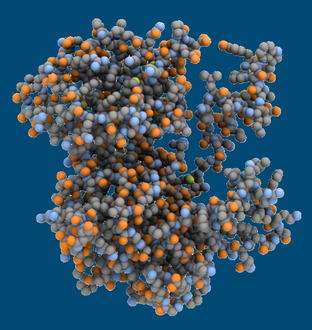

Preliminary Monotherapy and Pharmacokinetic Results from an Ongoing Phase 1a Dose Escalation Study of NDI-101150, a Highly Selective Oral Hematopoietic Progenitor Kinase 1 (HPK1) Inhibitor

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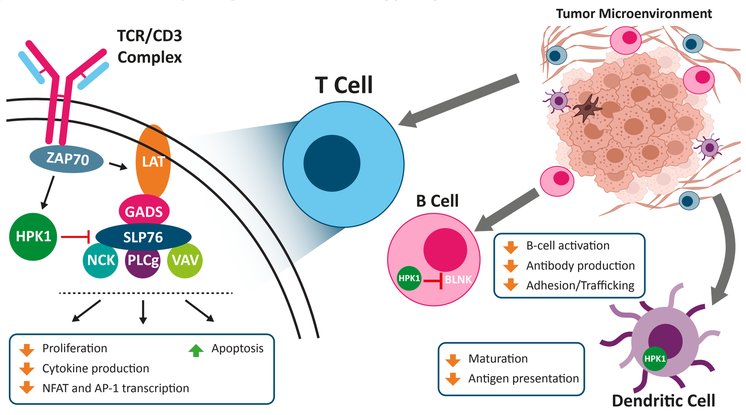
BACKGROUND

- NDI-101150 is a novel, oral, highly selective small molecule inhibitor of hematopoietic progenitor kinase 1 (HPK1), a MAP4K family kinase expressed only in hematopoietic cells[1–3]
- HPK1 inhibition has been demonstrated preclinically to enhance immune responses and exert anti-tumor activity as a single agent, or in combination with immune checkpoint therapies[1,2]
- Preclinical studies of NDI-101150 show immunogenic effects on T cells, B cells and dendritic cells (including SITC poster 1340) **(Figure 1)** as well as anti-tumor activity in mouse tumor models[4,5]
- NDI-101150 is currently being investigated in a first-in-human multicenter open-label phase 1/2 trial (NCT05128487) as monotherapy, or in combination with pembrolizumab in patients with advanced solid tumors

Figure 1. HPK1 is a compelling immuno-oncology target



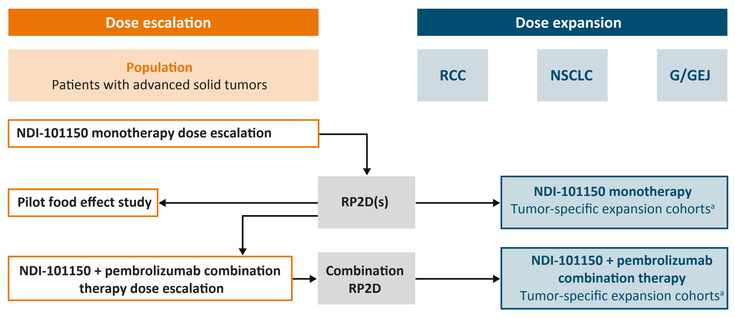
AP-1, activator protein 1; BLNK, B-cell linker protein; GADS, GRB2 related adaptor protein downstream of Shc; HPK1, hematopoietic progenitor kinase 1; LAT, linker for activation of T cells; NCK, non-catalytic region of the tyrosine kinase; NFAT, nuclear factor of activated T-cells; PLCg, phospholipase C, gamma 1; SLP76, SH2 domain containing leukocyte protein of 76kDa; TCR, T-cell receptor; ZAP70, zeta-chain-associated protein kinase 70

- Negative regulator of T-cell, B-cell and dendritic cell-mediated immune responses[1,2]
- Genetically validated target
  - HPK1 -/- mice have an enhanced anti-tumor T-cell response and are resistant to growth of Lewis lung carcinoma[1,2]
  - HPK1 kinase-inactive knock-in mice show impaired GL261 tumor growth, associated with increased T-cell infiltration[1,2]

METHODS

- NDI-101150 is being studied as monotherapy and in combination with pembrolizumab in a dose-escalation and expansion study **(Figure 2)**; we report here initial data from the monotherapy dose-escalation part
- Increasing doses of NDI-101150 are administered once daily in continuous 28-day cycles to patients with relapsed or 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)

Figure 2. Overall study scheme



[a]Response triggers opening of additional tumor-specific cohorts
G/GEJ, gastric/gastro-esophageal junction cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose

