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Second-line hormonal therapy with the enzalutamid in patients with castrate-resistant prostate cancer

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Prostate cancer (PC) is an actual problem of modern oncourology due to the continuing high rates of this disease morbidity and mortality. Despite improvements in diagnostic techniques, incidence of common forms of the disease remain to be high. Metastatic castrate-resistant prostate cancer (mCRPC) is a disease with an extremely poor prognosis, in which standard methods of hormonal treatment are ineffective. Heterogeneity of CRPC patient population requires differentiated approach to the administration of therapy based on the availability of various prognostic factors. Not so long ago chemotherapy with docetaxel was the main treatment for this group of patients. Second-line hormonal therapy was introduced into clinical practice in 2011 with the advent of new drugs aimed at the complete suppression of testosterone production. Enzalutamid, a new drug for second-line hormonal therapy, has essentially different mechanism of action. It is able to block androgen receptors selectively and disrupt translocation of the signal from the receptor into the cell and into the cell nucleus. Large randomized trials that studied the effectiveness of this drug allowed to register it for clinical use, including our country. An article presents a review of the literature on clinical trials devoted to the use of a drug in CRPC patients.

Key words: *castrate-resistant prostate cancer, second-line hormonal therapy, selective androgen receptor blocker, mechanism of action, androgen receptor signaling pathway inhibitor, affinity, nuclear signal translocation, xtandi, enzalutamid*

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Worldwide, prostate cancer (PC) is a pressing problem in cancer urology because of high morbidity and mortality rates. Annually, more than 1.1 million new cases of the disease are diagnosed. In Russia, PC is the 2nd most common malignant tumor in the structure of male morbidity: it comprises 14.3 % of all tumors [1]. In 2014 in Russia, 37,168 new cases of PC were registered, mean age of men with newly diagnosed PC was 64.4 years. Standardized morbidity rate for PC in Russia in 2014 per 100,000 people was 39.38. With mean yearly increment of 7.11 %, from 2004 to 2014 morbidity grew by 116.68 %. In 2014, compared to 2004, standardized mortality rate decreased (– 12.3 %) for all malignant tumors except PC, which increased. Per 2014 data, the increase was 26.2 %. In men aged 60–69, PC is the cause of death in 6.2 % cases; and in the above 70 age group, PC is the cause of death in 14.16 % cases, which makes it the 2nd most common cause after tumors of the trachea, bronchi, and lung [1]. Therefore, currently PC is one of the most pressing problems in oncology.

PC is a relatively slowly progressing and extremely heterogenous disease. From the moment of clinically insignificant PC appearance to disease symptoms, 15–20 years can pass. At the early stages the process is asymptomatic. As a result, patients seek medical help too late when radical treatment is impossible [2]. The main therapy method for disseminated PC is hormone therapy (HT). By blocking androgens, stabilization of disease can be achieved in more than 90 % of patients [3], but mean time to progression after HT in patients with metastatic PC is about 24 months [4]. Patients with tumor progression and stable castration testosterone level transfer to the stage of castration-resistant PC (CRPC). Additionally, in some patients (up to 20 %) the tumor is initially resistant to hormone exposure [5, 6].

Since 2004, the «golden standard» of CRPC therapy is cytostatic chemotherapy [7, 8]. Docetaxel was the first drug demonstrating increased overall survival in patients with CRPC [8]. In patients with CRPC, a next generation taxane – cabazitaxel – was implemented in clinical practice as the 2nd line drug therapy for disease progression after docetaxel therapy. The TROPIC large randomized trial has demonstrated effectiveness of the 2nd line therapy with cabazitaxel, and the drug was approved for use in patients with CRPC, including in Russia [9].

A deeper understanding of the pathogenetic mechanisms underlying castration resistance allowed to develop a number of new approaches to treatment of this patient group. Adaptation of the tumor cells to low testosterone level through hyperexpression of androgen receptors (AR), as well as other mechanisms, can serve as a convincing proof of their continued dependence on androgens. This fact suggests a necessity of continued androgen-deprivation therapy aimed at decreasing testosterone level in patients with CRPC. Moreover, development of new drugs blocking intracellular androgen production and inhibiting the signaling pathway from ARs in the tumor cells is a promising direction.

