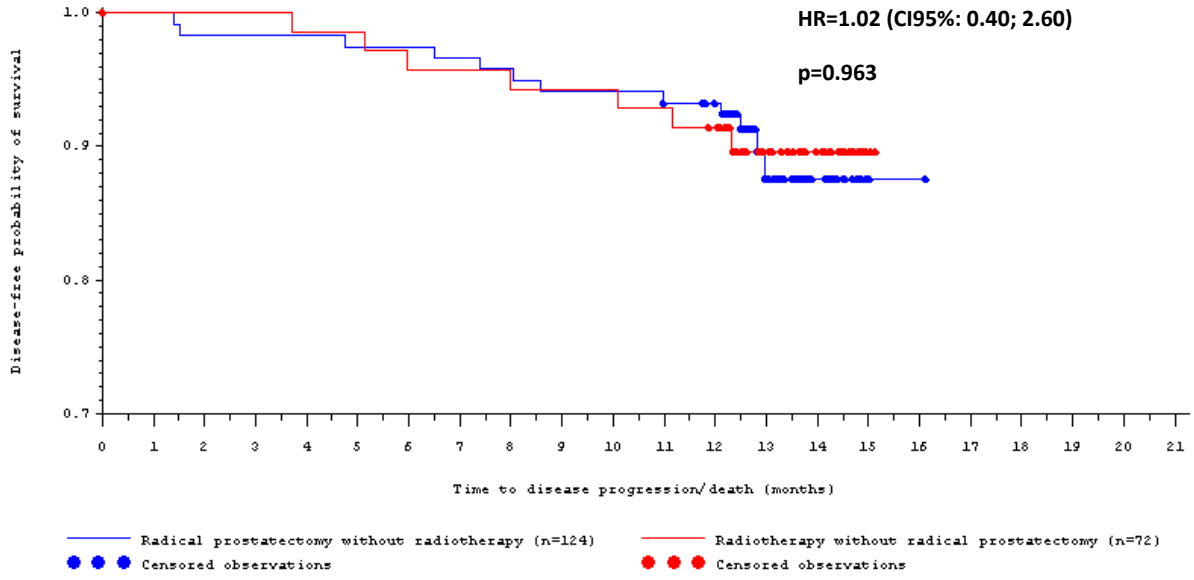
p-value is for chi square test of significance.
Source: Statistical Table 7.3 in Appendix 7.

Table 32 Analysis of Time to Disease Progression or Death from Any Cause, by ADT Type (Full Analysis Set)

Parameter/ Contrast	Total (N=202)	Cox hazard ratio	95% confidence interval	Likelihood ratio p-value
Number of patients in the analysis	114			
Castration and antiandrogens	57 (50.0%)			
Number of events	8 (14.0%)			
Number of censored events	49 (86.0%)			
Castration only, without antiandrogens	57 (50.0%)			
Number of events	4 (7.0%)			
Number of censored events	53 (93.0%)			
Castration and antiandrogens vs castration only, without antiandrogens		2.185	0.657, 7.260	0.202

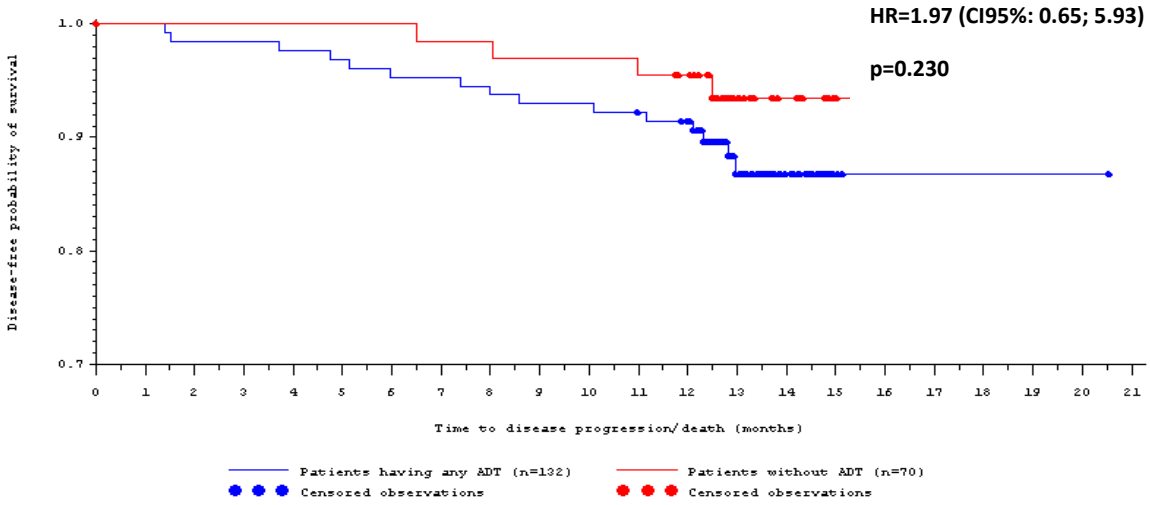
ADT = androgen deprivation therapy. Percentage is based on the number of patients in the model.
p-value is for chi square test of significance.
Source: Statistical Table 7.4 in Appendix 7.