RESULTS

Baseline characteristics

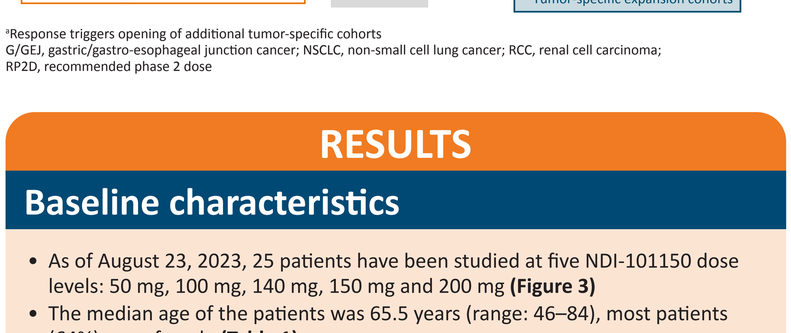
- As of August 23, 2023, 25 patients have been studied at five NDI-101150 dose levels: 50 mg, 100 mg, 140 mg, 150 mg and 200 mg **(Figure 3)**
- The median age of the patients was 65.5 years (range: 46–84), most patients (64%) were female **(Table 1)**
- The most common tumor types were pancreatic cancer, colon cancer and non-small cell lung cancer (16%, 12% and 12%, respectively) **(Table 1)**

Table 1. Patient and disease characteristics (safety analysis set; N=25)

Patient characteristics		Disease characteristics	
Age at diagnosis, years		Prior therapy lines, n patients (%)	
Median (range)	65.5 (46, 84)	1–2	10 (40)
Sex, n patients (%)		3–5	10 (40)
Female	16 (64)	≥6	5 (20)
Male	9 (36)	Most common tumor types, n patients (%)	
Race, n patients (%)		Pancreatic	4 (16)
White	18 (72)	Colon cancer	3 (12)
Black or African American	4 (16)	NSCLC	3 (12)
Not available	2 (8)	RCC	2 (8)
Unknown	1 (4)	Endometrial cancer	2 (8)

NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma

Figure 3. Dose escalation and refinement scheme (N=25)



Enrollment as of 23-Aug-2023.
DLT, dose-limiting toxicity; QD, once daily.

Safety

- Twenty-one patients (84%) experienced ≥1 treatment-related adverse event (TRAE) **(Table 2)**; five patients (20%) experienced serious TRAEs
- The most common TRAEs were vomiting, nausea, diarrhea, and fatigue, with the majority being grade 1 or 2 in severity
- NDI-101150 dose level 4 (200 mg/day) was considered a non-tolerated dose, with 2 of 9 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 were considered serious TRAEs) **(Figure 3)**
- Immune-related adverse events (irAEs; as determined by investigator) occurred in 8 patients (32%) **(Table 3)**
- No treatment-related deaths occurred

Table 2. TRAEs in the safety analysis set (N=25)[a]

TRAEs by preferred term, n patients (%)	Any grade[b]	Grade ≥3[c]	TRAEs by preferred term, n patients (%)	Any grade[b]	Grade ≥3[c]
Patients reporting ≥1 TRAE	21 (84)	5 (20)	Colitis	2 (8)	1 (4)
Vomiting	11 (44)	0	Abdominal pain	2 (8)	0
Nausea	11 (44)	0	Pruritus	2 (8)	0
Diarrhea	12 (48)	1 (4)	Rash	2 (8)	0
Fatigue	7 (28)	2 (8)	Hypokalemia	1 (4)	1 (4)
Pneumonitis	2 (8)	1 (4)	Acute kidney injury	1 (4)	1 (4)

[a]Patients reporting more than one event are counted only once for each preferred term
[b]Only the TRAEs occurring in ≥2 patients or those with grade ≥3 were listed
[c]Occurring in any patient; no grade 4 or 5 TRAEs were reported
TRAE, treatment-related adverse event

Table 3. Immune-related TRAEs in the safety analysis set (N=25)[a]