One of the first hormone drugs of the 2nd line therapy was abiraterone acetate, which showed effectiveness in a phase III study both in patients with previous docetaxel therapy and patients who never received docetaxel [10,

11]. Abiraterone is a drug inhibiting the CYP17 enzyme, one of coenzymes of cytochrome P450. This enzyme plays a crucial role in testosterone biosynthesis from extra-gonadal androgens and cholesterol in the adrenal gland, testes, and other organs and tissues. The mechanism of action of abiraterone is based on suppression of testosterone synthesis in patients with CRPC by selective inhibition of the CYP17A1 enzyme in the testes, adrenal glands, and prostate tissues. Blocking of the CYP17 coenzymes, in particular 17,20-lyase, leads to suppression of testosterone production from its precursors on all levels. Abiraterone doesn»t affect activity of enzymes taking part in production of aldosterone from cholesterol, therefore in response to suppressed testosterone synthesis, mineralocorticoid activity increases due to increased aldosterone production from its common with testosterone precursors, such as pregnenolone and progesterone (Fig. 1). Decreased blood cortisol and testosterone levels cause stimulation of adrenocorticotropic hormone production by the hypothalamus, which induces a so-called vicious circle of increased aldosterone production [12]. This leads to side effects of abiraterone therapy including arterial hypertension, hypokalemia, and liquid retention. This makes constant blood pressure and blood chemistry monitoring a necessity. Moreover, to decrease side effects during therapy, patients are recommended to take additional prednisolone which, in turn, also has some unfavorable side effects, especially if taken long-term. All these circumstances create some complications during abiraterone acetate therapy, even though generally its side effects aren»t severe.

A new superselective AR blocker, enzalutamide, is also a 2nd line HT drug. This drug was registered in the Russian Federation in May of 2016. The drug has a different mechanism of action compared to abiraterone: It doesn»t affect activity of the cytochrome P450 coenzymes and selectively blocks AR due to much higher affinity to the ligand-binding domain of the receptor. Furthermore, enzalutamide not only competitively binds ARs which leads to its competitive antagonistic inhibition, but also disrupts translocation, i. e. signal transduction from the receptor into the cell and nucleus, by irreversibly changing conformation of the receptor. The mechanism of action of enzalutamide is presented in Fig. 2. The drug doesn»t affect cytochrome P450 activity, therefore its use doesn»t cause side effects associated with increased mineralocorticoid activity such as hypokalemia, hypertension, and liquid retention. This renders monitoring of blood potassium and arterial pressure, as well as concomitant administration of prednisolone, unnecessary. Another advantage of enzalutamide is that it isn»t necessary to take it on an empty stomach, so it can be taken with food [13].

Experimental studies have shown that resistance to the first-generation AR antagonists, such as bicalutamide and flutamide, is associated with agonistic qualities in cells expressing higher levels of ARs but only if ARs contain a functional ligand-binding domain [14, 15]. Development of enzalutamide started from creation of a library of molecules using a non-steroid agonist RU59063 as a starting chemical matrix due to its relatively high affinity and selectivity to AR compared to other nuclear hormone receptors [13, 16–17]. Then selected structures and their activities were studied in a set of analogous molecules using expression of prostate-specific antigen (PSA) as a measured value. Two different human PC cell lines were used: normal (hormone-sensitive) cell line LNCaP and castration-resistant cell line LNCaR which was developed for expression of 3 and 5 times higher levels of wild type AR. MDV3100, which subsequently was named enzalutamide, is a derivative of phenylthiohydantoin with a sulfonamide side chain. Enzalutamide was selected because of its strong inhibition of the AR signaling pathway and favorable pharmacokinetic characteristics [18].

Enzalutamide blocks ARs in the LNCaP/AR cells with 5–8 times higher affinity than bicalutamide and 2–3 times lower affinity than 16β-fluoro-5α-dihydrotestosterone, a testosterone derivative. Treatment with enzalutamide doesn»t induce expression of phosphoserine aminotransferase 1, serine, and transmembrane protease 2 (TMPS2), which suggests that the drug doesn»t have antagonistic qualities in conditions of castration resistance [13]. Unlike enzalutamide, bicalutamide doesn»t prevent binding between AR and DNA, but activates accumulation of corepressors, such as NCoR and SMRT, in the promotor regions of AR target genes [19, 20]. One of the mechanisms of enzalutamide»s inhibition of the AR signaling pathway is inhibition of AR translocation into the nucleus which prevents binding between AR and DNA [13]. This allows enzalutamide to maintain effectiveness of the AR signaling pathway inhibition even if the receptor is overexpressed.

