Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) as a Component of Combined Treatment in Patients with Advanced Epithelial Ovarian Cancer and Peritoneal Carcinomatosis: A Randomized Phase II Trial (PrimPIPAC)

Phase: II

Study Design: Prospective, randomized, open-label, controlled trial

Sponsor: Peoples' Friendship University of Russia (RUDN University), in collaboration with P.A. Hertzen Moscow Oncology Research Institute and Moscow Regional Oncological Dispensary, Russian Federation

IND Status: To be determined (cisplatin approved agent; PIPAC delivery investigational use)

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2. STUDY SCHEMA

Population: Women aged 18-75 years with newly diagnosed FIGO IIIB-IIIC ovarian cancer, visually detectable peritoneal carcinomatosis.

Randomization (controlled, intraoperative):

- The source protocol defines the trial as randomized and controlled; a formal allocation ratio and stratification scheme are not specified.

Arm A - Experimental:

TC systemic chemotherapy plus cisplatin-based PIPAC x 3 procedures:

- At initial diagnostic laparoscopy/laparotomy (PIPAC-1)
- During induction treatment before interval cytoreduction (PIPAC-2)
- Immediately after interval cytoreductive surgery (PIPAC-3)

Arm B - Comparison:

Standard combined treatment with one PIPAC procedure performed simultaneously with interval cytoreductive surgery; this corresponds in timing to PIPAC-3 in the experimental arm.

Third study branch:

Patients from either arm in whom complete cytoreduction is not achieved receive postoperative TC courses 4 and 5, one additional PIPAC procedure, and then systemic chemotherapy course 6.

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3. OBJECTIVES

3.1 Primary Objective

To improve the efficacy of combined treatment in ovarian cancer with peritoneal carcinomatosis by incorporating repeated PIPAC into the drug-therapy component of standard management.

3.2 Secondary Objectives

- Evaluate induction-treatment efficacy by PCI dynamics, ascites and morphological response.
- Assess toxicity and tolerability of platinum-based PIPAC combined with systemic chemotherapy.
- Evaluate progression-free survival, overall survival, recurrence rate, time to recurrence, and patterns of progression.

3.3 Exploratory Objectives

- Standardize the integration of PIPAC with neoadjuvant and postoperative systemic therapy, including indications and contraindications.
- Assess whether additional postoperative PIPAC may improve outcomes after incomplete cytoreduction.

4. BACKGROUND AND RATIONALE

Peritoneal carcinomatosis is one of the principal manifestations of advanced ovarian cancer and a major cause of treatment failure. Although combined systemic therapy and surgery remain standard, prognosis worsens substantially when the peritoneal tumor burden is high and optimal cytoreduction is difficult to achieve.

In patients with extensive peritoneal dissemination, aggressive surgery alone may be technically infeasible or associated with significant morbidity. Locoregional intraperitoneal treatment therefore remains an important therapeutic objective.

PIPAC enables pressurized aerosol delivery of chemotherapy into the peritoneal cavity and is intended to improve tissue distribution while limiting systemic exposure. The protocol therefore evaluates repeated cisplatin-based PIPAC as an additional component of first-line combined treatment in ovarian cancer with peritoneal carcinomatosis.

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5. ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

- Female, age 18-75 years.
- Histologically verified ovarian cancer with peritoneal carcinomatosis.
- FIGO stage IIIB or IIIC.
- visually detectable peritoneal carcinomatosis.
- Peritoneal metastatic involvement documented preoperatively by ultrasound, CT, MRI, PET-CT, or equivalent imaging.
- Ability to comply with protocol procedures and provide written informed consent.

5.2 Exclusion Criteria

- Age > 75 years; ECOG 3-4; cachexia with BMI <= 16.
- Severe concomitant disease in exacerbation or decompensation.
- Extra-abdominal metastases, including metastatic pleuritis.
- Mucinous ovarian carcinoma or another active malignant neoplasm, except malignancies in clinical remission for more than 2 years.
- Pronounced adhesive disease of the abdominal cavity.
- Pregnancy or breastfeeding.
- Positive BRCA1 or BRCA2 status.
- Any condition precluding safe PIPAC or protocol execution, including hollow-organ perforation, gastrointestinal resection with anastomosis, or repair of a hollow-viscus defect.
- Refusal of treatment at any study stage.