Figure 1 Survival Functions of Time to Disease Progression or Death from Any Cause, by Radical Treatment Regimen (Full Analysis Set)



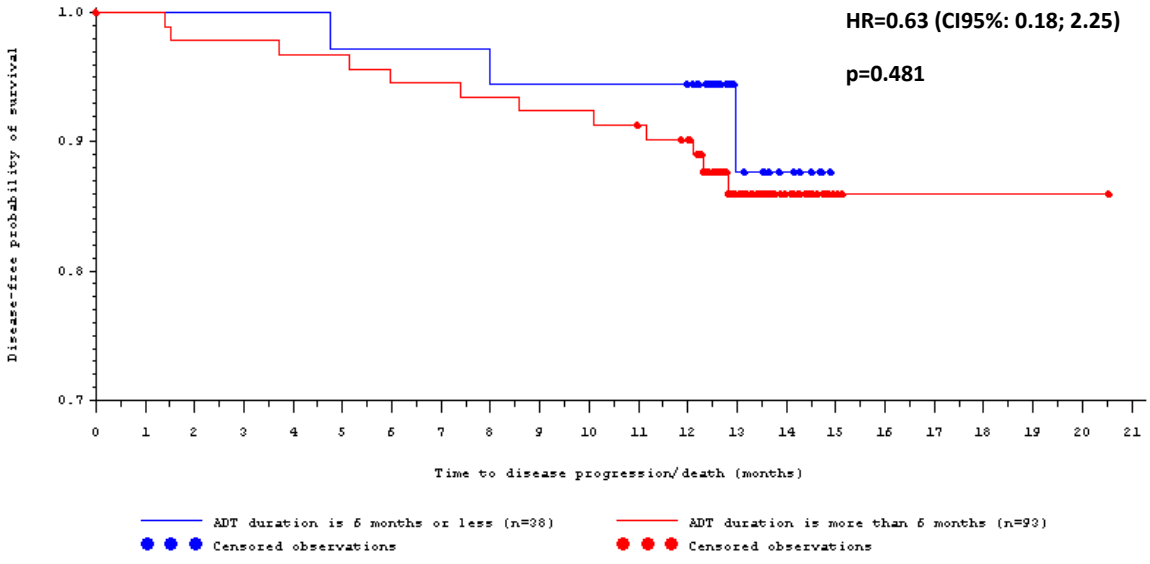
Source: Figure 1 in Appendix 8.

Figure 2 Survival Functions of Time to Disease Progression or Death from Any Cause, by ADT Presence (Full Analysis Set)



