THYROID CANCER

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Selpercatinib Is a Promising Treatment Option for *RET*-Mutated Medullary and *RET* Fusion–Positive Thyroid Cancers

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Review of: Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Lebourneux S, et al. 2020 Efficacy of selpercatinib in *RET*-altered thyroid cancers. *N Engl J Med* **383**:825–835. PMID: 32846061.

SUMMARY

Background

An uncommon type of thyroid cancer is medullary thyroid carcinoma (MTC), which accounts for roughly 5% of all thyroid cancers (1). *RET* mutations are common in MTC and can be due either to germline mutations such as multiple endocrine neoplasia type 2 (accounting for ~25% of MTCs) or somatic mutations (seen in ~60% of sporadic MTCs), while *RET* fusions can be present but are rare in differentiated and anaplastic thyroid cancers, accounting for <10% of all such cancers (2,3).

In patients with MTC, *RET* mutations are associated with a more aggressive course. Treatment options for MTC include surgery, external-beam radiation, and multitargeted kinase inhibitors such as vandetanib and cabozantinib (4,5), with the latter option of systemic therapy generally reserved for progressive or metastatic disease. Unfortunately, the use of vandetanib and cabozantinib is often limited by their toxic side effects, often requiring either a dose reduction or treatment discontinuation in many patients. This study (6) examined the efficacy and safety of selpercatinib, a highly selective small-molecule *RET* inhibitor, in patients with *RET*-mutated MTC and *RET* fusion–positive thyroid cancer.

Methods

This was an open-label, multisite phase 1–2 clinical trial of selpercatinib in patients ≥12 years of age with *RET*-mutated MTC (with or without previous vandetanib or cabozantinib treatment) and patients with *RET* fusion–positive thyroid cancer (LIBRETTO-001 trial). All subjects were consecutively enrolled and had an advanced or metastatic solid thyroid cancer tumor meeting the above criteria; tumor progression was not an explicit inclusion criterion, but systemic therapy had to be indicated. Selpercatinib was given continuously in 28-day cycles until disease progression, death, unacceptable toxic effects, or withdrawal from the study. Subjects enrolled in the phase 1 portion of the study received doses ranging from 20 mg once daily to 240 mg twice daily. All subjects enrolled in phase 2 received the recommended dose of 160 mg twice daily.

The primary outcome was an objective response (a complete or partial response) as determined by an independent review committee of expert radiologists. Secondary outcomes included the duration of response, progression-free survival, and safety. Radiologic tumor assessments were done at baseline, every 8 weeks for 1 year, and every 12

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weeks thereafter. Serum calcitonin and carcinoembryonic antigen (CEA) concentrations were followed in the subjects with MTC.

Results

A total of 162 subjects were treated with selpercatinib, including 55 with *RET*-mutated MTC previously treated with vandetanib and/or cabozantinib, 88 with *RET*-mutated MTC not previously treated with vandetanib and/or cabozantinib, and 19 with *RET* fusion-positive previously treated thyroid cancer. Of the latter group, 13 had papillary, 3 poorly differentiated, 2 anaplastic, and 1 Hürthle-cell thyroid carcinoma.

Of the 55 subjects with *RET*-mutated MTC previously treated with vandetanib and/or cabozantinib, 69% had an objective response (95% CI, 55–81%), with 5 subjects having a complete response and 33 a partial response. Responses were observed regardless of previous treatments and were seen across all qualifying *RET* mutations. At 1 year, 86% of the responses were ongoing (95% CI, 67–95%) and 82% of all patients remained progression-free (95% CI, 69–90%). A total of 91% (95% CI, 80–97%) had a biochemical response in their calcitonin levels.

Of the 88 subjects with *RET*-mutated MTC not previously treated with vandetanib and/or cabozantinib, 73% had an objective response (95% CI, 62–82%), with 10 subjects having a complete response and

54 a partial response. At 1 year, 91% of responses (95% CI, 72–97%) were ongoing and 92% (95% CI, 82–97%) of the patients were progression-free.

Of the 19 subjects with *RET* fusion-positive previously treated thyroid cancer, 79% had an objective response (95% CI, 54–94%). At 1 year, 71% of responses were ongoing (95% CI, 39–88%) and 64% (95% CI, 37–82%) of the patients were progression-free.

The most common grade 3 or 4 adverse events were hypertension (21% of subjects), increased serum alanine aminotransferase levels (11%), increased serum aspartate aminotransferase levels (9%), hyponatremia (8%), and diarrhea (6%). Overall, 30% of subjects required a dose reduction because of treatment-related adverse events, and 2% discontinued selpercatinib because of treatment-related adverse events.

Conclusions

In this phase 1–2 clinical trial, selpercatinib (a selective *RET* inhibitor) showed durable efficacy with mainly low-grade toxicity in patients with *RET*-mutated MTC with and without previous vandetanib or cabozantinib treatment and in patients with *RET* fusion-positive previously treated thyroid cancers. Efficacy was seen across all *RET* alterations and histologic types of thyroid cancers.

COMMENTARY

This study (6) shows that selpercatinib, a selective *RET* inhibitor, is a promising and durable treatment option for *RET*-altered thyroid cancers, most importantly MTC, and has a favorable side-effect profile. These findings resulted in its accelerated approval

by the U.S. Food and Drug Administration for the treatment of *RET*-altered MTCs in May 2020 (7).

Medullary thyroid cancer is far more aggressive than most differentiated thyroid cancers and therefore

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requires more aggressive treatments. Surgery and external-beam radiation are often used to control locoregional disease in the neck, but when there is progression and/or distant metastasis, systemic therapy is often recommended (4,5). Currently, the multitargeted kinase inhibitors vandetanib and cabozantinib are approved for the treatment of metastatic MTC. However, in my experience, use of these treatments is often limited owing to side effects; in some cases, patients have refused to start these medications out of fear of potential side effects. Selpercatinib offers another systemic treatment option with what appear to be less severe side effects.

In this study, approximately 70% of patients treated with selpercatinib had an objective response that was consistent across all groups. This compares favorably to the phase 3 trials for cabozantinib (8) and vandetanib (9) which had shown an objective

response in 28% of patients treated with cabozantinib and 45% with vandetanib. While these trials differed in eligibility criteria, it does provide a helpful comparison. Also, in these phase 3 trials, 12% of subjects receiving vandetanib and 16% receiving cabozantinib permanently discontinued the medication because of side effects (7,8), compared to only 2% receiving selpercatinib (6).

The major limitation of this phase 1–2 trial is that it was an open-label, non–placebo-controlled trial, making it difficult to truly compare it to the current standard of care for advanced MTC. Given these promising results, further study with a phase 3 clinical trial is expected for this treatment option. Effective screening approaches in patients with MTC to identify underlying germline or somatic *RET* mutations will be essential in the future use of this highly selective *RET* inhibitor.

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