Background:
The BCL-2 protein belongs to the family of intracellular protein factors that control the processes of apoptosis. The process of regulation of programmed cell death depends on the balance between pro- and anti-apoptotic proteins of this family. In most cases, activation of BCL-2 helps suppress apoptosis and increase the lifespan of tumor cells, as well as increase their resistance to chemotherapy. The ability to block apoptosis is a hallmark of many malignant neoplasms, including hematological ones.

Classical Hodgkin lymphoma (cHL) refers to a tumor of the hematopoietic system and has a relatively good response to treatment. However, in 15-20% of cases there is a lack of response to standard first-line chemotherapy. The data available in the relative literature regarding the relationship between BCL-2 expression in tumor cells and the effectiveness of treatment are contradictory. A number of authors confirms that the detection of this protein in Hodgkin and/or Reed-Sternberg cells (HRS) is an independent factor in the adverse outcome of cHL. But the inconsistency of the data indicates the advisability of further study of the association of the expression of the specified protein factor of apoptosis with the response to 1st line therapy.

Aims:
To study the relationship of BCL-2 expression with the response to frontline therapy in nodular sclerosis classical Hodgkin lymphoma (NSCHL).

Methods:
We used formalin-fixed paraffin-embedded (FFPE) lymph node samples of 37 patients with newly diagnosed NSCHL who were treated at the clinic of KRIHBT in the period from 2006 to 2018. Depending on the response to the 1st line therapy according to the BEACOPP-14 regimen, the subjects were divided into 2 groups: group 1 (n=17) included patients who achieved complete remission (CR). Group 2 (n=20) included patients with refractoriness to the first and subsequent lines of chemotherapy or minimal response to it, or patients who received autologous or allogeneic hematopoietic stem cell transplantation.

To identify BCL-2+ tumor cells an immunohistochemical staining method was used. Pathomorphological analysis and relative number counting of BCL-2+ tumor cells were performed in sequential fields of view in 100 HRS cells for each sample.

Results:
According to the response to 1st-line chemotherapy, differences in the relative number of BCL-2+ tumor cells were established. In patients with a partial response (PR) to treatment, the number of positive cells was statistically significantly higher than in patients with CR: 80% (58-88) vs. 24% (8-42), respectively, p<0.001. The optimal threshold value for the proportion of BCL-2+ tumor cells was 46%. Based on the established threshold, all subjects
were divided into two categories: with high (≥46%) and low (<46%) BCL-2 expression. Patients with a BCL-2+ cell count >46% are 18.4 and 59.5 times more likely to develop a PR and an adverse course, respectively, than those with a low threshold (p<0.05). The frequency of occurrence of BCL-2+ cells above the threshold level was detected statistically significantly more often in patients with frontline treatment failures of in relation to patients with CR: 17 (81%) versus 4 (19%) patients (p<0.001).

**Summary/Conclusion:** A high relative content of BCL-2+ tumor cells (≥46%) is associated with treatment failures in patients with NSCHL. Determining the proportion of neoplastic cells marked with this antibody could be used as an additional morphological criterion for predicting the course of the disease already at the stage of diagnosing patients in order to apply a personalized approach to therapy with BCL-2 inhibitors.