

## The assessment of the doctoral dissertation by Anna Erol

“Transcriptomic analysis of High-Grade Serous Ovarian Cancer uncovers molecular markers with potential use in therapy or diagnosis.”

### Scope and content

Ovarian cancer (OC) is one of the most fatal gynecological malignancies and a leading cause of cancer-mortality in women. The most common and aggressive type of OC is the high-grade serous ovarian cancer (HGSOC). Due to its asymptomatic nature, it is often diagnosed in an advanced stage. Furthermore, some of these patients develop chemotherapy resistance which drastically impacts their survival chances. A better understanding of the pathways involved in HGSOC progression and the development of multidrug resistances is needed to allow the development of new therapeutic approaches.

In her thesis, Ms. Erol aimed to characterize the transcriptomic signature of HGSOC tumor tissues (n=33) and to compare them with control samples of ovarian tissues without oncological disease (n=33). The analysis should also focus on the crosstalk between competing endogenous RNAs, including mRNA, lncRNAs and miRNAs. Through the identification of key differentially expressed genes, drug candidates for the treatment of HGSOC should be identified. The Bioethics Committee of the Medical University of Białystok approved the collection of the samples and written informed consent was obtained from all patients included in the study.

Ms. Erol work is well structured and begins with the isolation of mRNA from HGSOC tumor tissue and ovarian tissue controls. Thereafter, samples were subjected to RNA-sequencing followed by analysis of differential expression patterns of micro RNAs (miRNAs) and long noncoding RNAs (lncRNAs). With these data a competing endogenous RNA (ceRNA) network was proposed. Further functional analysis was performed using specific software (clusterProfiler in Gene Ontology database and Kyoto Encyclopedia of Genes and Genomes). In combination with the description and analysis of network-related transcription factors, the identification of key molecular mechanisms during HGSOC development and growth was feasible. As a result, the PI3K/Akt pathway was identified as possible therapeutic target. Based on further bioinformatic processing (e.g. Cmap Drug Repurposing Hub), Ms. Erol identified PI-103 and ZSTK474 as candidate molecules for the treatment of HGSOC by PI3K pathway.

This work provides new data on the interactions between cancer-associated genes, ceRNAs and transcription factors in HGSOC. Furthermore, the identification of differently expressed genes might help to establish potential biomarkers of the neoplastic disease.

## Structure

The introduction delivers a precise description of the relevance of the research topic. There is a particularly detailed description of the development of high-throughput methods. Also an excellent description of competing endogenous RNAs, which is fundamental for the understanding of the methodological strategy, was provided. To address her scientific aims, Ms. Erol uses state-of-the-art methods based on RNA-sequencing and an extensive bioinformatic analysis.

The description of the methods is sufficient but could profit from further details concerning the obtainment of the samples. However, the bioinformatic methods are very well explained and provide detailed information about tools and statistical corrections.

The results are presented in a logical, comprehensible manner accompanied by high quality figures. It must be mentioned that the figures/tables do not always follow the order presented in the text, though this represents no major inconvenience for the text comprehension.

There is a rich and clear discussion of the results with no overinterpretation of the data. The data is set in within the literature context and offers experimental alternatives for the enrichment of the statements presented. The conclusion is concise but straightforward and highlights the most important aspects of the work. The outlook section could have profit from a deeper discussion of the clinical aspects where the results can be applied. The monography follows the expected structure for a scientific work and is scientifically correct written.

## Conclusion

The thesis by Ms. Erol generated new knowledge in the field of oncology and demonstrated her solid understanding of the state-of-the-art in the research area and the knowledge of the most important and current literature. The results are presented clearly, with the appropriate controls and statistical analysis and discussed in relation to the research of others. The thesis also showed a good understanding of the implications of the work in a broader scientific context.

The submitted thesis complies with the requirements of the doctoral regulations of the Medical University of Bialystok to obtain the academic doctoral degree and are sufficiently large to award Ms. Erol with a doctoral degree. I recommend that the dissertation should be accepted for public defence.



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