In a prospective phase II study evaluating expression of molecular components of the AR signaling pathway activation in patients with CRPC receiving enzalutamide, localization of ARs had a shift from nuclear to cytoplasmic after 8 weeks of treatment, and concentration of testosterone in the bone marrow and blood increased, which suggested a physiological feedback loop. This proved that therapeutic benefits of enzalutamide can be explained by AR inhibition associated with transfer of nuclear ARs into the cytoplasm [21].

Preclinical studies have shown that in a mouse model of CRPC xenotransplant, enzalutamide decreased tumor size [22]. Based on high affinity to ARs, absence of agonistic action, and these promising preclinical results, enzalutamide was selected by the Association for PC Clinical Research for clinical development. This trial of the 1st use of the drug in humans (NCT00510718) was initially designed as a phase I study of safety and tolerability, as well as for calculation of the maximum tolerated dose [23]. After observed PSA response during a smaller dose administration, the study was changed and expanded to a phase I/II

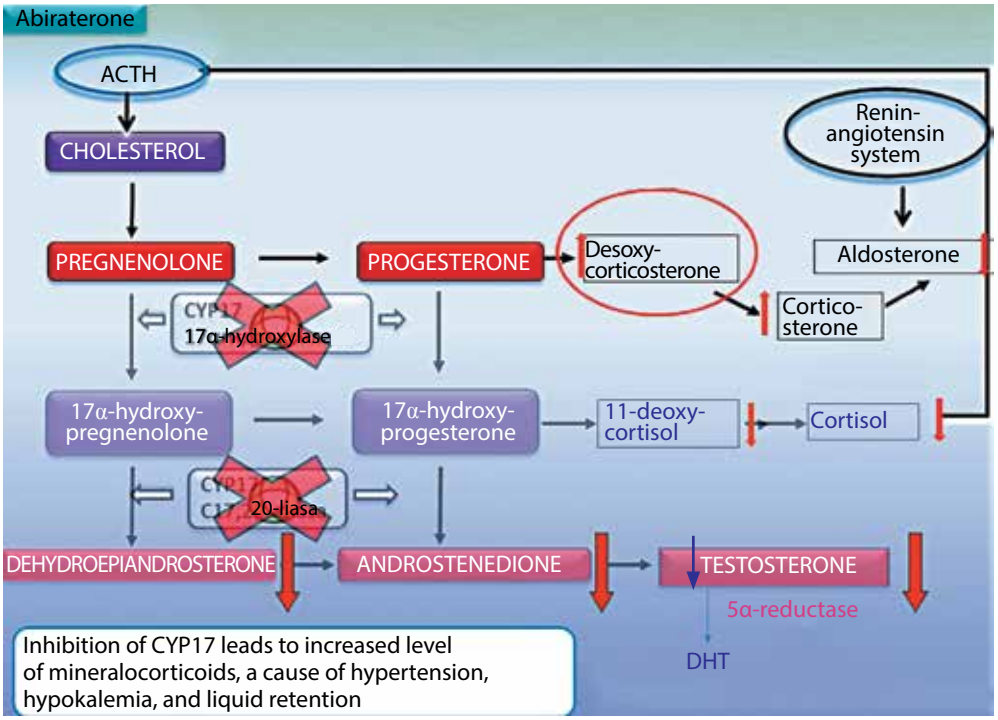

Fig. 1. *Testosterone biosynthesis and abiraterone mechanism of action. ACTH – adrenocorticotropic hormone*

