ABSTRACT

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Title of diploma thesis: Inhibitory effect of tepotinib, entrectinib, and sapanisertib on an activity of selected reductases from AKR superfamily.

The lung carcinoma has an increasing trend in the Czech Republic. These findings correspond to the fact that lung carcinoma is the most common type of cancer worldwide.

Carbonyl reducing enzymes occur in different types of tissues, and they are responsible for the development of inflammation, cancer, and cancer resistance. These NADPH-dependent oxidoreductase cause the reduction of carbonyl groups to alcohol compound and decrease the toxicity of drug for tumor cells. Last but not least, these enzymes are responsible for tumor cell proliferation, differentiation, and increased tumoral aggressivity.

This work aimed to study the inhibition effect of chosen cyclin-dependent kinase inhibitors (CDKi) on the activity of Aldo-keto reductases. Besides inhibition of CDK, the ability to inhibit efflux transporters and carbonyl reducing enzymes was proved at CDK inhibitors.

The inhibition effect of tepotinib, entrectinib and sapanisertib was determined by UHPLC analysis. The most significant inhibition potential to AKR1C3 was observed at tepotinib 50 μM (70,57 % of enzyme was inhibited). Thus tepotinib was selected for further tests. The value of IC_{50} of tepotinib was calculated in the range 8,48 – 12,20 μM, and the value of inhibitory constant was in the range 4,38 +/- 0,65 μM. The experiment shows that tepotinib is a competitive inhibitor.

We can assume that the combination of cytostatic and inhibitors of CDK may increase the effect of the treatment and eliminate the occurrence of side effects of conventional treatment.