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COMPARATIVE ANALYSIS OF APPROACHES IN RENAL CELL CARCINOMA PHARMACOTHERAPY IN DIFFERENT COUNTRIES AND IN UKRAINE

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Renal cell carcinoma (RCC) is one of the most common malignant kidney tumors, characterized by a steady increase in incidence and high mortality worldwide, including in Ukraine, which necessitates timely diagnosis and comprehensive multimodal treatment.

***The aim of the study** was to examine approaches to RCC pharmacotherapy in different countries to further develop measures to improve pharmaceutical care for RCC patients in Ukraine.*

***Materials and methods**. The study was based on scientific publications on RCC pharmacotherapy, international RCC treatment guidelines − National Comprehensive Cancer Network (USA), European Society for Medical Oncology (EU), and American Society of Clinical Oncology (USA) − national RCC treatment protocols, as well as Ukrainian regulatory legal acts governing pharmaceutical care for oncology patients. Content analysis, comparison, information synthesis, and analytical review were used.*

***Results**. International guidelines emphasize personalized therapy, wide use of immunotherapy–targeted therapy combinations, IMDC-based risk stratification, and multidisciplinary patient management. Combinations such as pembrolizumab + axitinib, nivolumab + cabozantinib, and nivolumab + ipilimumab are recommended as first-line therapy for metastatic RCC, while adjuvant pembrolizumab is indicated for patients at high risk of recurrence. The Ukrainian clinical protocol partially aligns with these standards but remains limited in immunotherapy options, risk stratification, adjuvant treatment, and the defined role of clinical pharmacists. Access to innovative medicines is further constrained by high costs and insufficient reimbursement.*

***Conclusions**. Significant differences in approaches to RCC pharmacotherapy between Ukraine and other countries were identified, indicating the need to harmonize national protocols with international guidelines, expand access to innovative therapies, and implement a multidisciplinary approach with pharmacist involvement to improve the effectiveness and accessibility of RCC treatment in Ukraine*

***Keywords**: renal cell carcinoma, pharmacotherapy, immunotherapy, targeted therapy, clinical guidelines, regulatory framework*

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1. Introduction

Timely diagnosis and treatment of renal cell carcinoma (RCC) remain pressing challenges for modern healthcare systems, as it is one of the most common malignant kidney tumors [1–4]. This type of cancer is often diagnosed at advanced stages, significantly complicating treatment and reducing the chances of full recovery for patients [4–6].

Within the overall cancer incidence structure among the European population, RCC ranks eighth, accounting for approximately 3.3% of all malignant tumors [1]. Over the past two decades, there has been a steady upward trend in RCC incidence, with an average annual increase of about 2% both in European countries and globally [3–5]. According to GLOBOCAN 2022–2023 data, nearly 431,000 new cases of kidney cancer were registered worldwide, with annual mortality reaching 179,000 [7]. Notably, recent years have seen a rise in RCC incidence among individuals aged over 60 [7].

According to the National Cancer Institute of the Ministry of Health of Ukraine [8], recent years have seen an increase in the proportion of incidentally diagnosed asymptomatic RCC cases in Ukraine, attributed to expanded access to imaging diagnostic methods, particularly ultrasound and computed tomography. For instance, in 1997, the incidence rate among men was 10.1 per 100,000 population, rising to 12.1 per 100,000 in 2020 [8]. Among women, this figure increased from 6.2 to 7.7 per 100,000 over the same period [5]. Mortality rates among men have remained nearly stable: 6.0 per 100,000 in 1997 compared to 6.1 per 100,000 in 2020 [8]. Among women, mortality rates rose from 2.7 to 2.9 per 100,000 during the corresponding periods [8].

Given the high incidence and mortality rates, RCC treatment requires a comprehensive approach that combines surgical methods, targeted therapy, immunotherapy, and other innovative pharmacological strategies [9, 10]. Since treatment efficacy depends on numerous factors, such as disease stage, individual patient characteristics, and the availability of advanced drugs and medical technologies, modern RCC therapy is a complex and multifaceted process.

Scientific publications indicates that systemic pharmacotherapy constitutes a key component of RCC treatment, particularly in patients with advanced and metastatic disease. Several studies report that the use of immune checkpoint inhibitors and targeted agents is associated with improved progression-free and overall survival compared with previously applied monotherapy regimens [11–13]

Several publications focus on the use of combination treatment regimens. It is noted that such approaches are applied in specific patient groups, considering prognostic risk and tumour-related characteristics [13, 14]

In addition, current studies emphasise the importance of sequential therapy and the possibility of modifying pharmacotherapeutic regimens in the event of treatment resistance or adverse reactions, which is relevant for long-term disease control [14, 15].

An analysis of international scientific literature on the economic, pharmacoeconomic, and regulatory aspects of RCC pharmacotherapy revealed that researchers increasingly focus on issues such as the rising prevalence of oncological diseases [3–5] and the growing costs of cancer therapy [6, 16, 17], underscoring the urgent need to optimize resource utilization within national healthcare systems.

Several studies address the issue of limited access to innovative oncology medicines, emphasizing that the high cost of immunotherapy remains a major barrier to completing full treatment courses, particularly in low- and middle-income countries [6, 18, 19].

At the same time, pharmacoeconomic analyses indicate that, despite its high price, immunotherapy for RCC can be considered cost-effective due to its substantial impact on patient survival outcomes [16, 17].

Research on pricing strategies for oncological medicinal products highlights the importance of improving market entry pathways for innovative therapies and developing sustainable reimbursement mechanisms [20, 21]. In this context, health technology assessment is increasingly regarded as a practical tool for supporting evidence-based decision-making, allowing healthcare systems to balance clinical benefit, economic feasibility, and treatment accessibility.

Limited access to effective pharmacotherapy remains a major challenge for oncology care in Ukraine, including the treatment of RCC. Analyses of oncology care delivery during wartime point to a growing financial burden on the healthcare system and highlight the need to revise existing funding approaches, particularly regarding improving access to innovative medicines through state-supported programmes [22].

In addition, economic instability has been shown to adversely affect the availability of high-cost targeted and immunotherapeutic agents, thereby limiting the implementation of contemporary treatment standards for cancer patients [23].

Thus, a review of the scientific literature demonstrates that RCC treatment in modern conditions requires not only proven clinical efficacy but also economic justification and proper regulatory support, which is particularly relevant in the context of developing national healthcare strategies. Overall, the review of scientific literature indicates that the economic aspects of cancer therapy in Ukraine require further development, both in terms of improving state funding mechanisms and actively applying health technology assessment methods to make decisions about the accessibility and effectiveness of medicines. Specifically, in RCC pharmacotherapy, the task of expanding access to modern targeted and immunotherapeutic agents remains pressing, necessitating the implementation of transparent reimbursement procedures and the active consideration of international clinical guidelines.