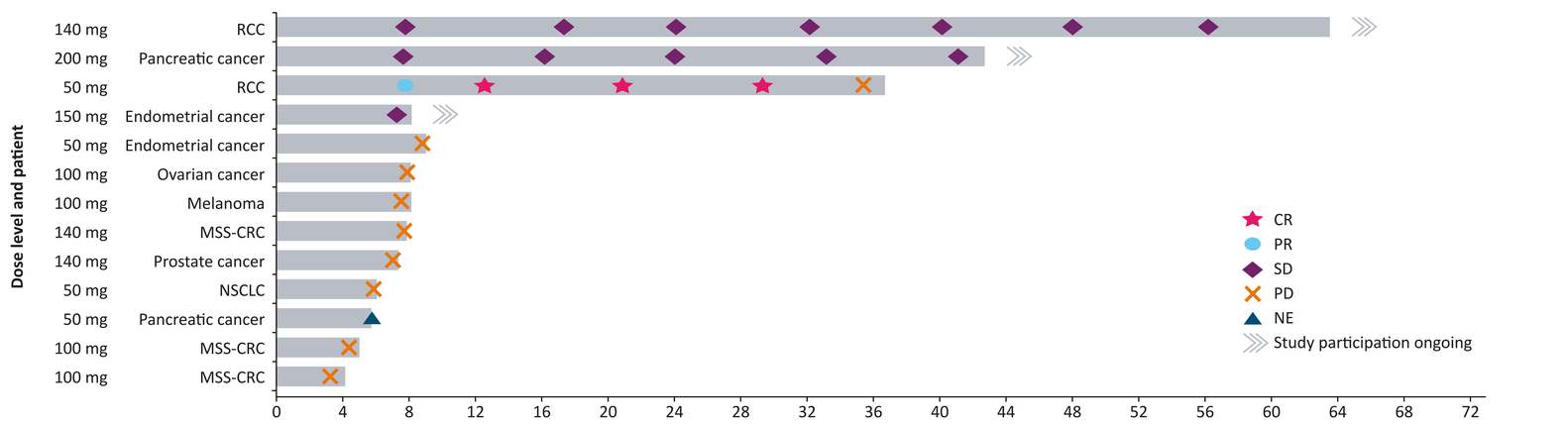
Immune-related TRAEs			Any grade
Patients reporting ≥1 immune-related AE, n patients (%)			8 (32)
Patient diagnosis	**AE term**	**AE grade**	**Cohort**
RCC	Pneumonitis	Grade 1	50 mg
Endometrial cancer	Maculopapular rash	Grade 1	50 mg
MSS-CRC	Rash (legs and torso)	Grade 2	140 mg
Endometrial cancer	TSH increased	Grade 1	150 mg
Pancreatic cancer	Rash	Grade 1	200 mg
	Vitiligo (hands)	Grade 2	
	Colitis	Grade 3	
NSCLC	Colitis	Grade 2	200 mg
Esophageal cancer	Pneumonitis	Grade 3	200 mg
NSCLC	Vomiting and diarrhea	Grade 2	200 mg

[a]Patients reporting more than one event are counted only once for each preferred term
AE, adverse event; MSS-CRC, microsatellite stable colorectal cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; TRAE, treatment-related adverse event; TSH, thyroid-stimulating hormone

Efficacy

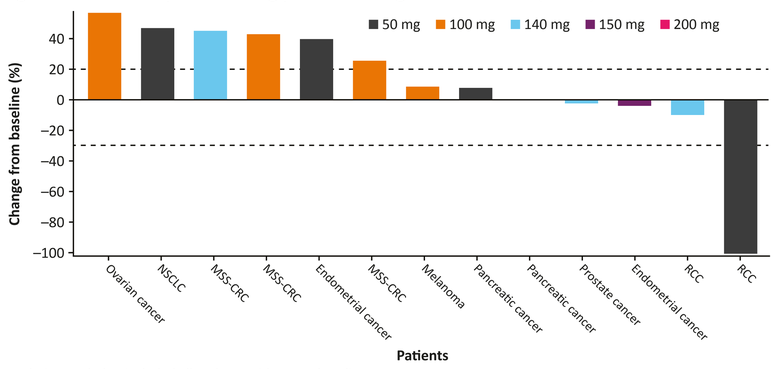
- Three patients have achieved clinical benefit defined as: objective response of partial response (PR) or complete response (CR), or maintenance of stable disease (SD) for >6 months
- One patient with renal cell carcinoma (RCC) in the 50 mg cohort 1 experienced a CR **(Figures 4, 5** and **6)**
- Two additional patients (with RCC and pancreatic cancer in the 140 mg and 200 mg cohorts, respectively) have experienced prolonged SD with evidence of tumor shrinkage and reduction in cancer antigen 19.9, respectively **(Figure 4)**
  - The patient with RCC remains on treatment at Cycle 17 after experiencing primary refractory disease to first-line pembrolizumab/axitinib
  - The patient with pancreatic cancer came off treatment in Cycle 10 due to an irAE of grade 3 colitis (occurred after data snapshot date); they had received 1 prior line of treatment (9 cycles of FOLFIRINOX) with a best response of SD
- Of 13 patients undergoing at least 1 response assessment, 4 had a reduction in target lesion sum of diameters **(Figure 5)**

Figure 4. Duration of treatment/BOR, according to RECIST 1.1 (N=13)[a]



