RESULTS OF PHASE IIA CLINICAL TRIAL OF THE RAS-GTPASE INHIBITOR («ING-RAS») FOR TREATMENT OF GASTROINTESTINAL TUMORS

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Peritoneal carcinomatosis remains one of the most challenging forms of dissemination in gastric and colorectal cancer. It directly determines the disease prognosis and is highly resistant to treatment. The use of the existing therapeutic approaches is often limited by low benefit-risk ratio. It is necessary to develop innovative strategies aimed at overcoming the molecular mechanisms of tumor progression associated with RAS mutations, which play a crucial role in the carcinogenesis of both colorectal and gastric cancer. The study aimed to estimate safety and preliminary efficacy of the novel peptide RAS-GTPase inhibitor «Ing-Ras» when included in the treatment regimen of patients with stage III–IV gastric and colorectal cancer, including patients with peritoneal carcinomatosis. A total of 35 patients with the confirmed diagnosis of stage III–IV gastric and colorectal cancer were included in the study. The «Ing-Ras» drug was administered at a dose of 1.8 mg/kg twice with a 7-day interval using the Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) technique. Primary efficacy was assessed by comparing the overall survival (OS) and progression-free survival (PFS) rates of the clinical trial patients with historical control groups. The OS and PFS rates for patients in the clinical trials were 92.1% and 84.22%, respectively, which significantly ($p < 0.05$) exceeded the values of these rates for the historical control group (50.8% and 65.25%). Thus, the use of «Ing-Ras» can significantly improve the treatment results for patients with advanced forms of colorectal and gastric cancer.

Keywords: peritoneal carcinomatosis, RAS-GTPase inhibitor, PIPAC therapy, progression-free survival, safety, KRAS G12C mutation, KRAS, HRAS, NRAS

Funding: the study was conducted with financial support from the Ministry of Health of the Russian Federation, the State Task project EGISU No. 1023021500033-4-3.2.21;3.1.5.

Author contribution: Kulinich TM — research concept and design, material collection and processing, data analysis, manuscript writing; Kukoleva EA — formation of patient groups, a set of clinical material, analysis of results, manuscript writing; Goncharov SV — design of the experimental part of the study, formation of patient groups, a set of clinical material, analysis of results; Kudinova EA, Goncharova OI — analysis of the clinical and experimental research results, manuscript writing and editing; Puchkov IA, Kaminsky VV — formation of patient groups, analysis of results, manuscript writing and editing; Bozhenko VK — research concept and design, manuscript editing and approval.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Russian Scientific Center of Roentgenoradiology (protocol No. 4 dated 28 April 2023). The 2022-1-"Инг-Рас" trial was approved by the Ministry of Health of the Russian Federation (approval No. 177 for the clinical trial dated 30.03.2023). It was conducted in accordance with the ethical principles set out in the World Medical Association Declaration of Helsinki.

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Received: 23.10.2025 **Accepted:** 21.11.2025 **Published online:** 09.12.2025

DOI: 10.24075/brsmu.2025.065

РЕЗУЛЬТАТЫ КЛИНИЧЕСКОГО ИССЛЕДОВАНИЯ IIA ФАЗЫ ИНГИБИТОРА RAS-ГТФАЗЫ («ИНГ-РАС») ДЛЯ ЛЕЧЕНИЯ ОПУХОЛЕЙ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Перитонеальный канцероматоз остается одним из самых сложных вариантов диссеминации при раке желудка и толстой кишки. Он напрямую определяет прогноз заболевания и весьма резистентен к лечению. Использование существующих терапевтических подходов часто ограничено низким соотношением «польза–риск». Необходима разработка инновационных стратегий, направленных на преодоление молекулярных механизмов прогрессирования опухолей, ассоциированных с мутациями RAS, играющими важную роль в канцерогенезе как колоректального рака, так и рака желудка. Целью работы было оценить безопасность и эффективность нового пептидного ингибитора RAS-ГТФазы «Инг-Рас» при его включении в схему лечения пациентов с диагнозом рак желудка и толстой кишки III–IV стадий, включая пациентов с перитонеальным канцероматозом. В исследование было включено 35 пациентов с подтвержденными диагнозами рак желудка и толстой кишки III–IV стадий. Препарат «Инг-Рас» вводили в дозе 1,8 мг/кг двукратно с интервалом семь дней с помощью технологии внутрибрюшинной аэрозольной химиотерапии под давлением (PIPAC). Оценку первичной эффективности проводили на основании сравнения показателей общей (OS) и безрецидивной (PFS) одногодичной выживаемости пациентов КИ с группами исторического контроля. Показатели OS и PFS для пациентов клинического исследования составили 92,1 и 84,22% соответственно, что достоверно ($p < 0,05$) превышает значения данных показателей для группы исторического контроля — 50,8 и 65,25%. Таким образом, применение препарата «Инг-Рас» позволяет существенно повысить результаты лечения пациентов с распространенными формами колоректального рака и рака желудка.

