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TARGETED THERAPIES

Precision medicine for ATC — BRAF and MEK inhibition shows promise

> tumour mutation screening should be performed for all patients with ATC as it can transform their outcomes

Anaplastic thyroid carcinoma (ATC) is a rare malignancy (accounting for 1–2% of all thyroid cancers) that holds a dismal prognosis, with median overall survival (OS) durations in the range of 5–12 months. The current standard-of-care systemic therapies are of limited or no benefit: response rates with chemotherapy are only ~15%. BRAF V600 mutations are a common driver of the well-differentiated tumours that often precede ATC and, correspondingly, are present in up to 50% of ATCs. Importantly, these aberrations present a therapeutic vulnerability, as demonstrated in patients with melanoma, lung cancer, and now ATC.

The new evidence in patients with ATC comes from a single-arm phase II study conducted as part of an international basket trial encompassing *BRAF*^{V600E}-mutant rare cancers of nine pre-specified histologies. Investigators at 47 centres worldwide collaborated to enrol 100 patients, 16 of whom had ATC. The patients received treatment with the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib.

In the ATC cohort, 11 patients (69%) had objective responses, including one complete response; another three patients (19%) had stable disease. After a median follow-up duration of 47 weeks, seven responses were ongoing, and the median response, progression-free survival (PFS), and OS durations were not reached. Notably, the estimated 12-month PFS and OS outcomes were 79% and 80%, respectively, which is extremely encouraging considering that typically only 20–40% of patients with ATC survive for 1 year after diagnosis.

The safety profile of dual BRAF and MEK inhibition was mostly as expected based on the current clinical experience in the fields of melanoma and lung cancer. Nevertheless, 93% of patients experienced adverse events, with grade 3–4 toxicities occurring in 42%.

"The results of our trial are practice changing; dabrafenib and trametinib are the first targeted agents with demonstrated clinical activity in patients with *BRAF*-mutant ATC," opines corresponding author Bhumsuk Keam. The authors acknowledge that further studies are needed to confirm their results, but highlight the challenges in conducting randomized trials in rare diseases.

Keam concludes, "I would like to emphasize the importance of precision medicine for rare cancers: our study indicates that tumour mutation screening should be performed for all patients with ATC as it can transform their outcomes, thus also demonstrating that the concept of precision oncology can work in extremely rare diseases with aggressive phenotypes."

David Killock

ORIGINAL ARTICLE Subbiah, V. *et al.* Dabrafenib and trametinib treatment in patients with locally advanced or metastatic *BRAF* V600–mutant anaplastic thyroid cancer. *J. Clin. Oncol.* http://dx.doi.org/10.1200/JCO.2017.73.6785 (2017)