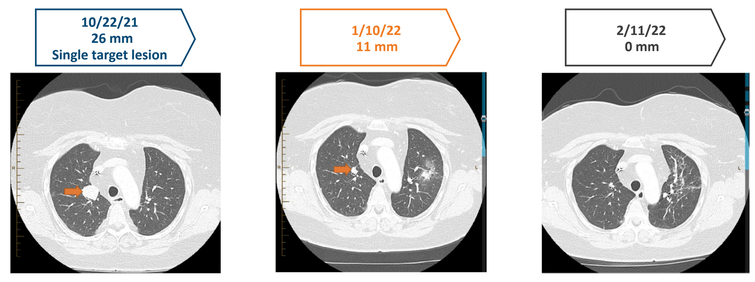
[a]Analysis population included all patients with a post-baseline assessment
BOR, best overall response; CR, complete response; MSS-CRC, microsatellite-stable colorectal cancer; NE, Not Evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease

Figure 5. Waterfall plot showing percent change in tumor size (N=13)[a]



[a]Analysis population included all patients with a post-baseline assessment
MSS-CRC, microsatellite-stable colorectal cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma

Figure 6. CT scans showing CR in patient with RCC



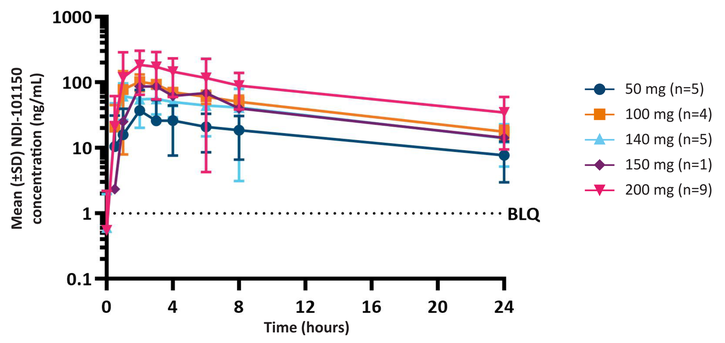
- Diagnosis and nephrectomy: 2013
- Pazopanib: Jan 2016 – Nov 2017
- Nivolumab: Dec 2017 – Sept 2021
- NDI-101150: started Nov 2021; patient remained on treatment for 9 months

CR, complete response; CT, computed tomography; PI, principal investigator; RCC, renal cell carcinoma

Pharmacokinetics/pharmacodynamics

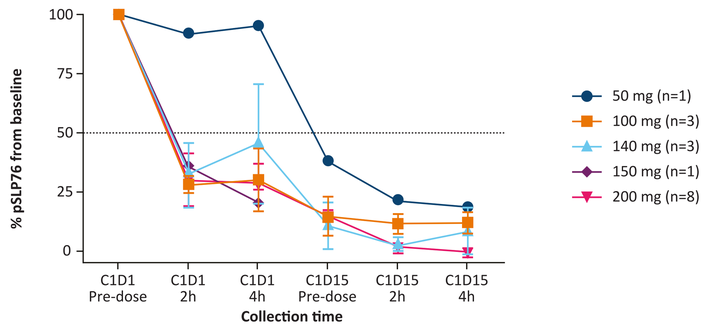
- Nearly dose-proportional increases in mean exposure were observed on Cycle 1 Day 1 **(Figure 7)**
- Steady state was achieved at or before Cycle 2 Day 1
- Accumulation was observed between Cycle 1 and Cycle 2
- PD results demonstrated >50% reduction of pSLP76 (proposed therapeutic target inhibition) in each cohort by Cycle 1 Day 15 **(Figure 8)**
- Nearly dose-proportional decreases in % pSLP76 were observed as NDI-101150 plasma concentration increased **(Figure 9)**

Figure 7. Mean NDI-101150 concentration on Cycle 1 Day 1 in the PK analysis set (N=24)[a]



[a]Patients with a plasma sample available for PK analysis; concentrations below the limit of quantification were plotted at half-BLQ
BLQ, below the limit of quantification; SD, standard deviation

Figure 8. Change in percentage pSLP76 from baseline to Day 15 of Cycle 1 in the PD analysis set (N=16)[a]



[a]Patients with a plasma sample available for pSLP76 analysis

Figure 9. Percentage of pSLP76 at Cycle 1 Day 1 relative to baseline, correlated with NDI-101150 plasma concentrations (N=16)[a]

[a]Each patient had a 2-hour and 4-hour time point represented

CONCLUSIONS

- NDI-101150 monotherapy demonstrated an acceptable safety profile up to 200 mg/day; most adverse events were mild in severity and easily managed
  - Emergence of irAEs supports the proposed mechanism of action of HPK1 inhibition, resulting in immune activation
- Clinical benefit was observed, including a CR and two patients with prolonged SD
- NDI-101150 showed a dose-dependent increase in plasma concentration and accumulation (data not shown) at steady-state, with pSLP76 inhibited at all doses
- The observed clinical benefit and safety profile support HPK1 as a viable next-generation immunotherapy target as well as continued clinical evaluation of NDI-101150
  - Plans for monotherapy dose optimization and expansion as well as combination dose escalation with pembrolizumab are ongoing (NCT05128487)

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