Ключевые слова: перитонеальный канцероматоз, ингибитор RAS-ГТФазы, PIPAC-терапия, выживаемость без прогрессирования, безопасность, мутация KRAS G12C, KRAS, HRAS, NRAS

Финансирование: исследование выполнено при финансовой поддержке Министерства здравоохранения Российской Федерации, рег. № ЕГИСУ 1023021500033-4-3.2.21;3.1.5.

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Соблюдение этических стандартов: исследование одобрено этическим комитетом при ФГБУ «РНЦРР» Минздрава России (протокол заседания № 4 от 28 апреля 2023 г.). Исследование 2022-1-«Инг-Рас» одобрено Минздравом России разрешением № 177 на проведение клинических исследований от 30.03.2023. Проведено в соответствии с этическими принципами, изложенными в Хельсинкской декларации Всемирной медицинской ассоциации.

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Статья получена: 23.10.2025 **Статья принята к печати:** 21.11.2025 **Опубликована онлайн:** 09.12.2025

DOI: 10.24075/vrgmu.2025.065

Peritoneal carcinomatosis is one of the most prognostically unfavorable sequelae of malignant neoplasms. It's aggressive course and resistance to standard systemic chemotherapy determined by the peritoneum structural and physiological features, including its limited vascularization and formation of biological barriers, which leads to the rapid progression and adverse prognosis, as well as prevention of the penetration of cytostatics [1]. Systemic chemotherapy usually demonstrates limited efficacy. By now local drug therapy methods, such as PIPAC (Pressurized Intraperitoneal Aerosol Chemotherapy) and HIPEC (hyperthermic intraperitoneal chemotherapy) are being developed and implemented to improve treatment outcomes.

The PIPAC technique involving spraying a cytostatic agent aerosol under increased pressure of carbon dioxide ensures its uniform distribution in the abdominal cavity, even in the presence of adhesions after surgical interventions, and promotes its further penetration into tumor tissues to a depth up to 500 μm, which 3–5-times exceeds the values reported for the traditional intraperitoneal chemotherapy [2]. The use of this approach is particularly relevant for the treatment of tumors with RAS-mutations, which are highly prone to dissemination.

Mutations of RAS genes (KRAS, HRAS, NRAS) are found in 30–90% of cases of gastrointestinal adenocarcinomas, including cases of colorectal cancer (40–50%), pancreatic cancer (90%) and gastric cancer (> 8%) [3, 4]. Carcinogenic factors stabilize Ras-proteins in the GTP-bound state, blocking the GTP hydrolysis to GDP. This results in hyperstimulation of the MAPK/ERK and PI3K/AKT signaling pathways, enhancing proliferation, angiogenesis and the adenocarcinoma metastatic potential [5].