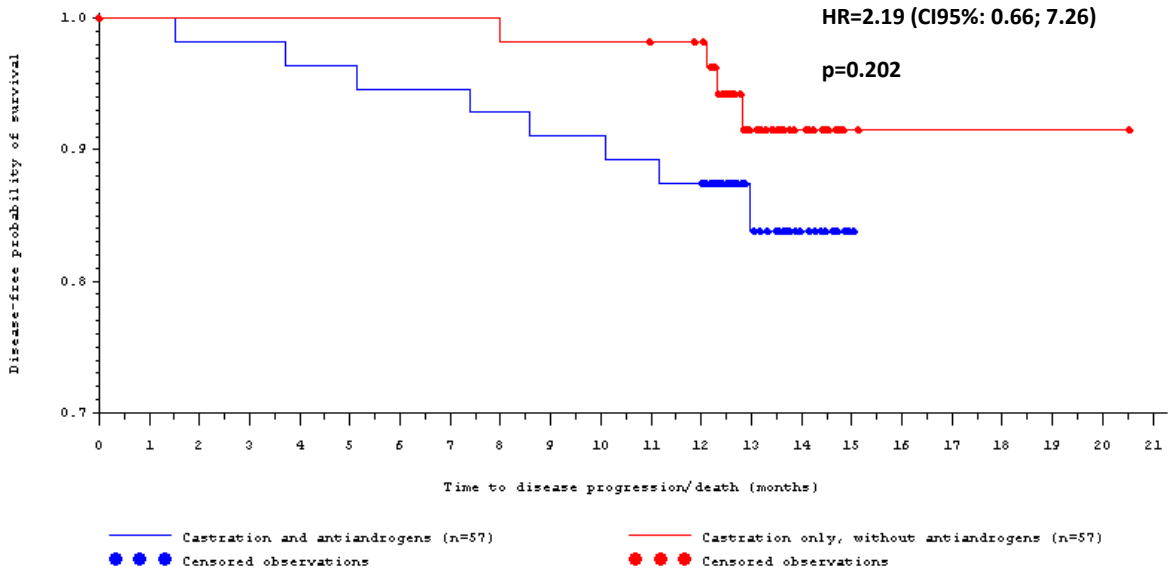
ADT = androgen deprivation therapy.
Source: Figure 2 in Appendix 8.

Figure 3 Survival Functions of Time to Disease Progression or Death from Any Cause, by ADT Duration (Full Analysis Set)



ADT = androgen deprivation therapy. ADT duration is for both neoadjuvant and adjuvant regimen.Source: Figure 3 in Appendix 8.

Figure 4 Survival Functions of Time to Disease Progression or Death from Any Cause, by ADT Type (Full Analysis Set)



ADT = androgen deprivation therapy.
Figure 4 in Appendix 8.

7. SAFETY EVALUATION

7.1 Adverse Events

The active collection of any safety data was not performed due to the non-interventional type of the study. No safety measurements and variables are applicable for this study.

8. CONCLUSION & DISCUSSION

8.1 Discussion

This observational study was planned to receive the information on current clinical practices in usage of antiandrogen deprivation therapy in patients with locally advanced prostate cancer. The primary objective of the study was to provide accurate and reliable information regarding the adjuvant endocrine treatment of patients with locally advanced prostate cancer with high and very high risk of recurrence after surgery or radiotherapy in the Russian routine clinical practice by evaluation of treatment approaches.

This was non-interventional multicentre study conducted in 18 sites in Russia. A total of 204 patients with locally advanced prostate cancer were enrolled and 202 patients were included in the Full Analysis set. Almost all patients were White with mean age of 64.9 ± 6.2 years. Family history of prostate cancer was noted only for 3.0% of patients (6 males).

Median duration of prostate cancer at the time of enrolment was less than 2.7 months, for 75% of patients disease duration did not exceed 7 months. It is foreseeable that median duration of prostate cancer was longer in patients, for whom ADT was performed, than for those who did not undergo ADT: about 5 months vs. 1 month.

Concomitant therapy during prostate cancer treatment was received by less than 10% of patients (8.9%).

About a half of patients (49.5%) had concomitant diseases at the time of enrolment into the study. The most often diagnoses were hypertension (32.7%) and myocardial ischemia (26.2%). 3.0% of males had neoplastic diseases other than prostate cancer. Other diseases were represented in less than 10% of patients.

About 60% of patients had disease stage T3a according to TNM classification, 37.6% had T3b and 2.5% had T4 stage. In 86.1% of patients lymph node metastases were absent and for 13.9% lymph nodes could not be assessed (stage Nx). No patients had distant metastases.

Primary prostate cancer diagnosis was based on PSA analysis in vast majority of patients (98.5%), finger rectal examination of prostate was carried out in 80.2% of patients, 50.5% of males underwent transrectal ultrasonography, 30.2% were diagnosed with MRI and radioisotope examination was used for 11.9% of patients. Other methods (including X-ray computed tomography, uroflowmetry) were used in less than 10% of cases. Transrectal ultrasound-guided prostate thick needle biopsy (TRUS) and histological examination were in the top of methods for diagnosis confirmation (96.0% and 92.6%, respectively). MRI, radioisotope examination and PSA blood test were used for diagnosis confirmation in 62.4%, 47.5% and 43.6%, correspondingly.

