

## Contemporary systemic therapeutic options in the management of thyroid cancer

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Cytotoxic chemotherapy has been virtually abandoned for the treatment of thyroid cancer due to toxicity and lack of efficacy. With the exception of anaplastic thyroid cancer, only patients with rapidly progressive (within one year per RECIST criteria) and/or symptomatic disease are candidates for therapy, due to an often indolent disease course. Asymptomatic patients with slowly-progressive disease should be closely monitored. Systemic treatment of advanced and progressive unresectable or metastatic radioiodine-refractory DTC is currently based on multiple kinase inhibitors (MKI) lenvatinib, cabozantinib, or sorafenib. The use of specific inhibitors directed against a *RET* or *TRK* gene fusion has produced extensive tumor responses. In patients with a *BRAFV600E* mutation, a BRAF-inhibitor (dabrafenib) alone or in combination with a MEK-inhibitor (trametinib) has induced a tumor response in up to 54% of patients. Moreover, the inhibition of the MAPK pathway with these drugs may induce the redifferentiation of refractory thyroid tumor cells and the reappearance of tumor radioiodine uptake. Larotrectinib and entrectinib are tumor-agnostic tropomyosin receptor kinase (TRK) inhibitors that are used agnostically for the treatment of advanced or metastatic solid tumor cancers with neurotrophic tyrosine receptor kinase (NTRK) gene fusions. NTRK fusion can be present in either DTC (usually papillary TC) or in ATC. In medullary thyroid carcinoma (MTC) patients, multikinase inhibitors (MKI) vandetanib and cabozantinib are used for the treatment of progressive or symptomatic metastatic/unresectable MTC. Two selective *RET*-kinase inhibitors, selpercatinib and pralsetinib, are available for the treatment of *RET*-mutant MTC. They are more efficient and less toxic than MKIs. In anaplastic thyroid carcinoma (ATC) with *BRAFV600E* mutation, therapy with dabrafenib and trametinib should be the treatment of choice: this combination has been approved by the FDA. Immunotherapy can sometimes be effective in tumors with a high mutational burden. Multidisciplinary tumor boards (MTB) of various specialists involved in the diagnostics and treatment of patients with TC in highly specialized centers with a high volume of patients provide optimal patient management.

Key words: differentiated thyroid cancer; medullary thyroid cancer; *RET*-proto-oncogene, molecular targeted therapy; anaplastic thyroid cancer; treatment