To overcome resistance of tumors with mutations in RAS genes, it is necessary to develop highly selective inhibitors capable of specifically suppressing the activity of overexpressed Ras-proteins. The peptide RAS-GTPase inhibitor «Ing-Ras» drug developed at the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation disrupts the formation of the Ras-Raf-GTP complex by suppressing signaling via the MAPK/ERK cascade pathway [6]. Pre-clinical trials have shown that «Ing-Ras» actively penetrates cell membranes, selectively binding carcinogenic Ras-isoforms, and induces apoptosis in colorectal cancer (HT-29) and ovarian cancer (OVCAR-3) cell lines [7].

A combined strategy for the inclusion of «Ing-Ras» in the standard treatment regimen with its intraperitoneal administration of the drug by PIPAC ensuring high intraperitoneal concentration of the drug has been proposed for patients with peritoneal carcinomatosis. Such a strategy will make it possible to overcome the limitations associated with the use of systemic chemotherapy and complement it to increase the treatment efficacy.

Combining PIPAC therapy with the targeted RAS inhibitors, such as «Ing-Ras», represents a promising approach to treatment of peritoneal carcinomatosis. This approach combines specific signaling pathway inhibition with the optimized drug delivery, ensuring high efficacy in tumors with RAS-mutations [8].

During the previously conducted phase I of clinical trials of the «Ing-Ras» under Protocol No. 2022-1-*Инг-Рас*, which was the first clinical trial of RAS-GTPase inhibitor in the Russian Federation, the tasks related to assessment of the drug safety and tolerability were successfully completed [6].

The study aimed to perform preliminary assessment of the efficacy of the «Ing-Ras» drug for treatment of patients diagnosed with gastrointestinal tumors, including patients with peritoneal carcinomatosis in the phase IIa clinical trial (second phase of the clinical trial protocol No. 2022-1-*Инг-Рас*).

METHODS

Patients and study design

The study was conducted as a phase I–IIa of prospective open-label non-randomized multicenter trial with adaptive design to assess safety and primary efficacy, as well as to determine the maximum tolerated dose of the drug based on the RAS-GTPase inhibitor («Ing-Ras»).

Safety of the 1.8 mg/kg «Ing-Ras» drug dose determined on the phase I results was assessed in phase II; the dose was approved at the session (05.12.2023) of the Independent Data Monitoring Committee (IDMC) founded at the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation [6]. A preliminary efficacy assessment of the optimal drug dose was also conducted in comparison with the historical control group. The phase II trial consisted of the following periods: screening — preliminary patient examination (up to 14 days); on day 1 of the trial the patients in hospital settings were administered the study drug intraperitoneally (using PIPAC) at a dose of 1.8 mg/kg. On day 8 of the trial the drug dose of 1.8 mg/kg was administered for the second time by the same method. Later the patients had eight outpatient visits to the research center between days 21 and 360 of participation in the trial. Parameters, safety and efficacy were assessed during each visit.

The trial was conducted from June 19, 2023 to December 25, 2024. The phase I trial results had been published earlier [6]. The phase IIa clinical trial was conducted at the clinic of the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation. The study included 35 patients with the morphologically confirmed peritoneal carcinomatosis in gastric and colorectal cancer, who received combination therapy with «Ing-Ras» and PIPAC (ITT population). Among them 23 patients were compliant with the trial protocol (PP population). Efficacy was assessed based on the RECIST 1.1 criteria, dynamic changes in the Peritoneal Cancer Index (PCI). Safety assessment was performed in accordance with the generally accepted Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The association of adverse events (AEs) and severe adverse events (SAEs) with the test drug was determined based on the researcher's clinical assessment. The median follow-up period was 388 days. The number of patients for assessment of safety and primary efficacy of the drug was determined in accordance with the guidelines on sample sizes for early phases of drug development [9]. Efficacy was analyzed for the entire populations of the patients enrolled (ITT, intention–to-treat) (n = 35).

Inclusion criteria: surgery due to one of the following conditions.

– Resectable gastric cancer showing signs of invading the serous membrane (T3) with the presence of cancer cells assessing with peritoneal lavage based on the cytological/immunocytochemistry analysis and/or showing signs of invading adjacent organs (T4) based on the preoperative assessment and/or intaoperative revision data or after radical surgery with the histologically confirmed regional metastasis (N+).