6. TREATMENT PLAN

6.1 Surgery

- Diagnostic laparoscopy or, when laparoscopy is not feasible, diagnostic laparotomy.
- Ascites volume, visceral and parietal peritoneal involvement, and the PCI according to Sugarbaker are documented.
- Peritoneal, ovarian, and omental biopsies are obtained; the primary tumor is not removed during the diagnostic stage.
- First PIPAC is performed immediately after pathologic verification of carcinomatosis.

6.2 Systemic Chemotherapy

- Systemic chemotherapy is administered according to the TC regimen at 3-week intervals.
- When PIPAC is combined with cytoreductive surgery, postoperative systemic chemotherapy starts 7-21 days after surgery.
- When PIPAC is performed as a standalone procedure, systemic chemotherapy starts 1-10 days after intraperitoneal treatment.

6.3 PIPAC Procedure

Performed laparoscopically under general anesthesia.
Drug: cisplatin 30 mg/m^2 diluted in 180 mL normal saline
Administration:

- Capnoperitoneum established with carbon dioxide at a target pressure of 12-14 mmHg.
- Flow settings depend on nozzle size: No. 150, 0.3-0.4 mL/s; No. 200, 0.7-0.8 mL/s.
- Nebulizer selection depends on patient height and body-mass index; tense ascites is evacuated before treatment.
- The aerosol flow is directed toward the largest free intraperitoneal space and away from hollow viscera, ligated vessels, and tumor beds.
- Exposure time is maintained for exactly 30 minutes.
- The abdomen is decompressed without aspirating the cytostatic solution, and no drain is left in place.

6.4 Interval Cytoreductive Surgery

- Performed after the second PIPAC session and the third course of neoadjuvant chemotherapy.
- The planned operative volume includes total hysterectomy with adnexa, omentectomy, peritonectomy, or multifocal peritoneal biopsy when indicated.
- The surgical aim is maximal cytoreduction; residual disease is categorized as complete or suboptimal cytoreduction.
- Before abdominal-wall closure, two trocars are positioned and a further PIPAC session is performed in the same operative setting.

6.5 Third Study Branch

- Patients from either arm in whom complete cytoreduction is not achieved receive postoperative TC chemotherapy courses 4 and 5, an additional PIPAC procedure, and then chemotherapy course 6.

7. STUDY ASSESSMENTS

7.1 Baseline / Screening

- Eligibility assessment, physical examination, vital signs, anthropometry, ECOG, gynecologic examination.
- CBC, urinalysis, biochemistry, coagulation studies, infection screening, venous Doppler, echocardiography, ECG, and thromboembolic-risk assessment.
- Tumor markers including CA-125, HE4, and CA 19-9; BRCA status; histology; ascites puncture if indicated.
- Imaging with CT, MRI, PET-CT, ultrasound, or clinically equivalent modalities.

7.2 During Treatment

- At each operative stage: ascites-volume assessment, PCI reassessment, biopsy sampling, histology, and adverse-event recording.
- At each systemic-chemotherapy visit: clinical examination, laboratory testing, dose calculation, premedication, and safety assessment.
- Histologic response is assessed after repeat procedures using treatment-regression evaluation specified by the protocol.

7.3 Follow-up

- Follow-up visits are performed every 3 months during the first 2 years after treatment.
- Assessments include physical examination, tumor markers when initially elevated, ultrasound of abdomen and pelvis, CT chest, MRI pelvis or CT abdomen as indicated, and ascites puncture when needed.
- Quality of life is evaluated with EORTC questionnaires during follow-up.

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8. ENDPOINT DEFINITIONS

8.1 Primary Endpoint Domain

Primary endpoint – is complete surgical cytoreduction (CRS R0).

