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CDK4 phosphorylation status and rational use of CDK4/6 inhibitors in advanced thyroid cancers

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Introduction and objectives: The cyclin-dependent kinases CDK4 and CDK6 are key regulators of the cell cycle entry, by phosphorylating the onco-suppressor retinoblastoma protein (pRb). CDK4/6 inhibitors (CDK4i) are already established as standard first-line treatment against advanced Estrogen Receptor-positive breast tumors, and have emerged as novel drugs to treat various pRb-proficient chemotherapy-resistant cancers. Presence of activating T172-phosphorylation of CDK4 in breast tumors correlates with their sensitivity to the CDK4i palbociclib (Raspé E, *et al*. EMBO Mol Med. 2017; 9,1052-1066). The molecular characterization of metastatic differentiated (DTC), poorly differentiated (PDTC) and anaplastic thyroid carcinomas (ATC) suggests that CDK4i could be considered for treating advanced thyroid cancers. We aimed to investigate the CDK4 activation state in thyroid cancer and its relationship with the sensitivity to CDK4i.

Methods and results: Sensitivity to three CDK4i was assessed (by BrDU incorporation and viability assays) in 11 ATC-, 2 PDTC- and 7 WDTC-derived cell lines. All except 3 cell lines were sensitive to CDK4i with either full or partial inhibition of DNA synthesis. CDK4 post-translational modifications were investigated using 2D-gel electrophoresis. As seen previously in breast cancer, detection of CDK4 T172-phosphorylation also predicted sensitivity to CDK4i in thyroid cancer cell lines. The three resistant cell lines were characterized by barely detectable pRb phosphorylation and high expression of CDK4 inhibitor p16, whereas in all sensitive cell lines, phosphorylated pRb was detected. A cohort of fresh-frozen primary tissues was also analyzed by 2D-gel electrophoresis. Consistent with their quiescent state, phosphorylated CDK4 could not be detected in 14 of 17 non-malignant thyroid tissues. CDK4 phosphorylation was detected in 29 of 32 DTC, in 8 lymph node metastases, in 17 of 19 PDTC and in 12 of 20 ATC. Analysis by RNA-sequencing revealed that in comparison to tumors with CDK4 phosphorylation, tumors without phosphorylated CDK4 presented lower pRb levels and the highest p16 levels. However, no pRb mutations were found in these samples. Palbociclib combination with MEK/BRAF inhibitors as evaluated by clonogenic assay was highly effective, being able to completely arrest proliferation. The combined drugs were shown to prevent known resistance mechanisms, most notably Cyclin E-CDK2 activation, as observed by immunoprecipitation assays.

Conclusion: The presence of the phosphorylated CDK4 (the actual CDK4i

presently are incurable and lead to patients death within few months.

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