– Resectable colon cancer showing signs of invading the serous membrane (T3) and/or invading adjacent organs (T4) based on the preoperative assessment and/or intaoperative revision data.

– Resectable colon cancer after radical surgery with the histologically confirmed regional metastasis (N+).

– Resectable rectal cancer showing signs of invading the mesorectal fascia and/or the presence of metastatic

lymph nodes in the mesorectum based on the preoperative assessment data.

– Patients after the rectal cancer surgical treatment with the quality criteria P. Quirke of the performed total mesorectal excision (TME) that are both satisfactory (grade 2) and unsatisfactory (grade 1) based on the morphological examination of the removed specimen.

– Patients showing progression of the earlier radically treated gastric cancer or colorectal cancer in the form of isolated peritoneal carcinomatosis.

Exclusion criteria: the presence of systemic extraperitoneal metastasis, including metastasis in the central nervous system and/or carcinomatous meningitis, as well as the fact of having any other malignant tumor, except for the radically treated basal cell carcinoma, cervical cancer in situ at the time of enrollment or within 5 years before enrollment.

Based on open access publications, a historical control group was formed which included patients with diagnosed gastrointestinal tumors having a high risk of carcinomatosis after surgery and patients with metastatic forms, including peritoneal carcinomatosis. An additional retrospective group was formed based on the database of follow-up results of the patients diagnosed with gastric and colorectal cancer of the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation [10]. The database contains data on the disease course of 1423 patients, 449 patients diagnosed with gastric cancer, the median follow-up period for these patients is 27.7 months, progression is reported for 42.24% of cases, and the average time to relapse is 18.7 months from the date of surgery. A total of 974 patients diagnosed with colorectal cancer are included in the database, the median follow-up period is 41.15 months, relapse is reported in 29.72% of cases and the median time to relapse is 20.04 months.

Safety assessment

Safety assessment included the analysis of vital parameters, physical examination data, laboratory and instrumental testing results. The patient's overall health was evaluated using the ECOG (Eastern Cooperative Oncology Group) score [11].

Disease progression assessment

Progression was assessed based on the target foci measured and selected for control and the non-target foci using the radiological and RECIST 1.1 criteria [12].

The Peritoneal Cancer Index (PCI) was also assessed by the method reported in the literature [13].

The length of the trial based on the phase IIa protocol was 388 days (including 14 days of screening).

Progression-free survival (PFS) was determined as the time from the date of surgery to the date of progression, death or last contact with the patient. The disease progression was determined in accordance with the RECIST 1.1 criteria based on the comprehensive response assessment performed during the current visit.

Efficacy assessment

The «Ing-Ras» drug efficacy was analyzed concerning the following indicators:

– Overall survival (OS) (share of patients, who survived within a year). Overall survival was determined as the time from the date of surgery to the date of death or the last documented visit to the research center.

– Progression-free survival (PFS) (share of patients, who had no disease progression within a year). Progression-free survival was determined as the time from the date of surgery to the date of the documented fact of disease progression (in accordance with the RECIST 1.1 criteria) or death (of any cause).

– Median progression-free survival (mPFS) (time, in which disease progression occurs in 50% of patients).

– Dynamics of the Peritoneal Cancer Index (PCI). Comparative assessment of the method efficacy and the historical control data was performed. The data from several publications showing the results of treatment and monitoring the disease course in patients with advanced forms of gastric and colorectal cancer were used as a historical control population [14–22].

Statistical methods

Data analysis was performed in the R-Studio version 2023.06.1 software package using language-R version 4.2.2. The statistical analysis was based on the data from all patients included in the study within the framework of pre-defined analytical cohorts.

Continuous (quantitative) data are provided as the number of observations, the mean, 95% confidence interval (CI) for the mean (unless otherwise specified), standard deviation, median, interquartile range, minimum and maximum. Ordinal, categorical, and qualitative ones are presented as absolute rates of incidence (number of observations), relative rates (percentage), and 95% CI (unless otherwise specified). Survival was estimated using the Kaplan–Meier estimator [23].

