THE EFFECT OF LNS8801 IN COMBINATION WITH PEMBROLIZUMAB IN PATIENTS WITH TREATMENT-REFRACTORY CUTANEOUS MELANOMA

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Background LNS8801 is an agonist of the G-protein coupled estrogen receptor (GPER). LNS8801 results in increased melanocytic differentiation, reduced c-Myc protein levels, inhibition of proliferation, and enhancement of immune recognition of cancer cells. In the first-in-human study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab (NCT04130516). LNS8801 also demonstrated monotherapy activity in cutaneous melanoma (CM) patients, including a patient that is on treatment for over 3 years with no evidence of active disease.

Methods Patients with refractory CM received LNS8801 (125 mg, QD, PO) and pembrolizumab (200 mg, Q3W, IV) (NCT04130516). The primary objective was safety and tolerability. Secondary endpoints include pharmacokinetic, pharmacodynamics, objective response rate (ORR) and disease control rate (DCR, CR+PR+SD). Presence of a consensus, fully-functional, germline GPER sequence was assessed as a potential predictive biomarker.

Results As of 6/15/23, 10 patients were treated. All patients received prior PD-1 and CTLA-4 directed ICIs, and were treated with a median of 2.5 prior lines of systemic therapies. 8 of 10 patients had AEs possibly related to study drugs (n=4 with grades 1–2 and n=4 with grade 3), with AST/ALT elevation, diarrhea, or fatigue occurring in more than 1 patient. Regarding efficacy, 2 had partial responses, 5 had stable disease, resulting in an ORR of 20% and DCR of 70%. Both patients with partial responses remained on treatment for > 24 weeks. Consensus germline GPER was present in 7 of 10 sequenced patients. Of patients positive for this biomarker, 2 had partial responses and 3 had stable disease, resulting in an ORR of 29% and DCR of 71%.

Conclusions LNS8801 and pembrolizumab is tolerable and demonstrates encouraging activity in patients with treatment-refractory CM, including patients who enrolled immediately after confirmed progression on ICIs. Consensus germline GPER is a promising predictive biomarker, and continues to be associated with improved outcomes in patients treated with LNS8801. These data support further development of LNS8801 in combination with pembrolizumab as a therapeutic approach to treat refractory CM patients.

Trial Registration NCT04130516

Ethics Approval The study was approved by Western Institutional Review Board, the central IRB for this study. The study was also approved by local IRBs at MD Anderson, Mass General, MSKCC, and START (Advarra IRB).

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