Background Plinabulin (BPI-2358) is a GEF-H1 releasing agent that has immune-enhancing function by inducing dendritic cell maturation and decreasing regulatory T cells.1–3 Preclinical studies support the hypothesis that plinabulin potentiates the antitumor activity of dual checkpoint inhibition (CPI) with nivolumab and ipilimumab.2 Plinabulin may also reduce immune-related adverse events (AEs) from CPI through its phosphodiesterase-4 (PDE4) inhibitory activity which is associated with anti-inflammatory effects. We report results from a Phase II study assessing plinabulin in combination with nivolumab and ipilimumab.

Methods In this multi-center phase II study (NCT03575793), patients with recurrent extensive-stage SCLC who had progressed on prior platinum-based chemotherapy and anti-PD(L)1 therapy were enrolled. Patients received nivolumab (1 mg/kg), ipilimumab (3 mg/kg) and plinabulin (as per dose escalation schema) IV on day 1 of each 21-day cycles. After completion of 4 cycles, patients continued therapy with nivolumab (240 mg) and plinabulin (30 mg/m2) every 2 weeks till progression or intolerable toxicity. The primary objective was median progression-free survival (PFS). Correlative analysis includes inflammatory biomarkers: hsCRP, ESR, SAA and haptoglobin.

Results Between 1/2020 and 2/2023, 31 patients with PD(L)-1 resistant, pre-treated SCLC were enrolled and 28 patients received at least one cycle of study treatment. Median age was 64 years (range 43 to 80); 12 patients were female. Median PFS was 1.6 months (95% CI 1.2 to 2.7). Three patients had PR (confirmed 1, unconfirmed 2) and all three had tumor reduction >50%. Median time to response was 6 weeks. An additional 6 patients had SD as the best overall response. The most common treatment-related AEs (all grades) were nausea (10; 46%), vomiting (10; 46%), infusion reaction (9; 32%), hypertension (7; 25%) and fatigue (6, 17%). Fourteen patients (50%) had at least one grade 3 or worse treatment-related AE with hypertension (5; 18%) being the most common. Four patients (14%) had grade 3 or worse irAE requiring steroids (1 diarrhea, 1 hepatotoxicity, 2 elevated lipase). There were no cases of immune-related pneumonitis reported.

Conclusions Plinabulin in combination with nivolumab and ipilimumab had limited clinical benefit for the treatment of pre-treated, PD(L)-1 resistant SCLC and the trial did not meet the pre-specified target median PFS of 3.5 months. The number of patients experiencing grade 3 or worse irAE was lower than expected with the addition of plinabulin to dual checkpoint inhibitors and warrants further study to explore if plinabulin plays a role in reducing irAEs.

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Trial Registration The trial is registered at clinicaltrials.gov as NCT03575793.

REFERENCES

Ethics Approval The study was approved by the IRB of each of the participating institutions. All participants gave informed consent before taking part in the trial.

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