RESULTS

Safety assessment

Safety assessment was performed in the ITT population based on the rate, type, association with the test drug administration, and severity of adverse events (AEs) and severe adverse events (SAEs) (including clinically significant deviation of laboratory parameters and instrumental assessment results). Safety was also estimated based on the rate of AEs associated with the PIPAC procedure (for which the association with the procedure was classified as "determined" or "probable"). The number of patients involved in safety assessment in phase IIa was 35 subjects. In the phase IIa trial, a total of 276 AEs were recorded in all 35 patients of the safety population. Among all the recorded 276 adverse events, 265 AEs (96.01%) were mild and 11 AEs (3.99%) were moderate. The following AEs and SAEs were recorded during the study. In the PP group (n = 23), five cases of AE were recorded, among these two cases (8.7%) of the grade 3 AE (elevated ALT/AST) associated with the drug were recorded in patients with gastric cancer. In the ITT group (n = 35), 12 AE cases were recorded, among these there were three cases (8.5%) of the grade 3 AE (elevated ALT/AST) and one case (2.8%) of the grade 4 AE (pancreatitis) also associated with the drug. The most common AEs included nausea (15% in ITT, 10% in PP), fatigue (12% in ITT, 8% in PP), and abdominal pain (10% in ITT, 5% in PP). No severe adverse events resulting in discontinuation of therapy were reported. All AEs were jugulated using symptomatic therapy.

When proceeding through phase II of the study, a total of three SAEs were recorded. Thus, the rate of SAE recording was 1.09% (3/276) of all AEs. The association of all SAEs with the use of the test drug and the applied PIPAC procedure was considered to be "dubious". The analysis of all the AEs in phase

IIa showed that none of these had any significant association with the tested drug or the procedure (the association was considered to be “dubious” based on the WHO classification). Furthermore, no association of the recorded changes in laboratory and vital parameters with the use of the test drug was determined.

Thus, therapy with the studied «Ing-Ras» preparation in patients diagnosed with gastrointestinal tumors, including patients with peritoneal carcinomatosis, was well tolerated by the patients, had a favorable safety profile and a high benefit-risk ratio.

Efficacy assessment

Overall survival (OS)

The one-year OS of the population of clinical trial patients was 92.1%. According to the data of official statistical reports in the RF mortality within 12 months after the diagnosis among patients diagnosed with colorectal cancer is 19.6% by this moment, while that among patients diagnosed with gastric cancer is 40.0% [14]. In 2023 in Russia, the average overall survival of patients diagnosed with gastric and colorectal cancer was 70.2%. According to the published data [15–16], the one-year survival of the historical control group is 50.8% [95% CI: 33.77–67.83%].

In the reported phase IIa clinical trial, the patient`s one-year OS was 92.1%, which almost twice exceeded the one-year survival of the historical control group and exceeded the official statistical data for the RF by 42.45%.

One-year progression-free survival (PFS) and median one-year PFS

Two patients (5.7%) had no data on the overall response estimate based on RECIST 1.1 due to withdrawal from the trial before visit 3.

During the study a total of nine cases of the underlying disease progression were reported. The one-year progression-free survival after surgery nevertheless was 84.22% [72.42–97.95%].

Considering the conditions of the clinical trial protocol, the specific characteristics of the «Ing-Ras» drug and the patient population included in the study a selection of publications was conducted to form the historical control group. This selection included data on the recurrence rate in patients with advanced gastric and colorectal cancer diagnoses who had a high risk of carcinomatosis and follow-up period of at least 12 months [17–22]. The analysis of open access publications made it possible to determine a number of indicators for certain disease entities. Thus, according to the papers focused on the studies of stage III–IV gastric cancer, the one-year PFS was less than 65% [17, 18], mPFS was within the range of 0.9–7.0 months [21]. The analysis of the data from open sources providing the treatment outcomes of patients diagnosed with metastatic colorectal cancer showed that mPFS was 5.5–12.3 months, depending on the treatment option [22].

