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Original Research

Exploratory analysis of biomarkers associated with clinical outcomes from the study of lenvatinib in differentiated cancer of the thyroid

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Abstract ***Background:*** Lenvatinib significantly prolonged progression-free survival (PFS) versus placebo in the phase III Study of (E7080) LEnvatinib in differentiated Cancer of the Thyroid (SELECT) of patients with radioiodine-refractory differentiated thyroid cancer. This exploratory analysis investigated potential predictive biomarkers of lenvatinib efficacy and target engagement.

Patients and methods: Circulating cytokine/angiogenic factors (CAFs) in blood samples collected at baseline and throughout treatment were analysed from patients randomised to receive lenvatinib or placebo from August 5, 2011 to October 4, 2012. For CAF biomarker analyses, patients were dichotomised by baseline levels. Tumour tissues were analysed for *BRAF* and *NRAS*/*KRAS*/*HRAS* mutations.

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Results: Tumours and CAFs were analysed from 183/392 (47%) and 387/392 (99%) patients, respectively. Lenvatinib PFS benefit was maintained in all assessments. For lenvatinib-treated patients, interaction-term analyses revealed that low baseline Ang2 level was predictive of tumour shrinkage ($P_{interaction} = 0.016$) and PFS ($P_{interaction} = 0.018$). Vascular endothelial growth factor and fibroblast growth factor 23 (FGF23) were significantly upregulated with lenvatinib, and FGF23 upregulation on cycle 1/day 15 was associated with longer PFS. In mutation analyses, no significant differences in clinical outcomes were observed. $BRAF^{WT}$ may be a negative prognostic factor for PFS in placebo-treated patients with papillary thyroid cancer ($P = 0.019$).

Conclusion: The lenvatinib PFS benefit was maintained regardless of baseline CAF or *BRAF*/*RAS* status. Baseline Ang2 was predictive of PFS in a subgroup of lenvatinib-treated patients, indicating that Ang2 may be predictive of lenvatinib sensitivity. $BRAF^{WT}$ may be a poor prognostic factor in patients with radioiodine-refractory papillary thyroid cancer. Improved PFS associated with upregulated FGF23 suggests that lenvatinib-induced FGF receptor inhibition contributes to lenvatinib efficacy.

Trial registration ID of the main study, SELECT: ClinicalTrials.gov: NCT01321554.

1. Introduction

Tumour angiogenesis is essential to cancer cell survival, local tumour growth, and development of distant metastases [1]. Increased vascular endothelial growth factor (VEGF) expression is significantly associated with angiogenesis and advanced-stage thyroid cancer [2]; therefore, the use of VEGF receptor (VEGFR) signalling pathway inhibitors represented a rational and attractive approach to control malignant thyroid cancer [3]. However, other molecular drivers of tumour growth beyond VEGF-driven angiogenesis contribute to the pathogenesis of cancer, including fibroblast growth factor receptor (FGFR) signalling [4]. Such pathways may provide escape mechanisms to VEGF-targeted therapies and lead to the development of resistance; this phenomenon has driven the development of multitargeted kinase inhibitors, such as sorafenib and lenvatinib, which are approved for the treatment of radioiodine-refractory differentiated thyroid cancer (RR-DTC).

Lenvatinib is an oral multikinase inhibitor of VEGFR 1–3, FGFR 1–4, platelet-derived growth factor receptor–alpha, and RET and KIT proto-oncogenes [5–7]. Lenvatinib was approved for the treatment of locally recurrent or metastatic, progressive RR-DTC in the United States, Europe and Japan based on results from the phase III Study of (E7080) LEnvatinib in differentiated Cancer of the Thyroid (SELECT) trial [8]. SELECT was a global, randomised, double-blind, multicenter, phase III study that demonstrated significant improvements in progression-free survival (PFS) and objective response rate (ORR) among patients with RR-DTC treated with lenvatinib compared with placebo [8]. Median PFS was 18.3 months in lenvatinib-treated patients versus 3.6 months in placebo-treated patients (hazard ratio [HR]: 0.21; 99% confidence interval [CI]: 0.14–0.31; $P < 0.001$). ORR was 64.8% in lenvatinib-treated patients versus 1.5% in placebo-treated patients ($P < 0.001$).

To date, there are no established biomarkers that are prognostic (for disease progression) or predictive (for response to therapy) of benefit in RR-DTC or its treatments. Several candidates of interest have been proposed based on the mechanisms of action of lenvatinib and the biology of DTC. Activation of the *RAS*/*RAF* pathway has been reported to increase VEGF production in thyroid cancer; however, it is still unclear if *RAS*/*RAF* activation is associated with tumour cell sensitivity to anti-VEGF therapy in thyroid cancer or other cancers [9].

Another molecular driver of tumour growth in the pathogenesis of thyroid cancer is FGF/FGFR. Elevated expression of FGF2, FGFR1, FGFR3 and FGFR4 have been detected in human thyroid carcinoma compared with normal thyroid tissue [10,11]. The FGF/FGFR pathway is part of an escape mechanism to VEGF-targeted antiangiogenic therapies [4]. One member of the FGF ligand family is FGF23, which is secreted by osteocytes, and has a key role in phosphorus homoeostasis and vitamin D metabolism [12]. Elevation of FGF23 levels has been shown to be a surrogate marker of FGFR1 inhibition [13].

Angiopoietin-2 (Ang2), a relatively novel regulator of angiogenesis that acts through the TEK tyrosine kinase, endothelial (Tie2) receptor, has been identified as a potential prognostic biomarker for some types of cancer, including hepatocellular carcinoma and melanoma, gastric, breast, bladder and prostate cancers [14]. The potential role of Ang2 as a predictive biomarker has not yet been comprehensively tested in multitargeted tyrosine kinase inhibitors of VEGFR-2 in RR-