Relevance: Prostate cancer (PC) is one of the most common malignant neoplasms in the male population. The widespread introduction of modern diagnostic methods and the determination of prostate-specific antigen (PSA) levels have increased the number of detected cases of localized and locally advanced PC forms. However, in some patients treated with radical methods and long-term androgen deprivation therapy (ADT), the disease continues to progress in the form of an increase in PSA levels with castration testosterone values and with no distant metastases. Such a course of the disease is referred to as non-metastatic castration-resistant prostate cancer (nmCRPC).

Purpose: The article reports the results of a meeting of the Expert Council arranged by the Kazakh Research Institute of Oncology and Radiology on December 25, 2020, on non-metastatic castration-resistant prostate cancer diagnostics and treatment.

Results: Large clinical studies highlight the critical importance of controlling the PSA doubling time as the main prognostic factor for an unfavorable outcome to increase patient survival and prevent the development of distant metastases.

Based on the results of large randomized studies, experts recommended using new-generation androgen receptor antagonists in combination with ongoing ADT to improve the clinical outcomes in nmCRPC patients at high risk of metastatic progression. The Expert Council was presented with the data of a registration clinical study on darolutamide efficacy and safety. The advantages of introducing this drug into clinical practice to expand the choice of therapeutic options were identified. Personalized adjustment of a treatment regimen will increase the treatment efficacy and ensure higher survival in this category of patients.

Conclusion: Increasing survival as the main objective in treating nmCRPC patients requires improved diagnostics through regular controlling of testosterone and PSA levels, calculation of PSA doubling time, and the use of radiological diagnostic methods to rule out distant metastases. The choice of therapy in patients at high risk of metastasis shall consider the patient’s status and the treatment efficacy and safety balance.

Keywords: non-metastatic castration-resistant prostate cancer (nmCRPC), selective androgen receptor blocker, combination therapy, darolutamide.

Introduction: Malignant neoplasms are leading in the structure of morbidity and mortality in the Republic of Kazakhstan. These figures will continue to grow with increased life expectancy and improved diagnosis of cancer. About 1.3 million new cases of prostate cancer (PCa) were reported worldwide in 2018, with 359,000 deaths. PCa is the second most common and fifth leading cause of death in the global male population [1].

According to the Indicators of the Oncological Service of the Republic of Kazakhstan for 2019 [2], the incidence of malignant neoplasms at the age of 65+ in 2019 was 1105.4 per 100 thousand population (1124.2 in 2018). In that age group, the PCa incidence decreased by 1.7%. However, it still exceeded the national average (174.8) by 6.3 times. In men over 65, PCa was the second most common oncopathology, accounting for 12.5%. PCa patients had one of the lowest 5-year survival rates of all cancers. As of 2019, only 29.9% of PCa patients survived for five years and more [2].

Thus, the diagnosis, prevention, treatment, and rehabilitation of patients with malignant neoplasms remain a public priority for the coming years.

Over time, some patients receiving castration therapy deliver a further progression of the disease in the form of an increase in PSA levels and/or local tumor recurrence without metastatic foci. This disease stage is called non-metastatic castration-resistant prostate cancer (nmCRCA) [3].

nmCRPCA is diagnosed based on the castration testosterone levels (<50 ng/dL or <1.7 nmol/L), biochemical progression (threefold increase in prostate-specific antigen (PSA) levels ≥50% of nadir, >2 ng/ml), absence of metastatic lesion on scintigraphy, and CT scanning [4].

In further progression, patients with nmCRPCA develop metastasis. Despite significant advances in nmCRPCA treatment with chemotherapy and new generation anti-androgens, the median survival of patients at this stage in different prognostic subgroups is 20-35 months [5-7]. Therefore, the increase in metastasis-free survival (MFS) is the main goal in treating patients with nmCRPCA. A longer MFS increases the overall survival (OS), a period before the onset of bone complications, and, consequently, improves the patients’ quality of life [3, 8].

Patients with a prostate-specific antigen doubling time (PSADT) ≤10 months have the highest risk of developing metastatic CRPCA. Leading clinical guidelines recommend treating this patient population with new generation non-steroidal anti-androgens combined with androgen deprivation therapy (ADT). This therapeutic approach statistically and clinically significantly reduces the risk of metastatic CRPCA development [4, 9-10].
Until recently, the two drugs registered in the Republic of Kazakhstan that delivered a significant increase in MFS and OS in patients with nmCRPCA were enzalutamide and apalutamide.

Although the above drugs were actively used in clinical practice with high efficacy and minimal toxicity, the issue of drug therapy with modified safety and toxicity levels and reduced risk of drug-drug interactions remained open [11].

According to preclinical studies, the chemical structure of darolutamide ensures lower and less severe toxicity than apalutamide and enzalutamide due to low blood-brain barrier penetration [12-14] and low-affinity binding to γ-aminobutyric acid type A receptors [11, 15]. Registration of the drug in the world is based on the ARAMIS phase III study results where darolutamide in combination with ADT demonstrates a favorable safety profile and a statistically significant increase in MFS compared to placebo and ADT [16].

