#5205: A circulating, surrogate-systemic biomarker correlates with anti-tumor benefit on LNS8801 therapy

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Background:
LNS8801 is an oral, highly selective agonist of the G protein-coupled estrogen receptor (GPER). LNS8801 depletes c-Myc levels in cancer cells, inhibits proliferation, suppresses invasion, and enhances immune recognition[1,2]. LNS8801 is being advanced through clinical trials (NCT04130516) for the treatment of advanced solid tumors[3,4].
GPER is a widely expressed across tumor types as well as normal tissues, including the pituitary gland[5]. Estrogens are endogenous ligands of GPER, and it is known that exogenous estrogen exposures can induce prolactin secretion that is detectable systemically[6]. GPER signaling is both sufficient and necessary to mediate this effect[7,8]. Due to circadian rhythms, systemic prolactin levels typically decrease throughout the day[9]. However, we hypothesized that prolactin will increase with LNS8801 treatment.

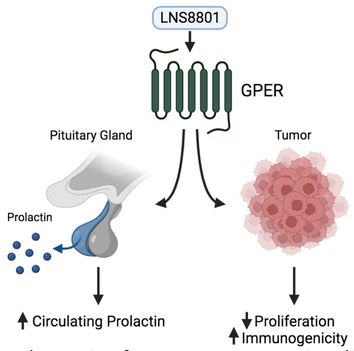

Figure 1: Schematic of concurrent GPER signaling occurring in the pituitary gland and tumor cells.

Methods:
Circulating prolactin levels were measured on the first day of treatment in patients with advanced solid tumors. Prolactin levels were measured before dosing LNS8801 and at 0.5, 1, 2, 4, 7 and 10 hours after dosing. Prolactin induction was calculated by dividing the average of prolactin levels at 4, 7 and 10 hours by the average of prolactin levels at 0, 0.5, 1, and 2 hours. Tumor responses were measured every 8 weeks for the 1st year and then every 12 weeks. These data are from patients across 6 dose levels in the phase 1 dose escalation portion of LNS-101 (NCT04130516).

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Results:
In up to 70% of patients treated with LNS8801, systemic prolactin increased over the first 10 hours after treatment. A retrospective analysis correlated this change in prolactin with exposure to LNS8801 and anti-tumor benefit from LNS8801 treatment. The kinetics of plasma prolactin levels immediately follows and tightly trends with LNS8801 plasma exposure.

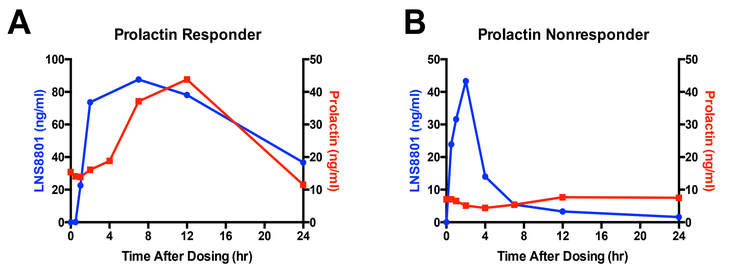

Figure 2: Representative pharmacokinetics and prolactin plots of (A) a patient with a prolactin induction and (B) a patient without a prolactin response.
A progression-free survival (PFS) analysis comparing patients with a robust prolactin response to those with a weak/nonresponse was performed. Patients with a robust prolactin response had a statistically significant increase in PFS ($p<0.01$).

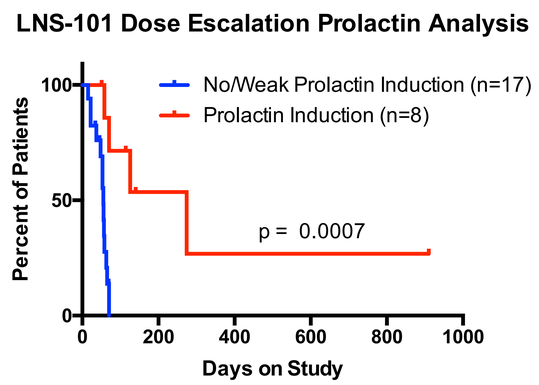

Figure 3: Progression-free survival analysis comparing evaluable monotherapy patients who have a strong prolactin induction (>/=1.4) to patients with no/weak prolactin induction. Patients were dosed at 6 different doses/regimen from 10 mg 3 consecutive days per week to 250 mg BID. Patients with a strong prolactin induction had NSCLC, colorectal cancer, cutaneous and uveal melanoma. Of the 8 patients with strong prolactin responses, only 2 patients had progressive disease at the first scan.

Conclusions:
These data suggest that prolactin induction may serve as a surrogate-systemic biomarker of pharmacodynamic target engagement of GPER. This biomarker will continue to be assessed in the ongoing clinical studies of LNS8801 for the treatment of cancer. Prolactin induction may be used to identify patients most likely to benefit from LNS8801 therapy in the first 10 hours of treatment.

Future Directions:
Early clinical data has been previously reported on LNS8801:

- In the Phase 1 dose escalation study in patients with advanced cancer, results demonstrate safety and tolerability with both monotherapy and combination therapy with pembrolizumab. Provocative signals of monotherapy and combinatorial activity are observed in multiple settings of high unmet medical need[3].
- In the Phase 1b study of LNS8801 in combination with pembrolizumab in patients with immune checkpoint inhibitor (ICI)-relapsed and refractory solid malignancies, results demonstrate that this combination is tolerable without unanticipated toxicities and demonstrates encouraging anti-tumor activity in patients that are r/r to ICIs, including patients who enrolled immediately after confirmed progression on pembrolizumab. An objective response rate of 15.4% (2/13) and a disease control rate of 69.2% (9/13) was observed, and 12 of the 13 patients had confirmed progression while taking ICI therapy immediately prior to entering the study[4].
  - The expected disease control rate (or atypical response rate) of continuing PD-1 ICIs alone after progression is considered to be less than 5% across indications[10].

Given that a prolactin induction in normal tissues correlates with an effect in tumor tissues, this suggests that germline variation may be a factor in drug response to LNS8801. Continued biomarker development has been focused on identifying genetic determinates underlying these effects that could potentially be used to predict which patients would benefit on LNS8801 before treatment.

During clinical trials prolactin induction will be used to aid in interpretation of other biomarker data such as germline GPER sequence, localization and expression of GPER, c-myc protein expression before and after treatment, TILs before and after treatment, and and other circulating biomarker data.

LNS8801 is continuing to be advanced in Phase 1b expansion cohorts and Phase 2 for the treatment of metastatic solid tumors, and particularly cutaneous and uveal melanomas.

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