The aim of the study was to scientifically examine approaches to RCC pharmacotherapy in different countries to further identification regulatory, health technology assessment, and organizational gaps that limit patient access to modern immunotherapeutic and targeted medicines, as well as to justify potential pathways for harmonizing national approaches with international standards within the functioning national healthcare system.

2. Research planning (methodology)

To achieve the stated aim, a research algorithm was developed in accordance with the principles of Quality by Design and a risk-based approach, comprising the five stages (Fig. 1).

The study was conducted in several consecutive stages. At the first, analytical and preparatory stage, scientific publications addressing the epidemiology, evolution, and current approaches to the pharmacotherapy of RCC were reviewed, with particular attention given to innovative treatment strategies.

Subsequently, the national regulatory and legal framework governing medical and pharmaceutical care for oncology patients in Ukraine was examined, along with the alignment of the national clinical protocol with international recommendations.

At the next stage, international clinical experience was analysed, including key clinical guidelines related to diagnosis, risk stratification, selection of pharmacotherapy regimens, and the role of multidisciplinary teams (MDT).

At the fourth stage, international and national approaches to the pharmacotherapy of RCC were analysed, including a comparison of treatment strategies outlined in clinical guidelines and national protocols, as well as an examination of the National List of Essential Medicines with regard to the inclusion of medicinal products used in RCC treatment.

Finally, the obtained results were synthesised, and recommendations were developed to support the harmonisation of national clinical protocols with international guidelines and to improve access to modern medicinal products.

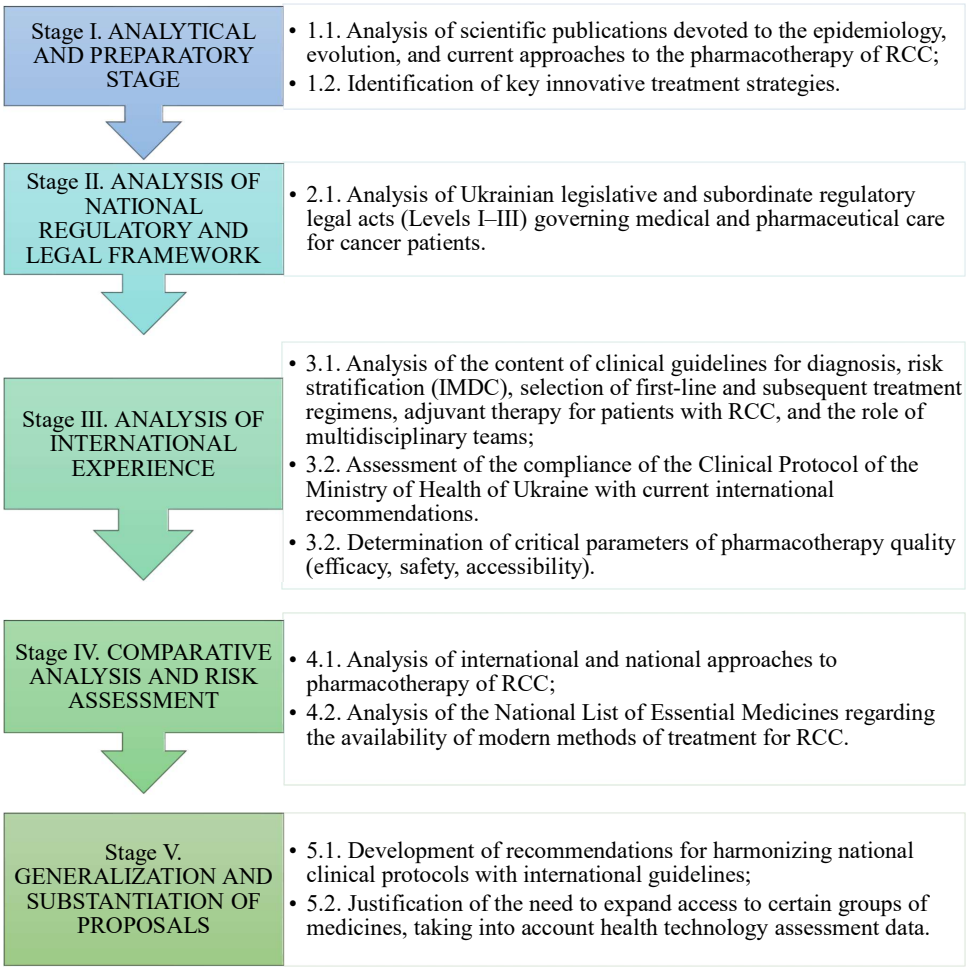

Fig. 1. Characteristics of the main stages of research

3. Materials and methods

Included scientific publications on RCC pharmacotherapy, international RCC treatment guidelines: National Comprehensive Cancer Network (NCCN, USA), European Society for Medical Oncology (ESMO, EU), American Society of Clinical Oncology (ASCO, USA), national RCC treatment protocols, as well as Ukrainian regulatory legal acts governing pharmaceutical supply for cancer patients.

Content analysis was used to examine international and national clinical guidelines with the aim of identifying key approaches to diagnosis, risk stratification, pharmacotherapy selection, and the organization of multidisciplinary care in RCC management. Comparative analysis enabled the assessment of similarities and differences between international recommendations and the Unified Clinical Protocol of Ukraine, particularly regarding the use of immunotherapy, targeted and adjuvant treatment strategies, and access to innovative medicines. The synthesis of results and analytical review were applied to integrate the findings, identify regulatory and pharmacoeconomic gaps, and substantiate directions for improving national approaches to RCC pharmacotherapy.

4. Research results

Given the rising incidence and significant mortality rates, RCC requires special attention from both clinical medicine and the healthcare system as a whole. A clear regulatory framework that defines standards for diagnosis, treatment, rehabilitation, and follow-up care plays a crucial role in ensuring effective and timely medical and pharmaceutical assistance for RCC patients.

Regulatory legal acts (RLAs) in the field of oncology serve as the foundation for developing unified clinical patient pathways, implementing evidence-based medical practices, and ensuring access to advanced treatment methods. At the same time, the effectiveness of national strategies for combating oncological diseases largely depends on the degree of adaptation of international protocols to the realities of Ukraine's healthcare system, the state's economic capabilities, and the overall level of pharmaceutical provision for the population as a whole.

In this context, analyzing Ukraine's existing regulatory framework for the prevention, diagnosis, and treatment of RCC is highly relevant, as proper legislative support for the provision of medical and pharmaceutical care is a cornerstone of an effectively functioning healthcare system. Such an analysis helps identify the strengths and weaknesses of the regulations, assess the alignment of national standards with modern international recommendations, and determine areas for improving pharmaceutical care within the framework of healthcare system reform.

