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Title of diploma thesis: Determination of organ toxicity of BRAF inhibitors *in vitro*.

Malignant melanoma is one of the most serious skin diseases today. Therapy of advanced melanoma is difficult and often ineffective. BRAF inhibitors (dabrafenib and vemurafenib) have dramatically changed the results of melanoma treatment in the last few years. BRAF inhibitors are one of the most effective drugs against melanoma, but their clinical application is largely limited by drug resistance. Available clinical studies have shown an adverse nephrotoxic effect of BRAF inhibitors, but information on its mechanism is limited. Published studies further suggest that the toxic effect of BRAF inhibitors is primarily directed to podocytes located in the glomerular membrane. Thus, the aim of our study was to assess the cytotoxic effect of BRAF inhibitors on selected model renal cells *in vitro* in order to confirm the renal target toxicity. The main objective of the study was to analyse whether the nephrotoxic effect of BRAF inhibitors is specifically limited to podocytes or whether it can damage other renal cells. The experiments were performed on human cell lines representing different types of kidney cells (PODO/TERT256, HK-2) as well as on the standard liver cell line HepG2, which served as a comparator. Amphotericin B and paracetamol were used as reference toxins. A colorimetric method was used to measure the metabolic activity of the cells. IC_{50} values determined by analysis of inhibition curves were used for comparison.

The obtained experimental data showed a comparable toxic effect of the two BRAF inhibitors tested on all three cell lines used. However, vemurafenib showed significantly higher toxicity compared to dabrafenib. The *in vitro* toxicity of vemurafenib in podocytes was even stronger than that of the known renal toxins of amphotericin B. The results may suggest that toxic renal damage caused by treatment with BRAF inhibitors includes not only podocytes but also other kidney cell types, including renal tubule cells.