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NP-101 in Combination with Nivolumab and Ipilimumab in Metastatic Extra-pulmonary Neuroendocrine Carcinomas (EP-NECs): A Pilot Study

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BACKGROUND

Extrapulmonary Neuroendocrine Carcinomas (EP-NECs) are a heterogeneous group of rare tumors with poor clinical outcomes. These patients have limited treatment options after progression on first-line platinum-based chemotherapy. Although dual immune checkpoint inhibitors (ICPIs) with anti–CTLA–4 and anti–PD–1 blockade have significantly improved outcomes for several solid tumors, they demonstrated modest activity for EP-NECs with 9-26% response rates and low survival rates. Preliminary data demonstrated that NP-101 (Thymoquinone) enhances T-cell infiltration and is synergistic with dual ICPIs in NECs' cellular models. This pilot study evaluated the safety and feasibility of a novel drug (NP-101) plus nivolumab and ipilimumab in patients with metastatic EP-NECs refractory to first-line platinum-based chemotherapy.

METHODS

This is a single-arm pilot study (NCTNCT05262556) in which patients with metastatic EP-NECs received NP-101 (oral capsules), 3000mg daily, plus ICPIs (intravenous nivolumab 3 mg/kg and Ipilimumab 1 mg/kg) every 3 weeks for 4 cycles. Responders resumed NP-101 with the same daily dose (3000mg daily), plus maintenance biweekly nivolumab (240 mg), and completed 24 weeks of treatment. Treatment-related adverse events (TR-AEs) were characterized according to CTCAE v4.03. The response rate was estimated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as the ratio of responders to the total number of patients and reported along with its Clopper-Pearson Confidence Interval.

RESULTS

Twelve patients received ≥1 dose of NP-101 and nivolumab plus ipilimumab. There were no dose limiting toxicities (DLTs). Grade 1/2 TR-AEs occurred in 100% (12/12) of patients. The most common G1/2 TR-AEs were fatigue (75%), nausea (41.7%), pruritus (41.7%), muscle weakness (33.3%), vomiting (25%), arthritis (25%), and abdominal pain (25%). 58.3% (7/12) of patients experienced grade 3/4 TR-AEs including rash (33.3%), nausea (16.7%), vomiting (16.7%), and transaminitis (16.6%). No treatment-related Grade 5 toxicities or deaths were recorded. The objective response rate (ORR) was 41.7% (2/12 CR + 3/12 PR; 95% CI:15.2-72.3%) for all patients and 50% (2/8 CR + 2/8 PR, 95% CI: 0.16- 0.84) for patients with NEC of gastrointestinal origin. The median duration of response was 13.9 months (range: 1.4-15.2 months). Median OS was not estimable with the current follow-up data and is still in progress.

CONCLUSIONS

The combination of NP-101 plus dual ICPIs (nivolumab and ipilimumab) was safe and well-tolerated with preliminary evidence of anti-neoplastic activity. A randomized phase II clinical trial studying the combination is now under development.

ABSTRACT ID 28480