Background LNS8801 is an oral, selective, small molecule agonist of the G-protein coupled estrogen receptor (GPER). LNS8801 treatment results in reduced c-Myc protein levels in cancer cells, inhibition of proliferation, suppression of invasion, and enhancement of immune recognition. In preclinical models, LNS8801 has demonstrated increased activity in combination with immune checkpoint inhibitors (ICIs). In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT04130516).

Methods Patients who have secondary resistance to ICIs (CR/PR/>16w of SD followed by progression) and have measurable disease are enrolling in a Phase 1b cohort and receive LNS8801 (125 mg, QD, PO) and pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective is safety and tolerability assessed according to NCI CTCAE v5.0. Secondary endpoints include pharmacokinetic, pharmacodynamic, objective response rate (ORR) and disease control rate (DCR, CR+PR+SD) per RECIST v1.1, and assessment of biomarkers including germline GPER genotype at the single nucleotide polymorphism (SNP) rs11544331.

Results As of 7/15/22, patients with secondary resistance to ICIs (n=18) were treated with LNS8801 and pembrolizumab, including those who entered the study directly after confirmed progression on ICIs (n=16). Cancer types include lung (n=5), cutaneous melanoma (n=2), mesothelioma (n=2), neuroendocrine, colorectal, vaginal, nasopharyngeal, uterine, pancreatic cancer, uveal melanoma, small-cell cervical, and sarcoma. 7 of 18 patients had AEs possibly related to study drugs (n=6 with grades 1-2 and n=4 with grade 3), with colitis, dyspnea, and fatigue appearing in more than 1 patient. Of the 15 patients evaluable for efficacy, 3 had partial responses and 6 had stable disease, resulting in an ORR of 20% and DCR of 60%. All patients with partial responses had confirmed progression on ICIs immediately prior to entering the study. 4 patients continued on treatment for >6 months. Germline GPER genotype of C/C at SNP rs11544331 was associated with improved outcomes in patients treated with LNS8801.

Conclusions The combination of LNS8801 and pembrolizumab demonstrates encouraging anti-tumor activity in patients with secondary resistance to ICIs, including patients who enrolled immediately after confirmed progression on ICIs. The combination is tolerable without unanticipated toxicities. Germline GPER genotype is a promising predictive biomarker that could be used to select patients in future studies. These data support further development of LNS8801 in combination with pembrolizumab as a therapeutic approach to treat patients with secondary resistance to ICIs.

Trial Registration NCT04130516

Ethics Approval LNS-101 uses Western Institutional Review Board (WIRB) as a central IRB for this study. WIRB serves as the IRB for Cedars-Sinai Medical Center, the University of New Mexico, University of Pennsylvania, and Thomas Jefferson University. WIRB also serves as the IRB for the Yale University School of Medicine–Yale Cancer Center, but this site must be responsible for submissions due to institutional policies. Three sites do not use WIRB as the central IRB. South Texas Accelerated Research Therapeutics (START) is required to use Advarra IRB due to institutional policies, Massachusetts General Hospital is required to use their local IRB due to institutional policies, and MD Anderson Cancer Center is required to use their local IRB due to institutional policies.

Participants gave informed consent before taking part.