For histology assessment, mean number of cores taken during biopsy procedure was 9.6 (±4.9), mean percentage of cancer positive cores was 60.87% (±25.30%) and varied from 8.3% to 100.0%.

Description of prostate cancer cells morphology with Gleason grading system revealed that 39.6% of patients had moderately differentiated adenocarcinoma (Gleason score 7), about one third (29.7%) had poorly differentiated or anaplastic adenocarcinoma (score 8 or more) and approximately the same number (29.2%) of patients had well differentiated adenocarcinoma (score 6 or less).

Among males participated in the study, 64.4% were treated surgically, and 38.6% underwent radiotherapy. 6 patients (4.6%) underwent radical prostatectomy followed by radiotherapy.

Androgen deprivation therapy was carried out for 65.3% of patients (132 males). About one third (31.2%) of patients received both neoadjuvant and adjuvant therapy, 19.8% underwent only neoadjuvant therapy and 14.4%underwent only adjuvant therapy. For two thirds of patients received any ADT (70.5%), duration of treatment was more than 6 months.

Androgen deprivation therapy was received by almost all males underwent radiotherapy without radical prostatectomy (95.8%) and less than half of those underwent radical prostatectomy without radiotherapy (46.8%). For males treated with radiotherapy without radical prostatectomy adjuvant regimen alone was used seldom, vast majority of them (64 males of 72) received either neoadjuvant or both neoadjuvant and adjuvant therapy.

This result is in alignment with strong evidence to support the use of ADT in combination with radiotherapy for men with locally advanced prostate cancer (T3/4 N+/- M0) [18]. Optimal strategy for using of adjuvant ADT in addition to radical prostatectomy for locally advanced disease treatment is not certain, but adjuvant ADT in addition to radical prostatectomy is not recommended by NICE Guidelines [19]. Result of systematic review and meta-analysis of the survival outcomes of first-line treatment options in high-risk prostate cancer showed that ADT improved the cancer-specific survival of radical prostatectomy, but did not influence significantly on 10-years overall survival [21].

Among all patients underwent any ADT, percentage of males underwent radical prostatectomy was a little less than those treated with radiotherapy (47.7% vs. 56.1%). Among patients received adjuvant therapy approximately equal number of patients underwent radical prostatectomy or radiotherapy (51.1% and 54.3%, correspondingly). Among patients received neoadjuvant therapy prior to radical treatment 65.0% of patients were treated with radiotherapy and 37.9% of patients were treated with radical prostatectomy.

Castration (including orchidectomy, usage of LHRH analogs, hexestrol) was carried out in more than half of all patients (56.4%). This treatment was conducted in majority cases for both adjuvant and neoadjuvant regimen. Antiandrogens without castration were used by less than 10% of patients (8.9%). 28.2% of patients received treatment with both castration and antiandrogens and the same number of males underwent only castration. Combination of castrations and antiandrogens were used in about half of patients received either adjuvant or neoadjuvant regimen.

Patients' performance status and its dynamics were assessed with ECOG score at Visit 1 and after 1-year follow-up. At first visit ECOG score 0 or 1 was reported for 93.6% of patients, and ECOG score 2 and 3 was reported for 6.4% of patients. At the second visit scores 0 and 1 have been reported for 87.6% of males, and score 2 was registered for 6.9% of patients. Changes in performance status within 1 year were assessed in subgroups of patients by performance of ADT, type of radical treatment, duration of ADT and types of treatment combinations, but there was no significant difference revealed between any subgroups for ECOG status dynamic.

Data on PSA levels after radical treatment and after one year of observation were available for 48 and 169 patients, respectively. Median PSA levels after radical treatment were higher in patients after RT without RP than in those underwent RP without PR: 1.9 vs. 0.1 ng/ml. Similar situation was observed for those received any ADT: median PSA levels were 2.0 ng/ml in patients after RT without RP and 0.2 ng/ml in those underwent RP without PR. After one year there was no notable difference between subgroups of patients, median PSA level

was 0.1 ng/ml for all patients with available assessments. Median PSA levels did not exceed 0.7 ng/ml in any subgroup.

