Phase 1/2 Trial of the HPK1 Inhibitor NDI-101150 as Monotherapy and in Combination with Pembrolizumab: Clinical Update

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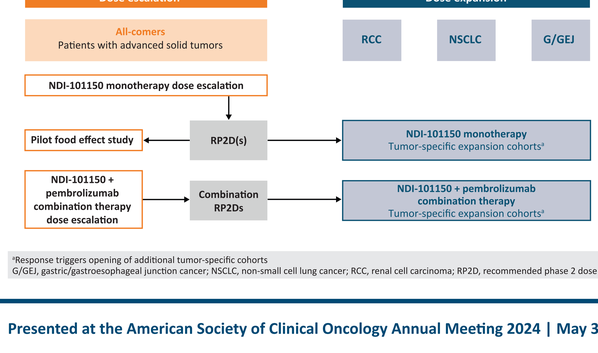
BACKGROUND

- NDI-101150 is a novel, oral, highly selective small molecule inhibitor of hematopoietic progenitor kinase 1 (HPK1), a negative regulator of T cells, B cells, and dendritic cells (**Fig. 1**). Preclinical studies of NDI-101150 show immunogenic effects as well as anti-tumor activity in mouse tumor models[1,2]

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

METHODS

- NDI-101150 is currently being investigated in a first-in-human, multicenter, open-label, phase 1/2 trial (NCT05128487) as monotherapy (50–200 mg) or in combination with pembrolizumab (200 mg/dose in 21-day cycles) in patients with advanced solid tumors; we report here updated data from dose escalation cohorts and new data from dose expansion cohorts
- NDI-101150 monotherapy expansion cohorts comprising patients with renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and gastric/gastroesophageal junction (G/GEJ) cancer are also being assessed (**Fig. 2**)
- Proximal pharmacodynamic target engagement of HPK1 measured phosphorylated SLP76 (pSLP76) in CD8+ cells by flow cytometry utilizing whole blood stimulated ex vivo with anti-CD3/CD28
- 4 µm formalin-fixed paraffin-embedded tissue sections from pre- and post-treatment patient samples were evaluated with Ultivue's InSituPlex® multiplex immunofluorescence assay, using a custom 12-plex U-VUE® panel (Ki67, GrzB, Lag3, CD8, PD-1, FoxP3, CD11c, CD3, CD4, CD20, and pan-CK)

Figure 2. Overall study schema

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

RESULTS

- As of March 18, 2024, 44 patients were dosed in the dose escalation cohorts (38 receiving NDI-101150 monotherapy and six receiving NDI-101150 + pembrolizumab) and 15 were dosed in the dose expansion cohorts
  - Mean age was 66.7 years (standard deviation: 10.5); 61.4% and 6.7% of patients were female in the dose escalation and dose expansion cohorts, respectively

Safety

- The most common any-grade adverse events considered related to NDI-101150 (TRAEs) were nausea, vomiting, diarrhea, and fatigue; grade ≥3 TRAEs were infrequent (**Table 1**)
- The most frequent any-grade immune-related (IR) TRAEs (as determined by investigator) were diarrhea, vomiting, constipation, nausea, and rash (10.2%, 6.8%, 5.1%, 5.1%, and 5.1% of patients, respectively); six (10.2%) patients experienced a grade ≥3 IR-TRAE (**Table 2 and footnote**)
- An NDI-101150 dose of 200 mg was not tolerated; an NDI-101150 dose of 150 mg dose is currently being assessed for safety and tolerability

Table 1. TRAEs (of any grade occurring in ≥3 patients) in the safety analysis set (n=59)[a]

	TRAEs, n (%)	
Event	Any grade	Grade ≥3[b]
At least one TRAE	45 (76.3)	10 (16.9)
Diarrhea	23 (39.0)	1 (1.7)
Nausea	23 (39.0)	0
Vomiting	18 (30.5)	0
Fatigue	14 (23.7)	2 (3.4)
Anemia	5 (8.5)	0
Abdominal pain	4 (6.8)	0
Constipation	4 (6.8)	1 (1.7)
Cutaneous rash[c]	4 (6.8)	0
Pruritus	4 (6.8)	0
Decreased appetite	3 (5.1)	0
Platelet count decreased	3 (5.1)	1 (1.7)
Proteinuria	3 (5.1)	1 (1.7)

[a]Patients reporting more than one event are counted only once for each preferred term; [b]One of each of the following grade ≥3 TRAEs was also observed: acute kidney injury, AST increased, colitis, dyspnea, hypokalemia, hypersensitivity, and immune-mediated lung disease; [c]Comprising rash (n=3) and rash maculopapular (n=1)
AST, aspartate aminotransferase; TRAE, adverse event considered related to NDI-101150

Table 2. IR-TRAEs (of any grade occurring in ≥2 patients) in the safety analysis set (n=59)[a]