trial to perform a more reliable evaluation of treatment effectiveness [24]. The following parameters were also studied: pharmacokinetics, antitumor activity including effect on the PSA level, circulating tumor cells, metastases into soft tissue and bones, and effect on capture of 2- [18F] -fluoro-5α-deoxyD-glucose (FDG) during positron emission tomography in selected patients [25]. Seven dose variants were evaluated (20, 60, 150, 240, 360, 480, and 600 mg/day). The study included CRPC patients who didn»t receive previous docetaxel therapy, and patients after docetaxel therapy, with histologically confirmed adenocarcinoma of the prostate, and castration level of testosterone < 50 ng/dl. The appropriate dose was selected based on several factors including pharmacokinetics, effectiveness, and safety. Enzalutamide at all doses caused significant changes in FDG binding, and the maximum effect was achieved at plasma concentrations of 5–15 μg/ml. This suggests that this is the concentration at which AR binding to enzalutamide is saturated [25]. Saturation plasma concentrations were consistently achieved in patients receiving the drug at 150 mg/day dose, but not in patients receiving lower doses. There weren»t any significant differences in antitumor effect for 150 and 240 mg/day doses, but grade III fatigue was reported in 10 % of patients receiving 240 mg/day, compared to only 2 % of patients receiving 150 mg/day. In 3 (1 patient in dose groups 360, 480, and 600 mg/day) patients, seizures were reported, though in the lower dose groups no seizures were observed. Therefore, since at higher doses it was often necessary to cancel the treatment, 240 mg/day dose was stated as the maximum tolerable dose. Hard gelatin capsules containing 30 mg of the drug were replaced by soft gelatin capsules containing 40 mg of enzalutamide to decrease the number of capsules necessary to ingest the required dose; therefore, phase III studies used 160 mg/day dose instead of 150 mg/day [26]. Determination of metabolite profile using liquid chromatography – mass spectrometry of residual patient samples after the phase I/II study has shown 2 overabundant metabolites: N-desmethyl metabolite and carbonic acid. Several months after this discovery, the liquid chromatography – mass spectrometry method was validated for simultaneous measurement of human plasma concentrations of enzalutamide and its two excessive metabolites. This served as an important instrument for enzalutamide dose and schedule optimization in different pathological conditions and for its combination with other drugs [27].

The TERRAIN phase II study comparing enzalutamide and bicalutamide clinical effectiveness in patients with metastatic CRPC included 375 patients randomized 1:1 for 50 mg/day bicalutamide and 160 mg/day enzalutamide therapies with continued castration therapy [28]. The primary endpoint was progression-free survival. Safety parameters were analyzed in all patients who received at least 1 dose of the studied drugs. Enzalutamide was administered to 184 patients, bicalutamide – to 191 patients. The treatment was canceled primarily due to disease progression in 126 (68 %) and 168 (88 %) patients, respectively. Median follow up period was 20.0 (15.0–26.6) months in the enzalutamide group and 16.7 (10.2–21.9) months in the bicalutamide group. In patients receiving enzalu-

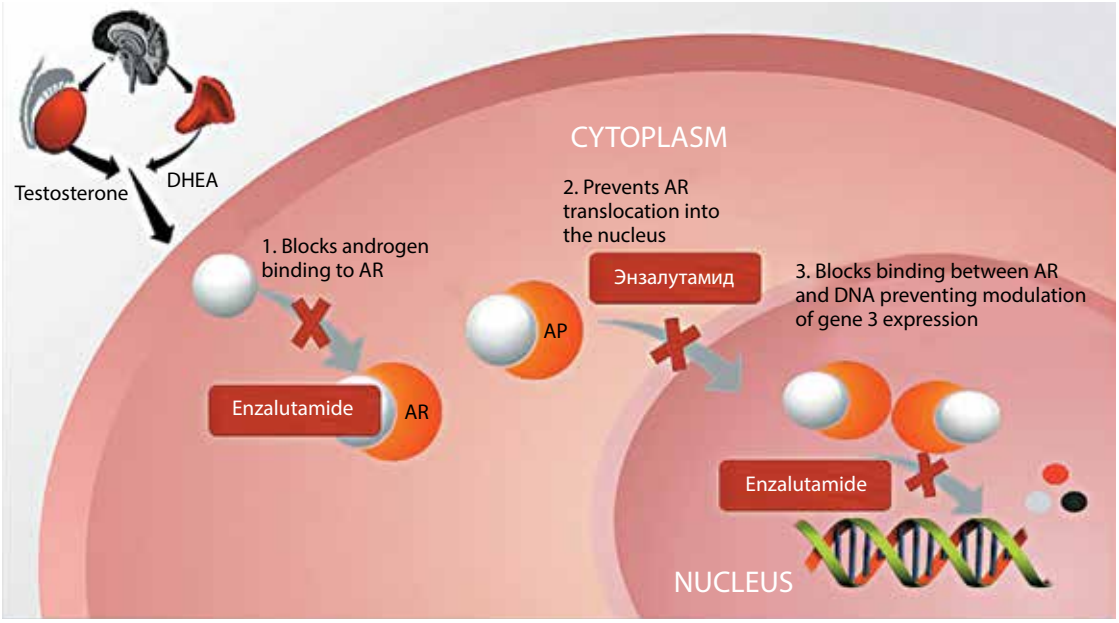

Fig. 2. *Mechanism of action of enzalutamide, a superselective inhibitor of the androgen receptor*

tamide, a significant increase in median progression-free survival was observed (15.7 months (95 % confidence interval (CI) 11.5–19.4)) compared to patients in the bicalutamide group (5.8 months (risk ratio (RR) 0.44; 95 % CI 0.34–0.57; $p < 0.0001$)), as shown in Figures 3 and 4.