Half of patients (50.5%, [95%CI: 43.2%; 57.9%]), for whom at least two PSA measurements at baseline and after 1 year were available, showed doubling of PSA level after 1 year. Similar situation was observed in subgroups by ADT presence, ADT duration and ADT type: approximately half of males in each subgroups, for whom at least two PSA measurements were available, had two times PSA increasing. Proportion of patients with PSA doubling after one year was greater among males underwent radical prostatectomy without radiotherapy than in group after radiotherapy without radical prostatectomy: 57.5% (CI95%: 47.9%; 66.8%,) vs. 40.0% (CI95%: 28.5%;52.4%), correspondingly. This tendency was present in all subgroups. But at the same time initial PSA levels after radical treatment were higher in group after radiotherapy than radical prostatectomy.

Disease progression was observed in 8.4% (16 males) of patients with conducted assessment. In most cases biochemical progression was observed without signs of clinical progression. Clinical progression was noted in 4 patients. There were no cases of death due to prostate cancer progression.

Percentage of patients with prostate cancer progression was 9.3% for males after radical prostatectomy without radiotherapy and 7.4% for those underwent radiotherapy without radical prostatectomy.

Percentage of patients showed cancer progression or dead was higher in those received ADT in both subgroups by radical treatment type, although numbers of subjects in groups were small. In patients with radical prostatectomy without any radiotherapy and received ADT percentage of males with progression or death was 13.8% (CI95%: 6.1%;25.4%) among those received ADT and 6.1% (CI95%: 1.7%;14.8%) among those did not receive ADT. In subgroup of patients underwent radiotherapy without radical prostatectomy and received ADT percentage of such patients was 10.1% (CI95%: 4.2%;19.8%) and there were no cases among those did not receive ADT.

Patients with locally advanced prostate cancer have 10-year cancer specific survival of over 87% and an overall survival of 65% [22], thereby observational period of 1 year is not enough to obtain sufficient number of cases of progression and for progression-free survival analysis.

As it was shown in meta-analysis [20], neoadjuvant and adjuvant therapy prior to prostatectomy did not improve overall survival, although other clinical benefits were observed for such treatment regimens like significant reduction in the positive surgical margin rate, improvement in lymph node involvement, pathological staging, clinical and biochemical disease-free survival. Adjuvant therapy following radiotherapy resulted in a significant overall survival at 5 and 10 years and disease-free survival at 5 years.

Disease progression or death was observed more frequent in patients received ADT more than 6 months, although groups were small. It is anticipated, because disease duration in this subgroup was longer than among males received ADT within more short period. In subgroups

by radical treatment disease progression or death among males received ADT more than 6 months was observed in 18.2% of patients with RP without RT and in 10.7% of patients with RT without RP.

Analysis of time to disease progression conducted for subgroups of patients by radical treatment regimen (radical prostatectomy without any radiotherapy vs. radiotherapy without radical prostatectomy), ADT presence (any ADT vs. no ADT), ADT duration (6 months and less vs. more than 6 months) and ADT type (castration and antiandrogens vs. castration only) did not reveal significant difference in time to disease progression between subgroups.

8.2 Conclusion

The study was conducted to obtain information on current clinical practices in usage of antiandrogen deprivation therapy in patients with locally advanced prostate cancer. Objectives of the study were achieved. Data on prostate cancer diagnostics, radical treatment, androgen deprivation therapy, patients performance status, PSA levels dynamics, cancer progression were obtained.

Data on clinical management strategy in Russia for locally advanced prostate cancer were obtained. Among males participated in the study, more than half were treated surgically, and other underwent radiotherapy. Androgen deprivation therapy was carried out for 65.3% of patients. Androgen deprivation therapy was received by almost all males underwent radiotherapy without radical prostatectomy and less than half of those underwent radical prostatectomy without radiotherapy. Castration (including orchidectomy, usage of LHRH analogs, hexestrol) was carried out in more than half of all patients. Antiandrogens without castration were used by less than 10% of patients. 28.2% of patients received treatment with both castration and antiandrogens and the same number of males underwent only castration.

The results are in alignment with international guidelines and standards and with data of studies conducted in other contries. Received data can help to improve management approaches for treatment of Russian patients with high risk locally advanced prostate cancer.

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10. APPENDICES

APPENDIX 1 Protocol and Protocol Amendments

APPENDIX 2 Case Report Form

APPENDIX 3 Patient Information Sheet and Informed Consent Form

APPENDIX 4 Ethical approvals of the study and protocol amendments by Independent Ethical Commetee

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APPENDIX 6 Statistical analysis plan

APPENDIX 7 Statistical Tables

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APPENDIX 9 Statistical Listings