In Ukraine, there is a range of RLAs governing access to medical care, pharmaceutical provision, treatment financing, and disease prevention. The effective functioning of the legal system is ensured through a hierarchical structure of the regulatory framework, where first-level RLAs, such as the Laws of Ukraine, primarily define general principles. For instance, the Law of Ukraine dated 19.11.1992 No. 2801-XII "Fundamentals of Ukrainian Legislation on Healthcare" is a foundational document that outlines the principles of state policy in the healthcare sector [24]. According to Article 6 of this document, every citizen has the right to healthcare, including qualified medical and rehabilitation assistance, and is guaranteed free medical care in state and municipal healthcare institutions.

The Law of Ukraine dated 06.09.2022 No. 2573-IX "On the Public Health System" establishes that the prevention of infectious and non-infectious diseases, including oncological conditions, is one of the state's priorities. The law provides for a comprehensive approach to healthcare, which includes educational initiatives, the promotion of healthy lifestyles, and the implementation of a system for monitoring and analyzing morbidity rates [25].

The provisions of the Law of Ukraine dated 25.12.2015 No. 922-VIII "On Public Procurement" set forth mechanisms for procuring medicines, medical devices, and services to meet healthcare needs, while ensuring transparency, competition, and efficiency in the use of public funds, which is particularly critical for providing high-cost treatments to oncology patients [26].

The Medical Guarantees Program, which defines the scope of free medical services funded by the state, is approved by the Law of Ukraine dated 19.10.2017 No. 2168-VIII "On State Financial Guarantees for Medical Services to the Population" [27]**.** Oncological diseases, including kidney cancer, are included in the priority areas of medical care, allowing patients to receive treatment free of charge within the approved medical service packages. Through this program, the state ensures full coverage of necessary medical services, including secondary (specialized) and tertiary (highly specialized) medical care, which encompasses medical and pharmaceutical assistance for oncological conditions.

Thus, the existing first-level regulatory framework in Ukraine, represented by the Laws of Ukraine, provides legal guarantees for delivering high-quality medical and pharmaceutical care to RCC patients.

The next stage involved analyzing the provisions of second- and third-level RLAs. A structured overview of the key provisions of RLAs at all hierarchical levels (I–III) relevant to RCC management are presented in Table 1.

Thus, the analysis of provisions from key RLAs of various hierarchical levels, which define approaches to providing medical and pharmaceutical care to patients with malignant neoplasms, has demonstrated that oncology is identified as one of the priority areas of healthcare in Ukraine.

Selected RLAs directly govern the treatment of RCC, while others provide organizational and systemic support for its implementation. In particular, the Unified clinical protocol "Renal Cancer" directly defines diagnostic pathways and pharmacotherapy algorithms for RCC patients. Orders of the Ministry of Health regulating MDT functioning support coordinated clinical decision-making in RCC management. In addition, the Concept for the Development of Electronic Healthcare, approved by the Order of the Cabinet of Ministers of Ukraine dated 28 December 2020 No. 1671-r (as amended), establishes the strategic principles for the formation and further development of the national electronic healthcare system. The Concept provides for the implementation of electronic medical records, digital prescribing, integration of data from different healthcare institutions, and monitoring tools aimed at improving access to medical care. In the context of RCC management, this digital framework supports patient registration, documentation of systemic therapy prescriptions, and monitoring of treatment outcomes. This enables efficient registration, monitoring, and analysis of oncological cases, including kidney cancer

The adoption of the Order of Cabinet of Ministers of Ukraine No. 730-r dated 02.08.2024, which establishes the National Strategy for Malignant Neoplasm Control until 2030, lays the foundation for the systematic implementation of modern approaches to prevention, early diagnosis, and treatment of oncological diseases by healthcare institutions.

Oncological care in Ukraine is governed by a system of RLAs issued primarily by the Ministry of Health, which define the organisational and clinical principles of medical care for oncology patients. In particular, Order No. 1680 of the Ministry of Health of Ukraine dated 02.10.2024 regulates the functioning of MDT that support coordinated clinical decision-making and interdisciplinary collaboration in patient management.

The organizational structure of cancer care is set out in more detail in Order No. 845 of the Ministry of Health of Ukraine dated 01.10.2013, which defines the framework for interregional cancer centers and promotes improved access to specialized treatment.

Order No. 2111 of the Ministry of Health of Ukraine dated 18.12.2024 regulates the collection of state statistical data using reporting form No. 7, which allows for the analysis of cancer incidence, detection rates, and treatment outcomes, including those related to kidney cancer. Such data forms the basis for planning and further evaluation of national cancer programs.

In addition, the implementation of evidence-based clinical guidelines and standardized treatment protocols, in particular the clinical protocol "Renal Cancer," promotes the harmonization of diagnostic and therapeutic approaches at different levels of healthcare provision and helps to reduce unjustified variability in pharmacotherapy practice in Ukraine.

The analysis of the regulatory and legal framework governing the provision of medical and pharmaceutical care in Ukraine, particularly in the field of oncology, indicates the existence of a set of documents that form the basis for supporting oncology patients. Legislative acts of the highest hierarchical level define the general principles of state healthcare policy and secure citizens' rights to prevention, treatment, and rehabilitation, including access to medical services provided within state-funded programmes. At the same time, Resolutions of the Cabinet of Ministers of Ukraine and Orders of the Ministry of Health specify the practical mechanisms through which these provisions are implemented.

Such mechanisms include the National Strategy for the Control of Malignant Neoplasms, regulations governing the establishment and functioning of MDT, as well as the introduction of unified clinical protocols. Taking together, these instruments shape a contemporary, evidence-based approach to the organisation of oncological care, including the management of patients with RCC.

Table 1

Summary of provisions from key RLAs, governing the provision of medical and pharmaceutical care to patients with oncological diseases

