Ovarian carcinoma is the most lethal gynecological cancer. According to the Polish National Cancer Registry, each year more than 2500 women die from this disease. Mortality rate is high since the majority of women are diagnosed with advanced stage disease where 5-year survival is less than 50%. Ovarian cancer is a heterogeneous disease with a distinct molecular background and clinical behavior, however it is treated with a single entity. The standard treatment consists of cytoreductive surgery followed by platinum-taxane chemotherapy. Despite initially high response rates to this treatment, most patients develop recurrent disease within few years. Thus, there is pressing need to develop novel treatment strategies to improve patients outcome.

The phosphatidylinositol 3-kinase (PI3K) signaling pathway is an attractive target for therapeutic interventions. This pathway plays an essential role in cell proliferation, survival, growth and metabolism. Deregulation of this cascade is frequently observed in human cancer. In this project, status of two components of this cascade will be analyzed: *PIK3R1*, the gene that encodes the p85α regulatory subunit of PI3K, and *INPP4B,* the tumor suppressor gene for inositol polyphosphate-4-phosphatase, which functions as a PI3K inhibitor. We will evaluate the role of *PIK3R1* and *INPP4B* in ovarian cancer pathogenesis. Moreover, we will determine the associations between alterations in these genes and clinico-pathological features of tumors, response to treatment and patients outcome. Furthermore, we will analyze the coexistence of *PIK3R1* and *INPP4B* alterations with mutations in *PIK3CA*, *PTEN* and *KRAS* to verify the hypothesis if dysfunction of one gene in the PI3K pathway is sufficient to ovarian cancer development.

In this project, extensive studies on DNA, RNA and protein level will be conducted and supported by statistical analyzes. The material will comprise frozen or formalin-fixed paraffin-embedded (FFPE) tumor sections from ovarian cancer patients and blood samples from healthy women as a reference material.

Mutation analysis in the *PIK3R1* gene will be done with the use of direct sequencing, whereas in the other genes (*INPP4B*, *PIK3CA*, *PTEN* and *KRAS*) with the use of the sensitive screening method HRM. Analysis of the copy number variation (CNV) and mRNA expression for *PIK3R1* and *INPP4B* will be conducted using quantitative real-time PCR method (Real-Time qPCR) for approximately 130 ovarian cancers including cases previously analyzed for mutations. Evaluation of the level of *INPP4B* promoter methylation will be carried out with qMSP method. Level of p85α and INPP4B proteins will be evaluated immunohistochemically (IHC) in a group of about 400 cancers from patients treated with either the cisplatin/cyclophosphamide (PC regimen) or taxanes/cisplatin (TP regimen).

Results of this study will concur to the widening of the knowledge about the role of *PIK3R1* and *INPP4B* in ovarian cancer pathogenesis, biology and clinics. While assessment of their prognostic and predictive significance may increase diagnostic and therapeutic options for ovarian cancer patients. Evaluation of *PIK3R1* and *INPP4B* status may broaden the window of therapeutic application for PI3K pathway inhibitors and should be taken into consideration while planning clinical trials.