However, the available open access data on the treatment outcomes and follow-up of patients of appropriate groups did not allow us to conduct the necessary statistical analysis to yield the reliable results. In this regard, to further assess the results for primary efficacy of the «Ing-Ras» preparation and to obtain the statistically significant information, we used the database of follow-up results of the patients diagnosed with gastric and colorectal cancer of the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation [10].

To compare the patients included in the 2022-1-*Инг*-Рас clinical trial and the patients from the database of the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation, the database censoring procedure was applied, and the patients were selected, who were most closely matched according on such criteria as sex, age, disease stage, and follow-up period to the clinical trial patients. Personal data of control patients were completely blinded for the research team members, who formed the group and conducted the data analysis.

Preliminary PFS was determined from the date of surgery (data of patient enrollment or date of the beginning of follow-up — for the control group) to the date of patient’s death or the date of the documented fact of relapse or disease progression (in accordance with the RECIST 1.1 criteria). The mPFS analysis conducted using the Kaplan–Meier estimator allowing one to estimate the probability of the event (relapse) within the specified 12-year follow-up is provided in Fig.

Significance of intergroup differences in PFS was proven using several statistical methods/tests: Cox's F-test: (T1 = 65.99039; T2 = 12.00962; F(6.148) = 4.489096; p = 0.00033); Gehan–Wilcoxon test (WW = –1519; sum = 3881E3; variance = 4602E2; statistical test = –2.23850; p = 0.02519); Cox–Mantel test (I = 7.348708; U = –5.37040; statistical test = –1.98108; p = 0.04758).

The results of conducted analysis suggest an upward trend of progression-free survival (PFS) in the study group compared to the historical control group; inclusion of the «Ing-Ras» drug in the treatment regimen makes it possible to improve treatment outcomes in patients diagnosed with stage III–IV gastric and colorectal cancer.

Dynamics in Peritoneal Cancer Index

Comparative analysis of the Peritoneal Cancer Index (PCI) in the dynamics of treatment for the ITT population is provided in Table.

The differences in PCI estimates between visits were assessed using the Friedman’s test. The resulting p-value of 0.2484 did not allow us to draw a conclusion about the PCI differences between each pair of visits. Comparison of PCI with the historical control PCI values turned out to be inapplicable due to the lack of data or insufficient data on the comparison group.

DISCUSSION

In the phase IIa clinical trial, primary assessment of the efficacy of the «Ing-Ras» preparation (peptide RAS-GTPase inhibitor), intraperitoneally administered twice at a dose of 1.8 mg/kg with a 7-day interval to patients diagnosed with gastrointestinal tumors, including peritoneal carcinomatosis, was performed.

It was shown that the one-year OS was 100%, which almost twice exceeded the one-year survival rate of the historical control group [15, 16] and exceeded the official statistical data for the RF by 42.45% [14].

The one-year progression-free survival of the PP and ITT populations was 100% and 84.22%, respectively. The median PFS for both populations was 4.45 years.

The analysis of the recorded adverse events detected in phase IIa of the trial showed that none of these were significantly associated with the studied drug or research procedure (the association was considered to be “dubious”).

The use of the drug «Ing-Ras» in patients with gastrointestinal tumors, including cases of peritoneal carcinomatosis, was not associated with the development of severe adverse reactions,