Regulatory Legal Acts	Key Provisions
Level I	
Law of Ukraine dated 19.11.1992 No. 2801-XII "Fundamentals of Ukrainian Legislation on Healthcare" (as amended on 19.12.2024) [24]	Defines the principles of state policy in the healthcare sector, including every citizen's right to medical assistance, which encompasses access to qualified therapeutic and rehabilitative support. Provides for the free provision of medical services in state and municipal healthcare institutions
Law of Ukraine dated 06.09.2022 No. 2573-IX "On the Public Health System" (as amended on 10.10.2024) [25]	Identifies the prevention of infectious and non-infectious diseases, including oncological ones, as one of the priority directions of state policy in the healthcare sector. Establishes a comprehensive approach to preserving the health of the population
Law of Ukraine dated 25.12.2015 No. 922-VIII "On Public Procurement" (as amended on 19.09.2024) [26]	Regulates the procedure for procuring medicines, medical devices, and services to meet the needs of the healthcare system
Level II	
Order of the Cabinet of Ministers of Ukraine dated 28.12.2020. No. 1671-r "On Approval of the Concept for the Development of Electronic Healthcare" (as amended on 06.09.2024) [28]	The key principles for the development of the electronic healthcare system have been defined, aimed at improving access to medical services for cancer patients. These principles specifically address electronic medical records, patient access to information, telemedicine, monitoring systems, and the integration of data from various medical institutions, with the goal of creating a comprehensive approach to the treatment of oncology patients
Order of the Cabinet of Ministers of Ukraine dated 02.08.2024. No. 730-r "On the approval of the National Strategy for Malignant Neoplasm Control for the period until 2030 and the adoption of the action plan for its implementation until 2025" [29]	Outlined are key aspects regarding the prevention and early diagnosis of malignant neoplasms, access to treatment, including measures aimed at improving patient access to modern treatment methods such as chemotherapy, radiotherapy, and immunotherapy, training of medical professionals, patient support, scientific research, innovations, and more
Level III	
Order of the Ministry of Health of Ukraine dated 02.10.2024 No. 1680 «On the Approval of the Regulation on Multidisciplinary Teams in Healthcare Institutions Providing Specialized Medical Care to Patients with Oncological Diseases» (as amended on November 20, 2024) [30]	The integration of efforts by various specialists in the treatment process is envisaged, particularly within multidisciplinary teams, to provide comprehensive care to patients with oncological diseases
Order of the Ministry of Health of Ukraine dated 18.12.2024 No. 2111 «On the Approval of Reporting Forms and Instructions for Their Completion» (as amended on February 10, 2025) [31]	The requirements for data collection and processing standards have been established, including the approval of the annual reporting form No. 7, «Report on Malignant Neoplasms for the Year», along with instructions for its completion
Order of the Ministry of Health of Ukraine dated 01.10.2013 No. 845, «On the System of Oncological Care for the Population of Ukraine» [32]	The structure of the oncology care system has been defined, including the network of oncology institutions
Order of the Ministry of Health of Ukraine dated 20.06.2022 No. 1061 «On Approval of the Unified Clinical Protocol for Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care 'Kidney Cancer'» [33]	Modern approaches to diagnostics and the main stages of medical care for patients with kidney cancer
«Kidney Cancer». Evidence-based clinical guideline. CN 2022-1061 dated 20.06.2022 [8]	Recommendations for diagnostics, treatment, and management of patients with kidney cancer have been established based on international clinical guidelines, while considering local specifics, resources, and practices in Ukraine

Another important area of development within the Ukrainian healthcare system is the integration of electronic tools for managing medical information and documentation, particularly through the eHealth platform. The use of digital solutions supports more transparent monitoring processes, facilitates the assessment of treatment effectiveness, and contributes to more rational resource planning.

In general, the current regulatory framework in Ukraine not only provides formal guarantees for the provision of cancer care, but also creates the necessary conditions for its implementation in practice. At the same time, there is a clear need for regular updates to existing regulations, taking into account international recommendations and modern advances in the treatment of cancer.

Given the fundamental role of legal regulation in the implementation of innovative therapeutic approaches, the next stage of our study was devoted to analyzing the historical stages of development of RCC pharmacotherapy.

RCC pharmacotherapy has undergone several key stages of development, reflecting general trends in oncology, particularly in treating this specific pathology.

These stages can be conditionally divided into three periods: before the 1990s, the 1990–2000s, and post-2010 (Fig. 2).

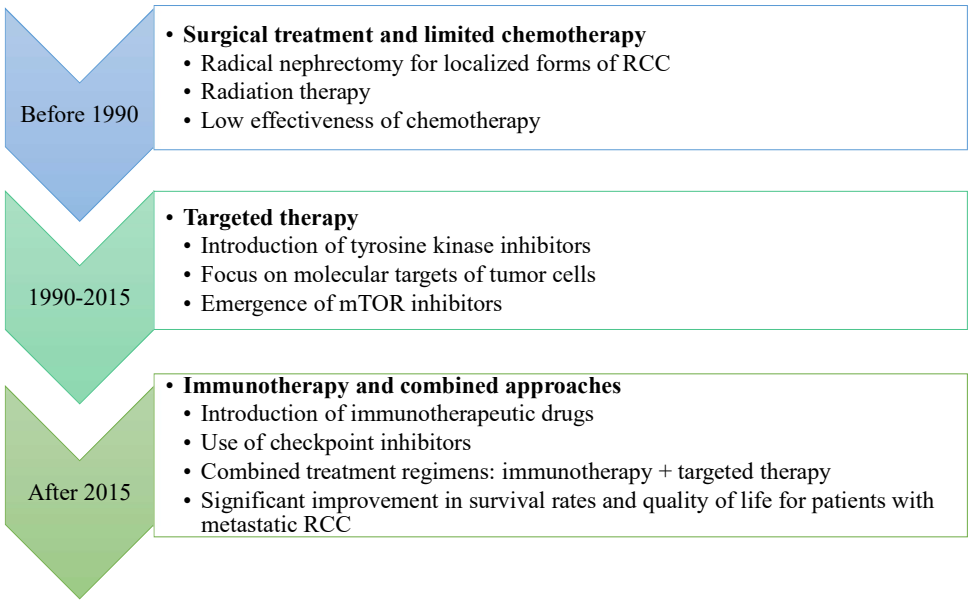

Fig. 2. Stages of RCC pharmacotherapy development

Before the 1990s, RCC treatment was limited to surgical methods, particularly radical nephrectomy, as well as traditional radiation therapy. Radical nephrectomy, used for localized cancer forms, provided survival rates of 50–60%. Chemotherapy, which was the primary treatment method for RCC until the mid-20th century, showed very low effectiveness due to the tumor's resistance to cytotoxic agents. Disease detection predominantly occurred at late stages, further reducing treatment effectiveness [34, 35].

The 1990s were marked by the beginning of the practical application of targeted therapy focused on specific molecular targets in tumor cells, which significantly improved the treatment outcomes for patients with metastatic RCC. First-generation tyrosine kinase inhibitors (TKIs), such as sorafenib and sunitinib, were the first targeted medicines to demonstrate efficacy in treating metastatic RCC by blocking signalling pathways that promote tumor growth. Subsequently, the use of TKIs and mTOR inhibitors improved overall survival to 26–28 months compared to 12–14 months without treatment [36]. In Ukraine, the introduction of targeted therapy enabled the adoption of modern treatment methods, but access remained limited due to the high cost of drugs and insufficient funding [37].

Since 2015, immunotherapy has been widely used in RCC treatment, marking a revolution in the pharmacotherapy of this cancer type. Immunotherapeutic medicines such as nivolumab, ipilimumab, pembrolizumab, and atezolizumab have shown high efficacy in combating metastatic RCC [38]. Immunotherapy involves the use of immune checkpoint inhibitors that activate the body's immune response against tumor cells. Combined therapy, for instance, using PD-1/PD-L1 checkpoint inhibitors in conjunction with targeted therapy, demonstrated significant improvements in treatment outcomes and patient survival [34].

Thus, the evolution of approaches to the treatment of RCC reflects a gradual transition from methods with limited effectiveness, including surgical treatment and chemotherapy, to modern systemic approaches based on targeted agents, immunotherapy, and combination treatment regimens.