8.2 Response Criteria

- PCI complete response - PCI < 3 together with negative results on at least three biopsy samplings.
- PCI partial response - reduction of PCI by at least 4 points.
- PCI progression - increase of PCI by at least 4 points or appearance of one or more new lesions.
- PCI stable disease - response pattern meeting neither partial-response nor progression criteria.

Clinical response is evaluated according to RECIST 1.1; morphologic response is assessed according to protocol-defined TRG criteria.

8.3 Secondary Endpoints

- Overall survival, progression-free survival, median survival, recurrence rate, and time to progression.
- Rate of ascites accumulation and proportion of patients with at least 50% reduction in tumor-marker levels.
- Frequency and severity of adverse events, wound-healing time, intestinal paresis, and laboratory abnormalities.

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9. STATISTICAL CONSIDERATIONS

9.1 Planned Sample Size

At least 160 patients will be enrolled. Accrual is planned for 5 years from enrollment of the first randomized patient.

9.2 Analysis Framework

The source protocol does not define a separate formal power calculation or detailed ITT/mITT/per-protocol populations.

- All enrolled and treated patients will contribute to the protocol evaluations.
- Analyses are planned according to study arm and extent of cytoreduction, as appropriate.

9.3 Statistical Methods

- Quantitative variables will be summarized by mean, standard deviation, and standard error of the mean.
- Nominal and ordinal variables will be summarized as frequencies and percentages.
- Safety endpoints will be reported descriptively and include all adverse events, events leading to withdrawal, and events considered treatment-related.

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10. SAFETY MONITORING

- All adverse events occurring after signature of informed consent must be identified and documented.
- For each adverse event, the investigator records onset date, duration, intensity, treatment required, outcome, and action taken with study treatment.
- Serious adverse events are defined as events leading to death, an immediately life-threatening condition, persistent or significant disability, hospitalization or prolongation of hospitalization, or another medically significant condition.

- During PIPAC, staff exposure to cytostatics must be minimized by use of disposable linen, double gloves, masks, protective eyewear, and sealed disposal containers.
- Pregnant and breastfeeding staff members must not work in the operating room during the procedure.

11. DATA MANAGEMENT

- Written informed-consent forms, discharge summaries, source medical records, and protocol-specific case documentation are retained by the investigator.
- CRF data are grouped in an Excel database; the case-report forms, source statistical processing, and supporting materials remain available for verification.
- CRFs are signed by the investigator and the head of department; patients are identified in study documents by coded identifiers rather than full names.
- All study documentation, including source data and protocol files, must remain accessible for direct review by monitors, auditors, ethics committees, and regulatory authorities.

12. ETHICAL CONSIDERATIONS

- The study is conducted in accordance with the Declaration of Helsinki, OST 42-511-99 on quality clinical trials, and applicable Russian regulatory requirements.
- Ethics Committee approval is required before study initiation and for any material protocol amendment.
- Written informed consent is mandatory before any study-specific procedure is performed.
- Patient rights, safety, well-being, and confidentiality take precedence over the interests of science and society.

13. CORRELATIVE STUDIES (OPTIONAL)

- BRCA status determination at screening; patients with positive BRCA status are excluded according to the source protocol.
- TRG-based histologic assessment of serial peritoneal and omental specimens.
- Serial tumor-marker evaluation and quality-of-life assessment during follow-up.

14. STUDY DURATION

Accrual period: up to 5 years from enrollment of the first randomized patient.

Follow-up: every 3 months during the first 2 years after completion of therapy.

Total duration: approximately 5 years of accrual plus protocol-defined follow-up.

APPENDICES (on request)

- Appendix A: Visit Schedule and Assessment Matrix
- Appendix B: PIPAC Technical Procedure
- Appendix C: TRG / Morphologic Response Assessment
- Appendix D: RECIST 1.1 and PCI Response Definitions
- Appendix E: Toxicity and Safety Reporting
- Appendix F: Informed Consent Template