*Nature Reviews Clinical Oncology* **12**, 189 (2015); published online 24 February 2015; doi:10.1038/nrclinonc.2015.30

NEUROENDOCRINE CANCER

## SELECT—LENVATINIB IN THYROID CANCER

"Radioiodine (RAI)-refractory thyroid cancer is rare (4–5 cases per million), but portends a poor prognosis, with a median overall survival of 3–5 years from the diagnosis of metastases," states Martin Schlumberger. However, multiple signalling pathways are involved in this disease, offering the potential for therapy with multitarget tyrosine kinase inhibitors (TKIs). Indeed, lenvatinib, which inhibits VEGFR1–3, FGFR1–4, PDGFRα, RET, and KIT, had previously shown promise in a phase II study, providing Schlumberger *et al*. with the rationale for the phase III SELECT trial.

The SELECT trial enrolled 392 patients who were randomly assigned 2:1 to receive oral lenvatinib (24 mg per day) or placebo. "Before the availability of kinase inhibitors there was no effective treatment, and for this reason placebo was used as the control," Schlumberger explains.

Lenvatinib improved progression-free survival (PFS) compared with placebo: 6-month PFS rate 77.5% versus 25.4%; median PFS 18.3 months versus 3.6 months. The objective response rate (ORR) was 65% in the lenvatinib arm, with four prolonged complete responses (1.5%). The PFS benefit was maintained across all subgroups, including histological tumour type, and independent of *BRAF*/*RAS*-mutation status. "Similar benefits were observed in TKI-naive patients and patients who had been treated with another TKI (median PFS 18.7 months versus 15.1 months), demonstrating the absence of cross resistance," says Schlumberger.

Adverse effects of lenvatinib were common, as expected for a multitarget TKI, occurring in 97.3% of the patients treated with this agent, with grade 3 or higher events in 75.9% (versus only 9.9% of the placebo group). Six lenvatinib-related deaths were reported. Nevertheless, toxicity could mostly be controlled by dose reduction and symptomatic treatment.

Of note, the PFS benefit of lenvatinib over placebo was 14.7 months—around 10 months longer (in relative terms) than that observed for sorafenib (5.0 months) in the phase III trial that led to its FDA approval for patients with RAI-refractory thyroid cancer. One explanation for this result is that lenvatinib inhibits different targets, such as FGFRs. "Thus, lenvatinib may become the standard treatment for these patients," Schlumberger concludes.

***David Killock***

**Original article** Schlumberger, M. *et al*. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. *N. Engl. J. Med*. **372**, 621–630 (2015)