Under current conditions, the pharmacotherapy of RCC is guided by the principles of personalized medicine, evidence-based practice, and interdisciplinary collaboration, which necessitates clear clinical and regulatory structuring of the treatment process. A leading role in the development of treatment standards is played by international professional organizations that synthesize the results of clinical research and formulate up-to-date clinical guidelines.

In this context, the next stage of the study involved a comparison of international clinical guidelines with national treatment protocols. The analysis covered recommendations issued by the NCCN (National Comprehensive Cancer Network, USA) [10], ESMO (European Society for Medical Oncology, EU) [9], and ASCO (American Society of Clinical Oncology, USA) [38].

NCCN, ESMO, and ASCO are key organizations in ensuring high-quality pharmacotherapy for cancer patients, playing a key role in the development of oncology through the development of clinical guidelines, educational programs and active international collaboration with leading cancer centers and hospitals. Their efforts contribute to improving the quality of cancer care and ensuring access to the latest treatment methods for patients worldwide, and the guidelines they develop are recognized as "gold standard" for designing oncology treatment strategies, including for patients with RCC. The creation of these guidelines involves leading multidisciplinary expert groups and incorporates results from multicenter clinical trials, ensuring high-quality and objective information [10, 11, 38]. Since these guidelines serve as a reference for decision-making in countries with advanced healthcare systems, comparing their content helps identify global approaches to therapy, current trends, and potential directions for adaptation to the national context. The results of the comparative analysis of international clinical guidelines and the unified clinical protocol of the Ministry of Health of Ukraine «Kidney Cancer» are presented in Table 2.

Table 2

Results of the comparative analysis of international and national guidelines on pharmacotherapy for metastatic RCC

Comparison Criteria of guidelines	Developing Organization (year of development, country)			
	NCCN (2025, USA)	ASCO (2023, USA)	ESMO (2024, EU)	Ministry of Health of Ukraine (2022, Ukraine)
Cancer Subtypes	Clear-cell RCC, non-clear-cell RCC	Primary focus on clear-cell RCC	Clear-cell RCC, non-clear-cell RCC	Generalized subtypes, emphasis on clear-cell RCC
Diagnostic Methods	CT with contrast, MRI, histological confirmation	Radiological + histological confirmation	CT, MRI, biopsy if necessary	CT, MRI, ultrasound, histological confirmation
Staging Assessment	TNM, IMDC	IMDC	TNM, IMDC	TNM
Risk stratification	Based on IMDC	Based on IMDC + individual patient condition	Based on IMDC + individual patient condition	IMDCis mentioned in the context of surgical strategy for metastatic RCC
Treatment of localized RCC	Surgical (partial/radical nephrectomy), active surveillance	Surgical as indicated	Surgical, active monitoring	Surgical treatment as the primary approach
Special cases (sarcomatoid forms)	Immunotherapy as the preferred option	Preference for combinations with PD-1/PD-L1[6]	Immunotherapy + targeted therapy	Not specified
First-line therapy for metastatic RCC	Combinations of immunotherapy and targeted therapy (pembrolizumab + axitinib, nivolumab + cabozantinib, nivolumab + ipilimumab)	Combinations of immunotherapy and targeted therapy (pembrolizumab + axitinib, nivolumab + cabozantinib, nivolumab + ipilimumab)	Combinations of immunotherapy and targeted therapy (pembrolizumab + axitinib, nivolumab + cabozantinib, nivolumab + ipilimumab)	Combinations of immunotherapy and targeted therapy (pembrolizumab + axitinib)
Adjuvant therapy	Pembrolizumab, is recommended for patients post-nephrectomy with a high risk of recurrence	Pembrolizumab, is recommended for patients post-nephrectomy with a high risk of recurrence	Pembrolizumab, is recommended for patients post-nephrectomy with a high risk of recurrence	Not specified
Follow-up monitoring	Regular imaging (CT/MRI), laboratory tests; frequency depends on the stage, typically every 3-6 months	Personalized approach; frequency is determined by the type of treatment, disease stage, and associated risk factors	CT/MRI; frequency depends on the stage, typically every 3-6 months	Annual follow-up examination or as indicated; depends on the clinical situation
Palliative care	Comprehensive palliative support for patients	Comprehensive palliative support for patients	Recommendations for integrating palliative care at early stages	Palliative care as part of comprehensive treatment (not detailed)
Genetic testing	Recommended in cases of suspected hereditary forms	Possible in specific cases	Yes, in young age or with a family history	Not regulated
Therapy side effects	Detailed instructions for monitoring side effects	Dose adjustments and management of complications	Some recommendations available for addressing adverse reactions	Depends on the instructions for medical use of the drug
Multidisciplinary team	Recommended participation of an oncologist, urologist, pharmacist, and palliative care specialist	Mandatory involvement of MDT in complex cases	The MDT approach is recognized as the standard of care	Participation of specialists from other fields is necessary for comprehensive patient evaluation
Pharmacist involvement	Active role in the multidisciplinary team: monitoring medicine interactions, side effects, and patient education	Ensuring adherence to medication schedules and providing consultations	Coordination and support for patients	Not regulated

Note: CT – computed tomography; MRI – magnetic resonance imaging; Ultrasound – ultrasonographic examination; TNM – tumor classification system based on criteria: Tumor (tumor), Node (lymph nodes), Metastasis (metastases); IMDC – International Metastatic Renal Cell Carcinoma Database Consortium; PD-1/PD-L1 – proteins that regulate immune response; targets for immunotherapy.

A comparative analysis of clinical guidelines revealed differences between international and national approaches to pharmacotherapy for RCC. Recommendations from NCCN, ESMO, ASCO provide a broad range of treatment options based on risk stratification and personalized approaches – combining immunotherapy with targeted agents has become the standard for first-line therapy.

Review of international clinical guidelines shows that the effectiveness of pharmacotherapy for RCC is most often assessed based on progression-free survival and overall survival outcomes achieved with the use of modern immunotherapeutic and targeted agents, including combination treatment regimens.

Pharmacotherapy safety in international recommendations is assessed regarding adverse event profiles, the need to monitor immune-mediated complications, and the timely adjustment of treatment, which underlines the role of a multidisciplinary approach and the involvement of the clinical pharmacist in patient care.

Access to pharmacotherapy is considered an important component of treatment quality and is linked to health technology assessment outcomes, reimbursement mechanisms, and the ability of national healthcare systems to incorporate innovative therapies. International guidelines consistently point to access to effective treatment as a necessary condition for the application of current standards of care in RCC.

Meanwhile, the unified clinical protocol of the Ministry of Health of Ukraine for 2022 also recommends the use of pembrolizumab + axitinib combination as first-line therapy. However, this only partially aligns with international approaches, as other recommended drug combinations, such as those involving nivolumab, are absent.