**Purpose:** The article reports the results of a meeting of the Expert Council arranged by the Kazakh Research Institute of Oncology and Radiology on December 25, 2020, on non-metastatic castration-resistant prostate cancer diagnostics and treatment.

On December 25, 2020, the Kazakh Institute of Oncology and Radiology (Almaty, Kazakhstan) organized a remote meeting of the Expert Council on treating patients with nmCRPCA and the registration in the Republic of Kazakhstan of a new innovative drug, darolutamide. The Expert Council included:

- **Dilyara Radikovna Kaidarova,** Doctor of Medical Sciences, Academician of the National Academy of Sciences of the Republic of Kazakhstan, Chairman of the Board of JSC “KazIOR” (Almaty)
- **Oksana Vladimirovna Shatkovskaya,** MBA, Director of the Department of Strategic Development and International Relations, JSC “KazIOR” (Almaty)
- **Maria Igorevna Volkova,** Doctor of Medical Sciences, Senior Researcher of the Department of Urology of the FSBE “N.N. Blokhin Russian Cancer Research Center” of the Ministry of Health of Russian Federation (Moscow)
- **Ramil Zufarovich Abdakhmanov,** Candidate of Medical Sciences, Chairman of the Chemotherapy Council of JSC “KazIOR” (Almaty)
- **Dauranbek Tursunkulovich Arybzhano,** Candidate of Medical Sciences, Head of the Department of Chemotherapy and Endovascular Oncology, SOPE on REM “City Cancer Center” (Shymkent)
- **Tatyana Ivanovna Belikhina,** Candidate of Medical Sciences, Deputy Director for Development and Strategic Planning of SOPE on REM “Center for Nuclear Medicine and Oncology” (Semey)
- **Aiman Bulatovna Bulatova,** Head of the Chemotherapy Department of SOPE on REM “Regional Oncology Center” (Petropavlovsk)
- **Zaure Dmitrievna Dushimova,** Candidate of Medical Sciences, Deputy Chairman of the Board of JSC “KazIOR” for Scientific and Strategic Work (Almaty)
- **Anatoly Fedorovich Krasnozhen,** Head of the Dispensary Department of SOPE on REM “Multidisciplinary Hospital No. 3” (Karaganda)
- **Bakytzhan Tolegenovich Ongarbayev,** Head of the Department of Oncourology, JSC “KazIOR” (Almaty)
- **Shukhrat Talgatovich Pazilov,** Head of the Day Hospital of SOPE “Almaty Oncology Center” (Almaty)

**Results:**

During the meeting, the Council addressed the following issues in the treatment of patients with nmCRPCA:

- Most significant factors in the choice of treatment of patients with nmCRPCA;
- The important aspects and criteria to be considered when choosing between the available nmCRPCA treatment options;
- Discussion of darolutamide efficacy and safety in treating patients with nmCRPCA;
- Defining the target groups for treating with darolutamide.

During the discussion, the experts noted an increase in the number of patients with nmCRPCA due to an increased number of patients who received topical treatment followed by ADT for PSA recurrence. The participants also highlighted some difficulties in diagnosing that stage of the tumor process and proposed certain steps to overcome those difficulties. In particular, they mentioned the need for careful monitoring of PSA levels, correct calculation of PSADT, and regular use of standard radiological diagnostic techniques [3].

The speakers emphasized the main factors of unfavorable course of nmCRPCA that can shorten the MSF. These are PSA levels >10 ng/ml at nmCRPCA detection and PSADT <10 months [17].

Due to the registration of a new-generation androgen receptor inhibitor, darolutamide, in the Republic of Kazakhstan, the experts discussed the efficacy and safety results in a randomized, multicentre, double-blind, placebo-controlled phase III trial ARAMIS. This study included 1509 patients randomized to the groups of darolutamide (600 mg 2 times a day) in combination with ADT or placebo with ADT in a 2:1 ratio. MFS was the primary endpoint of the study. The secondary endpoints included OS, time to first symptomatic skeletal complication, time to initiate cytotoxic chemotherapy, time to pain progression, and the safety profile. The ARAMIS trial results showed an increase in MFS in all subgroups of patients taking darolutamide from 18.4 to 40.4 months, regardless of PSADT, baseline PSA level, and Gleason score. The final analysis of the ARAMIS trial data showed a statistically significant benefit of darolutamide with ADT in increasing survival time and reducing the risk of death by 31%. The darolutamide group had a longer time to pain progression (40.3 months vs. 25.4 months). Also, darolutamide provided a significant benefit on other secondary endpoints, including the time to first cytotoxic chemotherapy and the time to first symptomatic skeletal complication. There was a significant benefit of darolutamide in median progression-free survival (36.8 months versus 14.8 months) and the time to PSA progression (33.2 months versus 7.3 months). Darolutamide has also provided an advantage on other research endpoints, such as increasing the time to the first invasive procedure for PCA and the time till the next antitumor therapy [17-18].

