

Trial finds adding immune modulator to targeted therapy does not improve survival in difficult-to-treat thyroid cancer

September 1 2023



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Results of a multicenter phase II clinical trial led by the University of Chicago Medicine Comprehensive Cancer Center show that adding an

immunomodulatory agent to treatment with the targeted tyrosine kinase inhibitor (TKI) cediranib did not make a difference in outcomes for treating patients with an advanced form of thyroid cancer that develops from thyroid follicular cells called differentiated thyroid cancer (DTC).

The findings were published in *Annals of Oncology*.

Most patients with DTC receive successful treatment. But a small group develops [cancer](#) that recurs or spreads to other parts of the body, making it hard to treat with traditional methods like surgery, hormonal therapies, chemotherapy, and radioactive iodine (RAI) therapy.

In recent years, there has been an increased interest in treating these patients with TKIs that target vascular endothelial growth factor receptor (VEGFR) signaling in the tumor microenvironment. These potent angiogenesis mediators target the formation of new blood cells, a process which plays an important role in the progression of thyroid cancer.

UChicago Medicine oncologists Ari Rosenberg, MD, and Everett Vokes, MD, set out to test the safety and efficacy of cediranib, a TKI that targets multiple VEGFRs. Furthermore, the researchers hypothesized that this group of patients would have an additional benefit if the drug was combined with an immunomodulatory agent known as lenalidomide.

This drug is also known to block angiogenesis and has anti-tumor properties in other cancers, and early clinical trials indicated that it exhibits similar activity against DTC. Recent combination therapies consisting of traditional therapies and immunotherapies have yielded superior results in many cancer conditions.

"With this scope, we set out to evaluate whether immunomodulation by lenalidomide in combination with cediranib would improve [disease-free survival](#) over cediranib alone," said Rosenberg, Assistant Professor in the

Section of Hematology and Oncology at the UChicago Medicine Comprehensive Cancer Center.

In a phase II clinical trial, 108 patients were enrolled from various hospitals in the United States and Canada. They were randomly assigned to either of the two treatment arms: 39 patients in the cediranib alone group and 69 patients in the cediranib with lenalidomide group.

The cediranib alone group achieved median progression-free survival (PFS) of 14.8 months, and 44% of patients had a complete or partial disappearance of tumor as assessed by objective response rate (ORR). Surprisingly, the addition of lenalidomide to cediranib didn't prove to be any better than treatment with cediranib alone.

"There are many recent examples in the literature demonstrating the combination of VEGF-targeted TKIs and immunotherapeutic strategies can be very effective, both preclinically and clinically, in multiple cancer conditions, like renal cell carcinoma and hepatocellular carcinoma," Rosenberg said. "And yet, this strategy does not appear to work in this particular disease with lenalidomide."

Final analysis of the data demonstrated that cediranib is an active agent, which means that the ORR and PFS of cediranib appear similar to other approved VEGFR-targeted tyrosine kinase inhibitors in DTC, including lenvatinib, sorafenib and vandetanib.

Rosenberg added that this study identifies the importance of randomized trial design, as single-arm studies can yield false-positive results and immunomodulation has been disappointing thus far in thyroid cancer.

"The most important point of this study is that the addition of lenalidomide, an immunomodulatory agent, didn't improve the progression-free survival over cediranib alone, despite what appeared to

be promising single-agent activity in DTC, and should not be combined with VEGFR-targeted TKIs," said Rosenberg.

Despite the advances in the field since the time of conceptualization and the enrollment of patients from 2010-2015, the implications remain quite relevant as outcomes beyond single VEGFR-targeted TKIs in DTC have not improved, Rosenberg added.

"Our study results highlight an unmet need with the current strategies of harnessing the body's immune system to treat [thyroid cancer](#) and the need to evaluate new combinations and new mechanisms, in particular new immunotherapeutic strategies that may be more effective than immunomodulatory strategies or immune checkpoint inhibitors alone," he said.

More information: A.J. Rosenberg et al, A multicenter, open-label, randomized, phase II study of cediranib with or without lenalidomide in iodine 131-refractory differentiated thyroid cancer, *Annals of Oncology* (2023). [DOI: 10.1016/j.annonc.2023.05.002](https://doi.org/10.1016/j.annonc.2023.05.002)

Provided by University of Chicago Medical Center

Citation: Trial finds adding immune modulator to targeted therapy does not improve survival in difficult-to-treat thyroid cancer (2023, September 1) retrieved 9 May 2024 from <https://medicalxpress.com/news/2023-09-trial-adding-immune-modulator-therapy.html>

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