Based on the results of the comparative analysis several conceptual similarities in approaches to the diagnosis and treatment of RCC can be identified: for instance, all documents emphasize the importance of morphological verification of the diagnosis, which is conducted through histological analysis. Additionally, both the Ukrainian protocol and international guidelines recognize the TNM (Tumor, Node, Metastasis) staging system as a universally accepted tool for determining the stage of the tumor process, assessing the size of the primary tumor (*T*), the presence of lymph node involvement (*N*), and distant metastases (*M*).

To stratify patients by risk level, international documents widely utilize the IMDC model, which serves as a prognostic tool for assessing survival in patients with metastatic RCC and forms the basis for treatment strategy selection. While the IMDC scale is used in the Ukrainian protocol to personalize approaches, its application is largely limited to decisions regarding cytoreductive nephrectomy, whereas in international guidelines, it also significantly influences the choice of first-line systemic therapy.

In all analyzed protocols, surgical intervention (partial or radical nephrectomy) is identified as the primary treatment method for localized kidney tumors.

In international recommendations NCCN, ASCO, and ESMO combinations of immunotherapy with targeted therapy are recognized as the standard for first-line treatment of metastatic RCC. The most recommended options include pembrolizumab + axitinib, nivolumab + cabozantinib and nivolumab + ipilimumab, which demonstrate higher efficacy in patients with varying prognoses according to IMDC stratification. These combinations are based on data from large-scale clinical trials and show improvements in survival and disease progression control.

The clinical protocol of the Ministry of Health of Ukraine also includes the pembrolizumab + axitinib combination as a standard first-line therapy regimen. However, other modern combinations widely recognized in global practice are not represented. This highlights the need to update Ukrainian recommendations to align with current international approaches to metastatic RCC treatment, particularly emphasizing personalized immuno-targeted therapy.

The analysis of international guidelines revealed a dedicated focus and personalized approach to treating elderly patients, those with sarcomatoid subtypes, comorbid kidney conditions, or cardiovascular insufficiency, in contrast to the Ukrainian protocol.

The recommendations also clearly define algorithms for monitoring treatment effectiveness, including the frequency of imaging studies, response assessment criteria, and approaches to therapy line adjustments. In contrast, the Ministry of Health protocol provides only general guidelines without referencing standardized methods for evaluating effectiveness.

International clinical guidelines consistently emphasise the value of a MDT approach in the provision of oncology care. In the ESMO recommendations, multidisciplinary management is regarded as a standard model of care that ensures coordinated and continuous patient management with the involvement of oncologists, urologists, pharmacists, palliative care specialists, and other healthcare professionals depending on the clinical context. At the same time, NCCN guidelines underline the necessity of mandatory MDT involvement in complex clinical cases that require individualised therapeutic decision-making, while ASCO recommendations draw attention to the importance of interprofessional collaboration in achieving optimal treatment outcomes.

Within this framework, international guidelines also define a clear role for the clinical pharmacist as an integral member of the MDT. Key responsibilities of this specialist include monitoring potential drug-drug interactions, contributing to the management and prevention of adverse drug reactions, providing patient counselling to support adherence to prescribed treatment regimens, and participating in clinical decision-making processes.

By comparison, the clinical protocol approved by the Ministry of Health of Ukraine refers only in general terms to the involvement of specialists from other medical fields to ensure a thorough assessment of patients. However, it does not define the structure of the MDT or clearly delineate the responsibilities of its members, including the clinical pharmacist. This indicates that further development of the multidisciplinary model in Ukrainian clinical practice is required to bring it into closer alignment with international standards.

An additional aspect that merits attention is the issue of patients' overall well-being throughout the entire course of treatment, including the palliative stage. International clinical guidelines place considerable emphasis on early integration of palliative care services, effective symptom management, attention to patients' psycho-emotional well-being, and the provision of social support. In contrast, these components receive only limited consideration within the current national protocol.

In general, the Ukrainian clinical protocol corresponds to the fundamental principles of RCC management; however, it does not fully reflect recent advances in pharmacotherapy, particularly in the areas of immunotherapy and personalised treatment strategies. Further refinement of the protocol would benefit from the inclusion of structured approaches to risk stratification, immunotherapeutic interventions, and palliative care, as well as more detailed guidance on treatment regimens,

therapy modification criteria, and the management of patients with comorbid conditions or complex clinical presentations.

Content analysis of international clinical guidelines developed by the NCCN, ESMO, and ASCO shows that current approaches to the pharmacotherapy of RCC rely on risk-oriented selection of treatment strategies. These approaches include the use of combination regimens involving immunotherapy and targeted agents, a clearly defined role of the MDT, and standardised methods for monitoring treatment effectiveness. A comparison with the national clinical protocol of Ukraine indicates that these elements are only partially reflected, particularly with respect to risk stratification, adjuvant therapy, and the involvement of the clinical pharmacist.

A comparison of contemporary international and national clinical guidelines for the treatment of RCC demonstrates broad consistency in general approaches to therapy selection, alongside noticeable differences in the management of certain patient groups. One of the areas that warrants particular consideration is the use of adjuvant therapy following nephrectomy in patients at high risk of recurrence. This component plays an important role in determining modern treatment strategies for RCC and therefore requires closer examination. In recent years, adjuvant therapy has increasingly taken a leading role in treatment strategies aimed at reducing the risk of disease progression.

In the NCCN guidelines, adjuvant pembrolizumab is recommended for patients with localized RCC who are considered to be at high risk of recurrence after radical or partial nephrectomy. The rationale for this recommendation is derived from the KEYNOTE-564 trial, which demonstrated an improvement in recurrence-free survival compared with placebo and supported the introduction of adjuvant immunotherapy into postoperative treatment strategies.

In the ESMO guidelines, pembrolizumab is likewise recommended in the adjuvant setting for patients with an elevated risk of disease progression following nephrectomy. These recommendations also highlight the importance of careful patient selection, indicating that the expected benefit of adjuvant therapy should be evaluated in the context of individual prognostic factors rather than applied uniformly to all patient groups.

The ASCO guidelines similarly refer to evidence from the KEYNOTE-564 trial when discussing the role of pembrolizumab in the adjuvant setting. In this context, ASCO places particular emphasis on an individualised treatment line, in which both tumour-related characteristics and the patient's general clinical status are considered when making therapeutic decisions.

The current clinical protocol approved by the Ministry of Health of Ukraine does not provide specific recommendations regarding the use of adjuvant immunotherapy following nephrectomy.

International clinical guidelines, however, increasingly incorporate adjuvant immunotherapy, particularly pembrolizumab, into treatment strategies for patients with RCC who face a high risk of recurrence after surgery. At present, the relevant sections of Ukrainian clinical protocols remain insufficiently aligned with these approaches, which limits the consistent implementation of such therapies through different stages of care.

A comparison of international and national guidelines highlights differences not only in diagnostic approaches and risk stratification, but also in the way therapeutic decisions are structured. International recommendations follow a risk-based and algorithmic model of treatment selection, whereas the Ukrainian protocol presents systemic therapy regimens in a more generalised format. This distinction becomes particularly apparent when the specific pharmacotherapy regimens recommended in international and national documents are compared.