The most frequent adverse events in the enzalutamide group were fatigue (51 (28 %) of 183 patients in the enzalutamide group compared to 38 (20 %) of 189 patients in the bicalutamide group), back pain (35 (19 %) and 34 (18 %) patients, respectively), and hyperemia (27 (15 %) and 21 (11 %), respectively). Events that were more common during the bicalutamide treatment were nausea (26 (14 %) and 33 (17 %) patients, respectively), constipation (23 (13 %) and 25 (13 %), respectively), and arthralgia (18 (10 %) and 30 (16 %), respectively). The most common grade III and higher adverse events in the enzalutamide and bicalutamide groups were, respectively, arterial hypertension (13 (7 %) and 8 (4 %) patients), hydronephrosis (3 (2 %) and 7 (4 %)), and back pain (5 (3 %) and 3 (2 %)). Severe adverse effects were reported in 57 (31 %) of 183 patients in the enzalutamide group and in 44 (23 %) of 189 patients in the bicalutamide group.

Therefore, the TERRAIN study demonstrated indisputable advantage of enzalutamide compared to bicalutamide in patients with metastatic CRPC and without symptoms or with minimal disease symptoms.

Clinical effectiveness and safety of enzalutamide in patients with CRPC were demonstrated in 2 randomized phase III clinical studies [26, 29]. The AFFIRM phase III clinical study included 1199 patients with CRPC who had previously received docetaxel therapy. They were randomized 2:1 for enzalutamide 160 mg/day ($n = 800$) or placebo ($n = 399$) [26]. Concomitant steroid treatment was allowed but wasn»t necessary. Additionally, evaluation of response rate of soft tissue lesions, functional evaluation of antitumor therapy per the FACT-P questionnaire were performed, number of circulating cells was measured, and detailed electrocardiographic examination was performed. After the planned intermediate analysis after 520 deaths, which showed statistically significant advantage of enzalutamide compared to placebo, an independent committee for data and safety monitoring recommended to stop the trial and offer enzalutamide to the patients receiving placebo. At the time of the intermediate analysis, a significant advantage of enzalutamide was demonstrated in the form of a decrease in risk of death by 37 % compared to placebo (RR 0.63; 95 % CI 0.53–0.75; $p < 0.001$, median overall survival 18.4 and 13.6 months, respectively). This effect was observed in all analyzed patient subgroups. Enzalutamide was associated with a significant improvement of all secondary endpoints compared to placebo including radiological progression-free survival, PSA relapse-free survival, response rate in respect to PSA and soft tissues [26]. Patients» quality of life associated with pain syndrome, bone complications, and general well-being was also significantly higher in the enzalutamide patient group [26, 30]. The AFFIRM study results are presented in Table 1.

A secondary analysis confirmed benefits of enzalutamide in respect to overall, relapse-free survival, as well as radiological survival, compared to placebo in older (> 75 years) and younger (< 75 years) patients [31] and in patients from various risk groups stratified per baseline PSA level [32].

The PREVAIL phase III study included 1717 patients with CRPC who previously didn»t receive docetaxel; patients were also randomized 1:1 for enzalutamide 160 mg/day and placebo [29]. In 12 % of patients included in the protocol,

