Phase II study of pembrolizumab and lenvatinib in advanced well-differentiated neuroendocrine tumors

Immune checkpoint inhibitors (CPIs) have not been shown to be active in well-differentiated neuroendocrine tumors (NETs), with response rates <5%. Lenvatinib is a multitargeted tyrosine kinase inhibitor which binds to vascular endothelial growth factor and fibroblast growth factor receptors and has demonstrated efficacy in pancreatic and gastrointestinal NETs [44% and 16% objective radiographic response rate (ORR), respectively]. The combination of antiangiogenic and CPI therapies can be synergistic. We therefore evaluated the combination of lenvatinib and pembrolizumab in well-differentiated gastrointestinal (GI) and thoracic NETs. Patients and methods: A prospective, phase II trial evaluated patients with advanced GI/thoracic NETs (pancreatic NETs were excluded due to high response rate of lenvatinib monotherapy in this patient population), with evidence of progression within 8 months of study entry and at least two prior lines of systemic therapy. Patients received lenvatinib 20 mg daily and pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or progression of disease. Primary endpoint was objective response rate, and an interim analysis was planned once 20 patients were enrolled. Four ORRs were required to continue enrollment.

Twenty patients were enrolled on protocol from April 2021 to January 2022 (nine small intestine, five lung, two thymic, two unknown primary, one cecal, one presacral primaries). Two patients (10%) achieved a partial response (atypical lung and small intestinal primaries). Median progression-free survival (PFS) was 8 months (95% confidence interval 5.8-10.2 months). Twelve (60%) patients experienced probably or definitely associated grade 3 adverse events (10 hypertension). Fourteen patients (70%) required dose reductions or discontinued one of the medications. Two patients discontinued treatment before radiographic assessment.

The combination of pembrolizumab and lenvatinib did not show sufficient response in patients with NETs to warrant continued enrollment on trial.

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