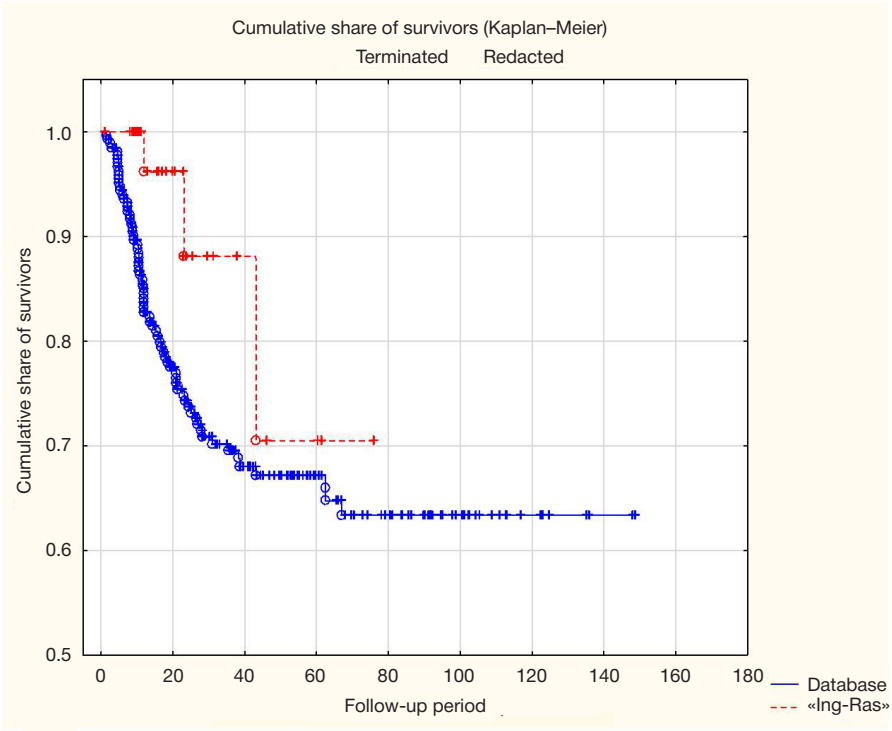

Fig. Comparison of progression-free survival (PFS) in the groups of the 2022-1-*Инг*-Рас clinical trial protocol and the group of patients from the database of the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation within the 12-year follow-up period.

was characterized by a low frequency of undesirable effects, and demonstrated an optimal benefit-risk ratio. The data confirm that it is promising in terms of further assessment in phase IIb–III of clinical trials.

To date, only two RAS-GTPase inhibitors have been approved for clinical use: Sotorasib and Adagrasib. Both drugs selectively inhibit the KRAS G12C mutation, which represents an important, but highly specific achievement in the field of precision oncology. Sotorasib (AMG-510), the first covalent inhibitor targeting KRAS(G12C)-positive non-small-cell lung cancer (NSCLC) [22], obtained the FDA's accelerated approval in May 2021 based on the CodeBreak 100 trial results [24]. And already in June 2023 the drug was registered in Russia under the brand name Lumykras®. In clinical trials oral Sotorasib at a dose of 960 mg taken once daily showed its efficacy in 37.1% of patients with the average PFS of 6.8 months [25].

Adagrasib (MRTX849/Krazati) became the second inhibitor [24, 26] that was first approved by FDA (in 2022) for the therapy of locally-advanced or metastatic non-small-cell lung cancer (NSCLC) with the KRAS-G12C mutation [27]. In 2024, after receiving the clinical trial results demonstrating a significant anti-tumor response, the Adagrasib+Cetuximab combination was assigned the status of "breakthrough therapy" and received the FDA's accelerated approval for the use for patients with the locally-advanced or metastatic colorectal cancer (CRC) associated with the KRAS-G12C mutation [27].

However, despite high clinical efficacy, marked side effects are observed when using both drugs. In particular, Sotorasib can cause hepatotoxicity, including elevated liver enzymes (ALT/AST), with severe cases in 3% of patients and critical abnormalities (degree 3/4) in 6%, leading to subsequent treatment discontinuation. As for severe complications (in 50% of patients), pneumonia (8%), hepatotoxicity (3%), diarrhea (2%), as well as fatal outcomes (3%) and sporadic cases of interstitial lung damage (0.8%) were reported during the post-marketing follow-up period [28].

Adagrasib can cause hepatotoxicity and provoke gastrointestinal disorders, so the dose adjustment is often required [29, 30]. Specific risks associated with the use of Adagrasib include prolongation of the QT interval increasing the likelihood of arrhythmia when combined with other QT prolonging drugs, as well as high rate of dosage adjustment (52% of patients) and temporal therapy discontinuation (61%) [30, 31].