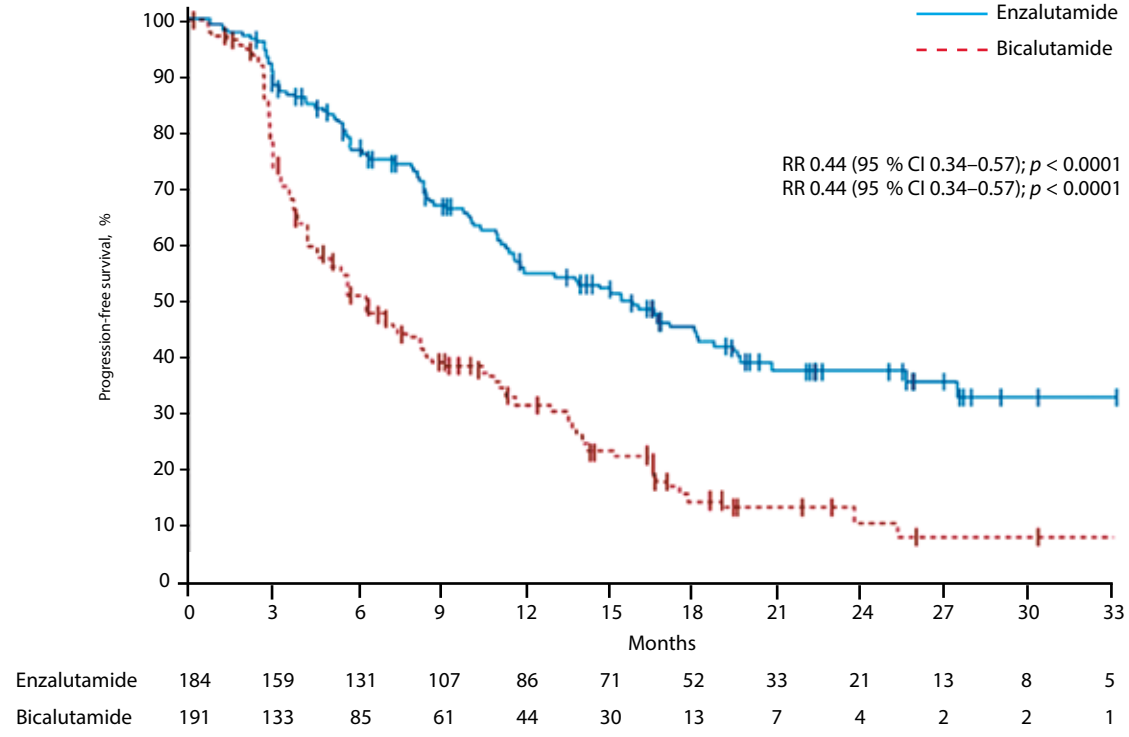

Fig. 3. *Survival without progression in patients receiving enzalutamide and bicalutamide*

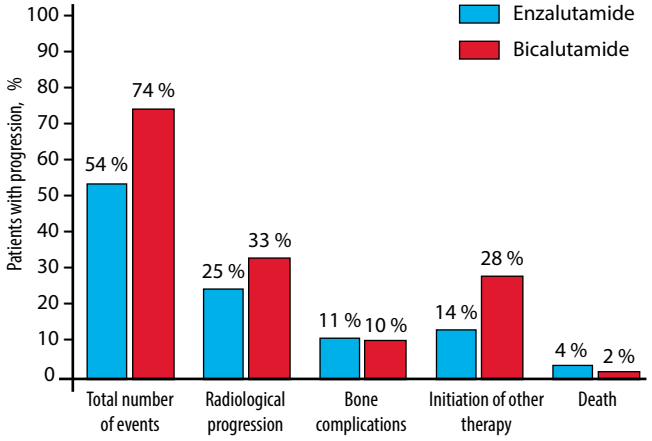

Fig. 4. *Treatment outcomes in patient subgroups receiving enzalutamide and bicalutamide*

visceral metastases were detected. At the time of the planned intermediate analysis (at 540 deaths), in the enzalutamide group a significant decrease of radiological progression risk was observed compared to placebo (RR 0.19; 95 % CI 0.15–0.23; $p < 0.001$), as well as a decrease in risk of death by 29 % (RR 0.71; 95 % CI 0.60–0.84; $p < 0.001$). Advantages of enzalutamide were observed in all patient subgroups including subgroups stratified by age, baseline pain intensity, number of bone lesions, and other prognostic factors. Furthermore, enzalutamide therapy was associated with increased time to initiation of chemotherapy (RR 0.35; 95 % CI 0.3–0.4) and time to PSA progression (RR 0.17; 95 % CI 0.15–0.20). Decreased PSA level, objective soft tissue response, and better quality of life were also observed in the enzalutamide group [29]. Summary results of the PREVAIL study are presented in Table 2.

In the PREVAIL study, enzalutamide demonstrated a mostly favorable tolerance profile. Side effects included fatigue (36 % in the enzalutamide group and 26 % in the placebo group), back pain (27 and 22 %, respectively), constipation (22 and 17 %, respectively), and arthralgia (20 and 16 %, respectively). Adverse events in respect to the cardiovascular system were observed in 10 % of patients receiving enzalutamide, and in 8 % of patients receiving placebo. Arterial hypertension was significantly more common in the enzalutamide group compared to the placebo group (13 % compared to 4 %).