Because adjuvant therapy represents only one component of systemic treatment for RCC, the subsequent stage of the analysis focused on comparing systemic therapy regimens recommended in international guidelines. This approach enabled the identification of prevailing first- and second-line treatment strategies and facilitated an assessment of their relevance within the Ukrainian healthcare context (Table 3).

Table 3

Results of comparative analysis of pharmacotherapy regimens recommended for patients with metastatic RCC

Pharmacotherapy regimen	Year of FDA drug approval	Organization developing the recommendations (year of approval)			
		NCCN (2025)	ESMO (2024)	ASCO (2023)	Ministry of Health of Ukraine (2022)
First-line treatment					
Nivolumab + Ipilimumab	2018	+	+	+	–
Pembrolizumab + Axitinib	2019	+	+	+	+
Pembrolizumab + Lenvatinib	2021	+	+	+	–
Nivolumab + Cabozantinib	2021	+	+	+	–
Avelumab + Axitinib	2020	-	-	+	–
Sunitinib	2006	+	+	+	+
Pazopanib	2009	+	+	+	+
Tivozanib	2021	+	–	–	–
Cabozantinib (as monotherapy)	2016	+	–	–	+
Toripalimab + Axitinib	*	**	–	–	–
Second-line treatment					
Cabozantinib	2016	+	+	+	+
Nivolumab	2015	–	+	+	+
Lenvatinib + Everolimus	2016	+	+	+	+
Tivozanib	2021	+	+	+	+
Sorafenib	2005	–	–	Limited	Limited

*Note: *– no data available; ** – highlighted in ESMO 2023 updates as a promising combination.*

A comparison of international clinical guidelines with the clinical protocol of the Ministry of Health of Ukraine shows that, overall, there is considerable consistency in current treatment approaches for RCC, particularly with regard to first-line therapy. The analysis also demonstrates variability in available pharmacotherapy options, which allows treatment decisions to be adapted to individual patient characteristics, including disease stage and the presence of comorbidities.

Immunotherapy is playing an increasingly significant role in modern treatment protocols for metastatic RCC, particularly with drugs like Nivolumab, Pembrolizumab, and Ipilimumab, which are part of the most recommended first-line combinations. The combinations of Nivolumab + Ipilimumab, Pembrolizumab + Axitinib, and Pembrolizumab + Lenvatinib demonstrate high efficacy and are included in the guidelines of all leading oncology societies, including NCCN, ESMO, and ASCO.

It is important to specifically highlight the medications that are utilized in both first- and second-line therapies – Sunitinib, Pazopanib, Cabozantinib, and Lenvatinib. Their long-term use (since FDA approval: Sunitinib in 2006, Pazopanib in 2009, Lenvatinib in 2015, and Cabozantinib in 2016) demonstrates clinical stability, versatility, and the ability to adapt to various clinical scenarios [37].

At the same time, despite a high level of consensus, there is some variability in the recommendations of international organizations, indicating ambiguity in clinical approaches and the need for further research, particularly regarding newer regimens such as Toripalimab + Axitinib. This combination is not yet included in most international protocols but has already been noted by ESMO.

Thus, the Unified Clinical Protocol for Primary, Secondary (Specialized), and Tertiary (Highly Specialized) Medical Care «Kidney Cancer» of Ukraine reflects the main international approaches to the treatment of metastatic RCC, although it does not include all currently available therapeutic options. Its partial alignment with international guidelines points to ongoing harmonisation of clinical standards, while underscoring the importance of their timely revision in response to new clinical evidence and emerging combination regimens. This is particularly relevant given the growing use of immunotherapy and the increasing need for individualised treatment decisions.

In this context, the support of international organizations plays a key role in recognizing treatment regimens at the global level, enabling other countries, including Ukraine, to integrate global expertise into their national protocols. Meanwhile, the ongoing need for knowledge updates among physicians remains critically important, as new therapeutic approaches emerge regularly, and effective RCC treatment requires flexibility and adaptability in strategy selection.

The comparative assessment of international clinical guidelines and the national clinical protocol indicates that the use of contemporary approaches to the treatment of RCC is generally reflected at the level of clinical recommendations in Ukraine. However, the presence of such recommendations in clinical documents does not necessarily ensure their implementation in routine practice, as the actual availability of pharmacotherapy is determined by regulatory and financial mechanisms within the public healthcare system. As stipulated by the Law of Ukraine "On State Financial Guarantees for Medical Services to the Population" dated 19.10.2017 No. 2168-VIII, patients with oncological diseases are entitled to free medical care under the Medical Guarantees Program (MGP). In 2025, the MGP includes the package "Chemotherapeutic Treatment for Adults and Children in Outpatient and Inpatient Settings", which covers chemotherapy, including targeted medicines if procured centrally, as well as supportive therapy [27]. However, in practice, access to high-cost immunotherapeutic agents remains inconsistent due to limited reimbursement mechanisms and budget constraints due to limited reimbursement mechanisms and budget constraints.

In this regard, particular attention should be paid to the National List of Essential Medicines as a key regulatory instrument that directly influences the feasibility of introducing modern RCC treatment regimens.

The inclusion of medicinal products in the National List of Essential Medicines is a required condition for their state-funded provision through the Medical Guarantees Program or centralized procurement mechanisms in Ukraine [39]. Therefore, the National List functions as a central regulatory mechanism that directly affects the practical availability of pharmacotherapy for patients with RCC within the public healthcare system.

An analysis of the current version of the National List of Essential Medicines was carried out to evaluate its consistency with contemporary international standards for RCC pharmacotherapy. The assessment involved a comparison between medicines included in the National List and pharmacotherapy regimens recommended by leading international clinical guidelines (NCCN, ESMO, ASCO), with particular attention to first- and second-line systemic therapy, immunotherapy-based regimens, and combination treatment approaches.

According to the Order of the Ministry of Health of Ukraine dated 25 December 2024 No. 2148, which entered into force on 1 January 2025, the National List was expanded by the inclusion of 52 additional medicinal products [40]. Nevertheless, the findings of this assessment show that, despite this update, the National List remains only partly consistent with current treatment approaches for RCC.

Specifically, the List includes primarily targeted agents of earlier therapeutic generations, such as sunitinib and sorafenib, which were historically used as monotherapy in RCC management.

By contrast, most medicines that now constitute the foundation of contemporary RCC treatment strategies are not represented in the National List. In particular, immune checkpoint inhibitors (nivolumab, pembrolizumab), as well as several next-generation targeted agents (pazopanib, axitinib, cabozantinib, lenvatinib), recommended by international clinical guidelines as components of first- and second-line therapy, including

combination regimens, are not included in the National List of Essential Medicines. Importantly, some of these medicines are formally mentioned in the Ukrainian clinical protocol; however, their absence from the National List substantially limits their routine state-funded use.

