Background NDI-101150 is a novel, oral, highly selective small molecule inhibitor of HPK1, a MAP4K family kinase that negatively regulates T cells, B cells, and dendritic cells. HPK1 inhibition is postulated to enhance immune responses and exert anti-tumor activity as a single agent and in combination with immune checkpoint therapies. 1

Methods NDI-101150 is being studied in a dose escalation and expansion study as monotherapy and in combination with pembrolizumab. Monotherapy data are presented here. Increasing doses of NDI-101150 were administered once daily to patients with relapsed and metastatic solid tumors following a 3+3 cohort design. Primary objectives include determination of recommended phase 2 dose(s) and maximum tolerated dose. Secondary objectives include characterization of safety, pharmacokinetic (PK) profiles, and preliminary antitumor activity. Exploratory analyses include evaluating proximal pharmacodynamic (PD) target engagement of HPK1 by measuring phosphorylated SLP76 (pSLP76).

Results As of 17 May 2023, 22 subjects have been studied at 4 dose levels. Eighteen subjects (81.8%) experienced at least 1 treatment related adverse event (TRAE). Three subjects (13.6%) experienced serious TRAEs. The most common TRAEs were vomiting, nausea, diarrhea, and fatigue, with the majority being Grade 1 or 2. Immune-related adverse events occurred in 4 subjects (18.2%). There were no treatment-related deaths. Dose level 4 was considered a non-tolerated dose, with 2 out of 6 patients experiencing the only dose-limiting toxicities observed (Grade 3 pneumonitis and Grade 3 acute kidney injury in the setting of vomiting and diarrhea; both serious TRAEs). Nearly dose proportional increase in Cmax/AUC was observed. PD results demonstrated >50% reduction of pSLP76 in each cohort by Cycle 1 Day 15 (figure 1). One patient with renal cell carcinoma (RCC) in cohort 1 experienced a complete response and remained on treatment for 9 months. Two additional patients (RCC and pancreatic cancer in cohorts 3 and 4) have experienced prolonged stable disease with evidence of tumor shrinkage and response in CA 19.9 respectively. They remain on treatment at 13 months and 9 months, respectively (figure 2). Monotherapy dose optimization as well as combination dose escalation are ongoing.

Conclusions Preliminary results from the NDI-101150 monotherapy dose escalation demonstrate an acceptable safety profile, proximal target engagement and evidence of single agent activity with this novel class of oral immunotherapy in patients with relapsed and metastatic solid tumors. Updated clinical, PK and PD data will be presented.

Trial Registration NCT05128487

REFERENCE

Ethics Approval This trial was approved by the institutional review board and/or ethics committee as required for each participating site (IRB name and approval number for each site is available per request).

REFERENCE