Therefore, possibilities of treatment of patients with CRPC lately were significantly widened due to a better understanding of the mechanisms underlying development of castration resistance and introduction of innovative drugs into clinical practice aimed at selective inhibition of the ligand-dependent AR activation pathway. This new era of CRPC treatment is partially due to enzalutamide»s success. This powerful AR inhibitor was developed based on our knowledge of underlying biology and resistance to standard treatment. Enzalutamide promoted radical changes in therapeutic approach to CRPC patients by presenting a safe oral alternative to other drugs which not only improves overall survival, but also significantly postpones chemotherapy and improves patients» quality of life.

Table 1. *Summary results of the AFFIRM study*

Конечная точка	Enzalutamide (*n* = 800)	Placebo (*n* = 399)	Risk ratio (95 % confidence interval)	*p*
Median overall survival, months	18.4	13.6	0.63 (0.53–0.75)	< 0.001
Radiological progression-free survival, months	8.3	2.9	0.49 (0.35–0.47)	< 0.001
PSA level decrease > 50 % of baseline	395/731 (54)	5/330 (2)	–	< 0.001
Prostate specific antigen level decrease > 90 % of baseline	181/731 (25)	3/330 (1)	–	< 0.001
Patients with measurable lesions, *n* (%)	446 (56)	208 (52)	–	–
Complete/partial objective response, %	129/446 (29)	8/208 (4)	–	< 0.001
Median time to PSA progression, months	8.3	3.0	0.25 (0.2–0.3)	< 0.001
Median time to first bone complication, months	16.7	13.3	0.69 (0.57–0.84)	< 0.001
Response in respect to quality of life, *n/N* (%)	281/651 (43)	47/257 (18)	–	< 0.001

PSA – prostate-specific antigen

Table 2. *Summary results of the PREVAIL study*

Endpoint	Enzalutamide (*n* = 872)	Placebo (*n* = 845)	Risk ratio (95 % confidence interval)	*p*
Median overall survival, months	32.4	30.2	0.71 (0.60–0.84)	< 0.001
Radiological progression-free survival, months	Не достигнута	3.9	0.19 (0.15–0.23)	< 0.001
Median time to chemotherapy, months	28.0	10.8	0.35 (0.30-0.40)	< 0.001
PSA level decrease > 50 % of baseline	666/854 (78)	27/777 (3)	–	< 0.001
Prostate specific antigen level decrease > 90 % of baseline	400/854 (47)	9/777 (1)	–	< 0.001
Patients with measurable lesions, n/N (%)	396 (45)	381 (45)	–	–
Complete/partial objective response, %	223/396 (59)	19/381 (5)	–	< 0.001
Median time to PSA progression, months	11.2	2.8	0.17 (0.15–0.20)	< 0.001
Median time to first bone complication, months	31.1	31.3	0.72 (0.61–0.84)	< 0.001
Response in respect to quality of life, n/N (%)	328/827 (40)	181/790 (23)	–	< 0.0001

REFERENCES

1. Malignant tumors in Russia in 2014 (morbidity and fatality). Ed. by: A.D. Kaprin, V.V. Starinskiy, G.V. Petrova. Moscow, 2016. (In Russ.).
2. Matevev V.B. The role of hormone therapy at patients with local and locally spread prostate cancer, using the definitive therapy. Onkourologiya = Oncourology 2005;(2):54–7. (In Russ.).
3. Garnick M.B. Prostate cancer: screening, diagnosis, and management. Ann Intern Med 1993;118:804–18.
4. Per-Anders A. Revolutions in the management of hormone-refractory prostate cancer. Eur Urol 2003;2:1–2.
5. EAU Guidelines 2016.
6. Matveev V.B., Babaev E.R. Survival forecast factors of patients with spread prostate cancer, receiving hormone therapy. Onkourologiya = Oncourology 2011; (2):78–83. (In Russ.)].
7. Oh W. Chemotherapy for patients with advanced prostate carcinoma: a new option for therapy. Cancer 2000;88:3015–21.
8. Tannock I.F., de Wit R., Berry W.R. et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502–12.
9. de Bono J.S., Oudard S., Ozguroglu M. et al; Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147–54. DOI: 10.1016/S0140-6736(10)61389-X.
10. de Bono J.S., Logothetis C.J., Molina A. et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995–2005. DOI: 10.1056/NEJMoa1014618.
11. Ryan C.J., Smith M.R., de Bono J.S. et al. Abiraterone in metastatic prostate