In general, both inhibitors demonstrate serious toxic effects, but the use of Adagrasib is associated with the more frequent dosage adjustment and cardiovascular risk [31].

The «Ing-Ras» antitumor drug developed at the Russian Scientific Center of Roentgenoradiology of the Ministry of Health of the Russian Federation showed high therapeutic efficacy in the phase I–IIa of clinical trials (2023–2024) when administered intraperitoneally to patients with gastrointestinal tumors diagnoses, including patients with the peritoneal

Table. Dynamics of the Peritoneal Cancer Index in the ITT population

Parameter	Visit	*n*	Med	Mean	95% CI	SD	min	max	Q1	Q3	IQR
PCI, overall score	Screening	35	0	2.09	[0.23–3.95]	5.41	0	22	0	0	0
	Visit 3, day 28 (±1)	33	0	2.24	[0.09–4.39]	6.06	0	24	0	0	0
	Visit 6, day 180 (±14)	27	0	1.63	[–0.63–3.89]	5.71	0	25	0	0	0
	Visit 7, day 270 (±14)	27	0	0.93	[–0.48–2.33]	3.56	0	17	0	0	0
	Visit 8, day 360 (±14)	12	0	1.42	[–1.7–4.53]	4.91	0	17	0	0	0
	End of the trial	26	0	0.65	[–0.69–2]	3.33	0	17	0	0	0

carcinomatosis. The following results of the trial conducted were reported: 100% overall survival (OS) within 12 months in both PP and ITT populations. The median progression-free survival (PFS) was 4.45 years (53.4 months), and 84.22% of patients in the ITT group showed no signs of disease progression [32]. These values significantly exceed the historical data on Sotorasib and Adagrasib, which in CodeBreak100 and KRYSTAL-1 studies involving patients with metastatic colorectal cancer, demonstrated a median progression-free survival of 5.6 and 6.5 months, respectively, with an annual overall survival (OS) of approximately 45% trials [33–35].

The «Ing-Ras» mechanism of action is fundamentally different from that one of the KRAS-G12C covalent inhibitors (Sotorasib, Adagrasib). The drug directly inhibits the RAS-protein GTP-active form, suppressing the MAPK/ERK signaling pathway, regardless of the tumor mutational status [32]. The key of «Ing-Ras» advantage is high therapeutic efficacy in patients with peritoneal carcinomatosis, which is traditionally characterized by resistance to systemic therapy. The use of the PIPAC technique for local drug administration provides its maximum concentration in the abdominal cavity with the minimum systemic effect, thereby reducing the rate of AEs [32, 35].

The use of Adagrasib is associated with serious side effects. The potential of the «Ing-Ras» use is related to its capability to overcome tumor cell resistance to the drug, a characteristic not typical of first-generation RAS-GTPase inhibitors. While disease progression develops within 6–12 months in 60% of patients undergoing therapy with first-generation drugs due to the activation of alternative signaling pathways (PI3K/AKT, STAT3), 84.22% of patients receiving 'Ing-Ras' treatment showed no signs of progression over 4.45 years. This can be due to the drugs simultaneous effect on the tumor microenvironment in addition to the direct RAS-GTPase inhibition [32].

CONCLUSIONS

In the I–IIa phase of clinical trials the «Ing-Ras» drug administered intraperitoneally by PIPAC to patients with gastrointestinal tumors (including peritoneal carcinomatosis) showed high efficacy, beneficial safety profile and optimal benefit-risk ratio. The data demonstrate that more than 80% of patients had no disease progression, and progression-free survival increased approximately by 30%. These findings need to be confirmed in the randomized IIb–III phase trials. It is planned to conduct a IIb phase to expand the analysis of the long-term safety and efficacy in the larger cohort of patients, as well as to validate the results using independent groups. The studied «Ing-Ras» preparation demonstrated higher efficacy and safety compared to foreign analogues of RAS-GTPase inhibitors, which poses it as a promising targeted antitumor drug.

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