Adjuvant Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) with Cisplatin and Doxorubicin in Patients with Suboptimally Cytoreduced Advanced Epithelial Ovarian Cancer: A Randomized Phase II Trial (PIPAC-OVA)

Phase: II

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

Sponsor: Moscow Regional Oncological Dispensary, Balashikha, Russian Federation

IND Status: To be determined (cisplatin and doxorubicin approved agents; PIPAC delivery investigational use)

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Protocol Version/Date:
Protocol #661, April 9, 2021 (Version 1.0)

Kommentiert [AT1]: NB,please!

2. STUDY SCHEMA

Population:
Women with FIGO IIIB–IIIC epithelial ovarian cancer with residual disease >1 cm following primary cytoreductive surgery (no neoadjuvant chemotherapy).

Randomization (1:1, stratified):

- Stratification factors:
    - FIGO stage (IIIB vs IIIC)
    - Histology (HGSOC vs other epithelial)

Arm A – Control:
Carboplatin (AUC 5–7) + Paclitaxel (175 mg/m^2) IV q3 weeks × 6 cycles

Arm B – Experimental:
Carboplatin + Paclitaxel (as above)
PLUS
PIPAC cisplatin (10.5 mg/m^2) + doxorubicin (2.1 mg/m^2) × 3 procedures:

- Immediately post-PCS
- Before cycle 3
- Before cycle 5

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3. OBJECTIVES

3.1 Primary Objective

To compare **progression-free survival (PFS)** between treatment arms.

3.2 Secondary Objectives

- Compare overall survival (OS)
- Compare CA-125 normalization rates
- Evaluate peritoneal disease regression (PCI and PRGS)
- Evaluate ascites control
- Assess safety and tolerability (CTCAE v5.0)

3.3 Exploratory Objectives

- Correlate PRGS with PFS and OS
- Evaluate translational biomarkers (optional)

- Assess patient-reported outcomes (FACT-O or EORTC QLQ-C30/OV28)

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4. BACKGROUND AND RATIONALE

Patients with residual macroscopic disease >1 cm after primary cytoreductive surgery have inferior outcomes. Intraperitoneal chemotherapy has demonstrated survival benefit in selected populations.

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) enhances intraperitoneal drug distribution and tissue penetration while using reduced systemic doses.

The supporting randomized phase II data demonstrate:

- Median PFS improvement: 20.0 vs 12.0 months
- Median OS improvement: 46.2 vs 38.1 months
- No increase in Grade ≥3 toxicity

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These data support confirmatory evaluation under NCI-compliant standards.

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5. ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

1. Female, age 18–75
2. Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
3. FIGO stage IIIB or IIIC
4. Residual disease >1 cm following primary cytoreductive surgery
5. No prior systemic therapy
6. ECOG 0–3
7. Adequate organ function:
    - ANC ≥ 1,500/μL
    - Platelets ≥ 100,000/μL
    - Creatinine clearance ≥ 50 mL/min
    - Bilirubin ≤ 1.5× ULN
8. Signed informed consent

5.2 Exclusion Criteria

- Extra-peritoneal metastases
- Malignant pleural effusion
- Prior chemotherapy or radiotherapy
- Active second malignancy
- ECOG 4
- Pregnancy or breastfeeding

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6. TREATMENT PLAN

6.1 Surgery

Standard primary cytoreductive surgery including:

- Total hysterectomy
- Bilateral salpingo-oophorectomy
- Omentectomy
- PCI assessment
- Peritoneal biopsies

6.2 Systemic Chemotherapy

Paclitaxel 175 mg/m^2 IV over 3 hours
Carboplatin AUC 5–7 IV

Every 21 days × 6 cycles

Dose modifications per CTCAE v5.0.

6.3 PIPAC Procedure (Experimental Arm Only)

Performed laparoscopically under general anesthesia.

Drugs:

- Cisplatin 10.5 mg/m^2
- Doxorubicin 2.1 mg/m^2

Administration:

- Aerosolized via CE-marked injector
- 12 mmHg capnoperitoneum
- Exposure time: 30 minutes
- Closed aerosol waste system

Biopsies:

- Collected at each PIPAC
- PRGS assessment

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7. STUDY ASSESSMENTS

Baseline

- CT chest/abdomen/pelvis
- CA-125
- ECOG
- Labs

During Treatment

- Labs prior to each cycle
- CA-125 each cycle
- Adverse events continuous monitoring

6-Month Assessment

- Imaging (both arms)
- Diagnostic laparoscopy (PIPAC arm)
- PCI reassessment
- PRGS scoring

Follow-up

- Every 3 months × 2 years
- Then every 6 months

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8. ENDPOINT DEFINITIONS

Primary Endpoint

Progression-Free Survival (PFS):
Time from surgery to radiologic progression (RECIST 1.1) or death.

Secondary Endpoints

- OS: Time from surgery to death
- CA-125 response: GCIG criteria
- PRGS response
- Ascites resolution
- Safety (CTCAE v5.0)

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9. STATISTICAL CONSIDERATIONS

9.1 Sample Size Calculation

Assumptions:

- Median PFS control: 12 months
- Median PFS experimental: 20 months
- HR = 0.60 (conservative estimate vs observed 0.31

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- Power 80%
- Two-sided alpha 0.05

Required sample: ~180 patients (90 per arm)

9.2 Analysis Populations

- ITT
- mITT
- Per-protocol
- Safety population

9.3 Statistical Methods

- Kaplan–Meier method
- Log-rank test
- Cox proportional hazards

- Logistic regression for response endpoints

Interim safety analysis after first 40 patients complete 3 cycles.

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10. SAFETY MONITORING

- CTCAE v5.0 grading
- DSMB oversight
- SAE reporting within 24 hours
- Annual IND safety reporting (if applicable)

Stopping rules:

- 20% unexpected Grade 4 non-hematologic toxicity
- Procedure-related mortality >3%

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11. DATA MANAGEMENT

- Electronic data capture (21 CFR Part 11 compliant)
- Source document verification
- On-site monitoring

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12. ETHICAL CONSIDERATIONS

- Conducted per ICH-GCP
- Declaration of Helsinki
- IRB approval required
- Written informed consent mandatory

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13. CORRELATIVE STUDIES (OPTIONAL)

- BRCA mutation status
- HRD status
- Peritoneal fluid cytology
- Translational tissue banking

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14. STUDY DURATION

Accrual period: 36 months
Follow-up: Minimum 24 months
Total duration: ~5 years

APPENDICES (on request)

- Appendix A: Dose Modification Tables
- Appendix B: PIPAC Technical Manual
- Appendix C: PRGS Scoring System
- Appendix D: RECIST 1.1 Criteria
- Appendix E: Informed Consent Template