cancer without previous chemotherapy. N Engl J Med 2013;368(2):138–48. DOI: 10.1056/NEJMoa1209096.
12. Attard G., Belldegrun A.S., de Bono J.S. Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer. BJU Int 2005;96(9):1241–6.
13. Tran, C., Ouk S., Clegg N.J. et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009;324: 787–90.
14. Chen C.D., Welsbie D.S., Tran C. et al. Molecular determinants of resistance to anti-androgen therapy. Nat Med 2004;10:33–9.
15. Kelly W.K., Slovin S., Scher H.I. Steroid hormone withdrawal syndromes. Pathophysiology and clinical significance. Urol Clin North Am 1997;24:421–31.
16. Teutsch G., Goubet F., Battmann T. et al. Nonsteroidal antiandrogens: synthesis and biological profile of high-affinity ligands for the androgen receptor. J. Steroid Biochem. Mol Biol 1994;48:111–9.
17. Van Dort M.E., Robins D.M., Wayburn B. Design, synthesis, and pharmacological characterization of 4-[4, 4-dimethyl-3-(4-hydroxybutyl) – 5-oxo-2-thioxo-1- imidazolidinyl] – 2-iodobenzonitrile as a high-affinity nonsteroidal androgen receptor ligand. J Med Chem 2000;43:3344–7.
18. Jung M.E., Ouk S., Yoo D. et al. Structure-activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC). J Med Chem 2010;53:2779–96. DOI: 10.1021/jm901488g.
19. Hodgson M.C., Astapova I., Cheng S. et al. The androgen receptor recruits nuclear receptor CoRepressor (N-CoR) in the presence of mifepristone via its N and C termini revealing a novel molecular mechanism for androgen receptor antagonists. J Biol Chem 2005;280:6511–9.
20. Baek S.H., Ohgi K.A., Nelson C.A. et al. Ligand- specific allosteric regulation of coactivator functions of androgen receptor in prostate cancer cells. Proc Natl Acad Sci USA 2006;103:3100–5.
21. Efstathiou E., Titus M., Wen S. et al. Molecular characterization of enzalutamide-treated bone metastatic castration-resistant prostate cancer. Eur Urol 2015;67:53–60. DOI: 10.1016/j.eururo.2014.05.005.
22. Guerrero J., Alfaro I.E., Gomez F. et al. Enzalutamide, an androgen receptor signaling inhibitor, induces tumor regression in a mouse model of castration-resistant prostate cancer. Prostate 2013;73:1291–305. DOI: 10.1002/pros.22674.
23. Morris M.J., Basch E.M., Wilding G. et al. Department of Defense prostate cancer clinical trials consortium: a new instrument for prostate cancer clinical research. Clin Genitourin Cancer 2009;7:51–7. DOI: 10.3816/CGC.2009.n.009.
24. Bambury R.M., Scher H.I. Enzalutamide: Development from bench to bedside. Urol Oncol 2015;33:280–8. DOI: 10.1016/j.urolonc.2014.12.017.
25. Scher H.I., Beer T.M., Higano C.S. et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. Lancet 2010;375:1437–46. DOI: 10.1016/S0140-6736(10)60172-9.
26. Scher H.I., Fizazi K., Saad F. et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
27. Bennett D., Gibbons J.A., Mol R. et al. Validation of a method for quantifying enzalutamide and its major metabolites in human plasma by LC–MS/MS. Bioanalysis 2014;6:737–44. DOI: 10.4155/bio.13.325.
28. Shore N.D., Chowdhury S., Villers A. et al. Effcacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomized, double-blind, phase 2 study. Lancet Oncol 2016;13:2016. DOI: 10.1016/S1470-2045(15)00518-5.
29. Beer T.M., Armstrong A.J., Rathkopf D.E. et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33. DOI: 10.1056/NEJMoa1405095.
30. Fizazi K., Scher H.I., Miller K. et al. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration- resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol 2014;15:1147–56. DOI: 10.1016/S1470-2045(14)70303-1.
31. Sternberg C.N., de Bono J.S., Chi K.N. et al. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. Ann Oncol 2014;25:429–34. DOI: 10.1093/annonc/mdt571.
32. Saad F., de Bono J., Shore N. et al. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial. Eur Urol 2014;67:223–30. DOI: 10.1016/j.eururo.2014.08.025.