Consequently, the absence of these medicines from the National List restricts the practical application of modern RCC treatment strategies within the public healthcare sector. In particular, this regulatory limitation affects the use of immunotherapy-based regimens, combined immuno-targeted therapy (e.g., pembrolizumab plus axitinib, nivolumab plus ipilimumab), and adjuvant immunotherapy for patients at high risk of recurrence following nephrectomy. Thus, although clinical recommendations support these approaches, their real-world implementation remains influenced by regulatory and reimbursement frameworks.

Overall, the findings point to a marked inconsistency between international clinical recommendations for RCC pharmacotherapy and the existing regulatory framework governing medicine provision in Ukraine. Further revision of the National List of Essential Medicines is needed to improve its correspondence with current evidence-based treatment standards and the actual clinical needs of patients with RCC. Updating the List to include effective immunotherapeutic and next-generation targeted agents represents an essential step toward improving equitable access to advanced RCC treatments within state-funded healthcare programs.

5. Discussion of research results

The results of this study demonstrate several differences between international clinical guidelines (NCCN, ESMO, ASCO) and the Clinical Protocol of the Ministry of Health of Ukraine in terms of approaches to pharmacotherapy for RCC. These differences are most evident in the areas of immunotherapy use, risk stratification, adjuvant treatment, and the organisation of multidisciplinary care.

One of the key discrepancies concerns the application of prognostic risk stratification tools. In international clinical practice, the IMDC model is widely used to guide the selection of first-line systemic therapy for patients with metastatic RCC. In contrast, within the Ukrainian clinical protocol, the use of IMDC criteria is largely confined to decisions related to surgical management. Such a limited application restricts the potential for individualised pharmacotherapy and may adversely influence treatment effectiveness.

An additional area of difference concerns adjuvant immunotherapy. It has been determined that international guidelines consistently recommend the use of pembrolizumab as adjuvant treatment for patients with RCC at high risk of recurrence following nephrectomy, based on evidence from the KEYNOTE-564 clinical trial [41–43]. However, the current Ukrainian clinical protocol does not provide specific guidance on adjuvant immunotherapy, which represents a gap in the continuity of care and may contribute to an increased risk of disease relapse.

Differences were also identified in the implementation of the MDT approach. In the NCCN, ESMO, and ASCO guidelines, MDT involvement is regarded as an essential component of oncology care, with clearly defined responsibilities for team members, including the clinical pharmacist. In particular, pharmacists are involved in monitoring medicine interactions, managing adverse effects, and supporting patient adherence to therapy. In the Ukrainian context, although multidisciplinary involvement is acknowledged in general terms, the composition of MDTs and the roles of individual specialists, including pharmacists, remain insufficiently regulated, which limits the contribution of pharmaceutical care to treatment safety and overall effectiveness.

Limited access to innovative medicines remains a practical constraint for the treatment of patients with RCC in Ukraine. In particular, the absence of several immunotherapeutic and targeted agents from the National List of Essential Medicines, together with restricted reimbursement under the MGP, continues to delay the broader use of modern therapies in routine clinical practice.

The results obtained in this study indicate that updating national clinical protocols in accordance with international guidelines requires not only clinical revisions but also changes at the regulatory and organisational levels. Specifically, increased attention to health technology assessment and the formal involvement of clinical pharmacists in MDT is likely to support a more consistent application of modern treatment approaches. Such measures support individualised therapeutic decision-making and are associated with improved access to innovative medicines and more efficient use of healthcare resources.

Practical relevance. The practical significance of the results obtained at this stage of the study lies in identifying priority areas for improving pharmaceutical care for patients with RCC in Ukraine. In particular, reviewing and updating the national regulatory framework in the outlined areas will allow for the introduction of modern evidence-based approaches into the practice of providing patients with medicines by increasing their availability and affordability through the expansion of the National List of Essential Medicines, public procurement programs, and reimbursement.

Research limitations. A limitation of this analysis is that it was based on the regulatory framework and clinical guidelines in force at the time of the research, which are subject to regular revision and updating. This factor is relevant for the interpretation of the results, particularly in the context of ongoing changes in oncology practice and pharmaceutical regulation.

In addition, regional differences in the availability of innovative medicines were not analyzed separately in this study, which should be considered when assessing the generalisability of the results.

Prospects for further research. Subsequent research could address a comprehensive health technology assessment of immunotherapeutic and targeted medicines used in the treatment of patients with RCC, taking into account national healthcare financing conditions. In addition, further investigation of the role of the clinical pharmacist within MDT is needed, with a focus on pa-

tient adherence to therapy, the management of adverse reactions, and treatment outcomes in routine clinical practice.

6. Conclusions

An overview of current approaches to RCC treatment shows that international clinical guidelines developed by organizations such as NCCN, ESMO, and ASCO play an important role in shaping contemporary standards of care. The use of these guidelines serves as a basis for updating national clinical protocols and supports the adoption of evidence-based practices within different healthcare systems, including that of Ukraine.

In this context, changes in approaches to treatment highlight the need for regular review of clinical practice and continuous professional development of healthcare specialists. Effective management of RCC requires an individualized selection of treatment approaches that considers both disease-related factors and patient-specific characteristics.

Limited access to modern medicines remains a significant issue in the treatment of patient with RCC in Ukraine, particularly with regard to targeted therapies and immunotherapy. Although the clinical effectiveness of these treatment modalities is well documented and they are widely included in international clinical guidelines, their high cost continues to restrict patient access and underscores the need for more consistent state-level support.

Particular attention should be paid to adjuvant immunotherapy, which is recognised in international guidelines as an effective option for patients at high risk of disease recurrence after surgery. In Ukraine, however, the use of this approach is constrained by insufficient public funding for the required medicines, indicating the need to revise existing standards of oncological care.

Expanding the National List of Essential Medicines to include effective targeted and immunotherapeutic agents could improve access to advanced treatment options within state-funded programmes and contribute to better quality and outcomes of oncology care in Ukraine.

Further research in the field of RCC pharmacotherapy should focus on the assessment of medical treatment technologies, particularly about the feasibility of introducing new medicinal products in the context of available financial resources.

Another important direction involves improving the availability of medicines through state procurement mechanisms and reimbursement programmes which continue to be a priority**.** Expanding international collaboration and professional exchange can support the introduction of modern therapeutic approaches, while the gradual updating of the regulatory can support timely responses to new challenges in the provision of oncology care.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available on reasonable request.

Use of artificial intelligence

Artificial intelligence tools were used to search for bibliographic sources of international research data. All data and analysis have been verified and conducted by the authors. In addition, AI was used to check the grammar of the text in Ukrainian and English without changing the meaning.

Authors' contributions

Oleksandr Kaiota: Formal analysis, Investigation, Validation, Visualization, Writing – original draft; **Alina Volkova:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration; **Natalia Khokhlenkova:** Conceptualization, Writing – review & editing, Project administration, Supervision.

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