The combination of darolutamide with ADT showed a favorable safety profile comparable to that of the placebo.
The most common adverse events in the darolutamide group with an incidence 2% higher than in the placebo group included weakness (16% vs. 11%), limb pain (6% vs. 3%), and rash (3% vs. 1%) [17-18]. During the discussion of the ARAMIS trial results, the participants of the Expert Council noted a high efficacy of darolutamide and a favorable safety profile in treating patients with nmCRPCA with a high risk of metastases.

Assessment of the quality of life in the ARAMIS study, carried out by interviewing patients, showed the preservation of the quality of life of patients on long-term treatment with darolutamide. In most cases, the cessation of therapy was caused by the disease progression (33% in the darolutamide group vs. 36.4% in the placebo group). Other reasons included adverse events (25.4% in the darolutamide group vs. 13.3% in the placebo group). The results indicated that the inclusion of another drug in the treatment regimen did not impair the patients’ quality of life [17-18].

In the ARAMIS trial, more than 98% of patients received concomitant therapy [17-18]. The participants of the Expert Council agreed that darolutamide showed the lowest drug-drug interaction profile in its class, suggesting minimum risks of adverse effects and reduced treatment efficacy due to darolutamide interactions with other drugs.

**Conclusion:**

The participants of the Expert Council hold on December 25, 2020 came to the following conclusions:

- The increase of MFS and OS is the main task in treating patients with nmCRPCA;
- Diagnostics of patients with nmCRPCA should be improved by regular determination of testosterone and PSA levels with PSADT calculation, and the use of radiological diagnostic methods depending on the course of the disease;
- The choice of therapy for patients with nmCRPCA with a high risk of metastasis should consider the patient’s status, balancing efficacy and safety;
- Potential drug-drug interactions should be considered when planning treatment to maximize the treatment efficacy for nmCRPCA with a high risk of metastasis since such patients may receive additional therapy for co-morbidities;
- The inclusion of darolutamide in the treatment standards delivers more treatment options for patients with nmCRPCA and allows a more individualized treatment regimen. This can increase treatment efficacy and ensure a longer time to metastasis, improved survival rate, and quality of life in this population.

**References:**

Резолюция Совета Экспертов на тему: «Новый подход к лекарственной терапии пациентов с неметастатическим кастрационно-резистентным раком предстательной железы»

Актуальность: Рак предстательной железы (РПЖ) является одним из наиболее распространенных злокачественных новообразований в мужской популяции. Повсеместное внедрение современных методов диагностики и определение уровня простатического специфического антигена (ПСА) привело к увеличению числа выявленных случаев локализованных и местно-распространенных форм РПЖ. При этом у ряда больных, после проведенных методов радикального лечения и длительной андроген-депрессивационной терапии (АДТ), отмечается дальнейшее прогрессирование заболевания в виде увеличения уровня ПСА при кастрационных значениях тестостерона с отсутствием отдаленных метастазов. Данное течение заболевания обозначают как неметастатический кастрационно-резистентный рак предстательной железы (nmКРРПЖ), который представляет собой крайне прогрессивное течение заболевания в виде увеличения уровня ПСА при кастрационных значениях тестостерона с отсутствием отдаленных метастазов, что требует строгого контроля за темпом его роста и прогнозирует развитие метастатического прогрессирования заболевания.

Цель: Освещение результатов заседания Совета экспертов, организованного КазНЦИОР, по проблеме диагностики и терапии пациентов с неметастатическим кастрационно-резистентным раком предстательной железы.

Результаты: По данным крупных клинических исследований, для увеличения показателей выживаемости данной популяции больных и предотвращения развития отдаленных метастазов, как основного прогнозистического фактора, ассоциированного с неблагоприятным исходом заболевания.

На основании результатов крупных рандомизированных исследований, проведенных рандомизированной экспертизой КазНЦИОР, неметастазирующий уровень простатического специфического антигена (ПСА) привел к увеличению числа выявленных случаев локализованных и местно-распространенных форм РПЖ. При этом у ряда больных, после проведенных методов радикального лечения и длительной андроген-депрессивационной терапии, отмечается дальнейшее прогрессирование заболевания в виде увеличения уровня ПСА при кастрационных значениях тестостерона с отсутствием отдаленных метастазов. Данное течение заболевания обозначают как неметастатический кастрационно-резистентный рак предстательной железы (nmКРРПЖ), который представляет собой крайне прогрессивное течение заболевания в виде увеличения уровня ПСА при кастрационных значениях тестостерона с отсутствием отдаленных метастазов, что требует строгого контроля за темпом его роста и прогнозирует развитие метастатического прогрессирования заболевания.

Заключение: Основной задачей лечения больных nmКРРПЖ должно стать увеличение показателей выживаемости. Для этого необходимо улучшить диагностику путем регулярного определения уровней ПСА и ПСА с расчетом ВУПСА и применения радиологических методов диагностики для исключения отдаленных метастазов. Выбор терапии у пациентов с высоким риском развития метастазов должен основываться на статусе пациента при соблюдении баланса между эффективностью и безопасностью терапии.

Ключевые слова: неметастатический, кастрационно-резистентный, рак, предстательной железы (nmКРРПЖ), андрогенный рецепторы, сертификация, метастазирование.