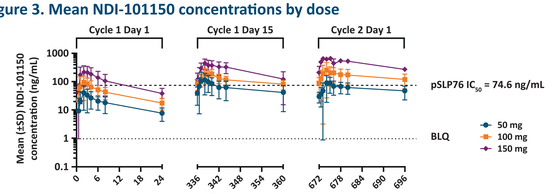
	IR-TRAEs, n (%)	
Event	Any grade[b]	Grade ≥3[c]
At least one TRAE	15 (25.4)	6 (10.2)
Diarrhea	6 (10.2)	0
Vomiting	4 (6.8)	0
Cutaneous rash[d]	4 (6.8)	0
Constipation	3 (5.1)	0
Nausea	3 (5.1)	0
Abdominal pain	2 (3.4)	0
Colitis	2 (3.4)	1 (1.7)

[a]Patients reporting more than one event are counted only once for each preferred term; [b]One SAE of cytokine release syndrome (grade 2 and hospitalization) has been reported in the 50 mg combination cohort (started prior to the data cut-off, data entry was ongoing); [c]One of each of the following grade ≥3 IR-TRAEs was also observed: AST increased, hypersensitivity, immune-mediated lung disease, platelet count decreased, and proteinuria; [d]Comprising rash (n=3) and rash maculopapular (n=1)
AST, aspartate aminotransferase; IR-TRAE, immune-related adverse event considered related to NDI-101150

Pharmacodynamics/pharmacokinetics

- NDI-101150 plasma concentrations increased in a near dose-proportional manner and, when administered with pembrolizumab, were similar to plasma concentrations observed with monotherapy
- Steady-state plasma concentrations at all doses were sufficient to cover the pSLP76 IC_{50} for a duration consistent with preclinical efficacy modeling (**Fig. 3**)

Figure 3. Mean NDI-101150 concentrations by dose



BLQ, below the limit of quantification; IC_{50}, half maximal inhibitory concentration; pSLP76, phosphorylated SH2-domain-containing leukocyte protein of 76 kDa; SD, standard deviation

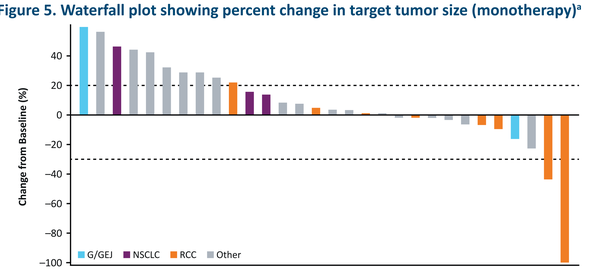
Efficacy

- NDI-101150 monotherapy induced clinical benefit in 5/30 (16.7%) response-evaluable patients: complete response (CR) in one patient with clear cell RCC; partial response (PR) in another patient with clear cell RCC; and stable disease (SD) ≥6 months in three patients (RCC [21 months], pancreatic cancer [14 months], and endometrial cancer [7 months]) (**Fig. 4** mono- and combination therapy)
- Of 30 patients receiving monotherapy who underwent at least one response assessment, two (6.7%) had a reduction from baseline in target lesion sum of diameters of ≥30%, including one patient with a CR[3] (**Fig. 5**)
- Compared to the archival biopsy, increases in activated CD8+ T cells and dendritic cells were observed in the on-treatment biopsy (day 1 of cycle 2) for a patient with RCC experiencing SD (**Fig. 6**)
- Six of eight patients with RCC had a best overall response of SD or better, including one with a CR, one with a PR and one with prolonged SD (21 months)
  - The patient with a PR was in the dose expansion phase
    - Diagnosed with metastatic RCC in Sep 2018
    - Previous therapy: cabozantinib Dec 2018–Sep 2021; nivolumab Oct 2021–Dec 2021; tivozanib Jan 2022–Apr 2023; pembrolizumab + ipilimumab Nov 2022–Jan 2023; lenvatinib + everolimus Apr 2023–Aug 2023
    - NDI-101150 was started on Sep 28, 2023, and the patient currently remains on treatment (cycle 8)
    - In addition to shrinkage in all 5 target lesions (**Fig. 7**, representative images), the patient also experienced a substantial reduction in pleural effusion in non-target lesion 10

Figure 4. Duration of treatment/BOR, according to RECIST v1.1, in the dose escalation and expansion cohorts

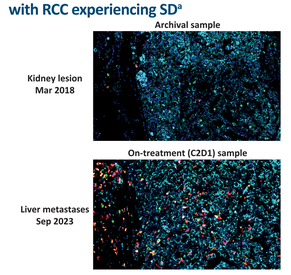
[a]Analysis population included all patients with a post-baseline assessment
BOR, best overall response; CR, complete response; CRC, colorectal cancer; G/GEJ, gastric/gastroesophageal junction cancer; NA, Not available; NSCLC, non-small cell lung cancer; P, pembrolizumab; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in; Solid Tumors version 1.1; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; SD, stable disease

Figure 5. Waterfall plot showing percent change in target tumor size (monotherapy)[a]



[a]Analysis population included all patients with a post-baseline assessment who were receiving NDI-101150 monotherapy
G/GEJ, gastric/gastroesophageal junction cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma

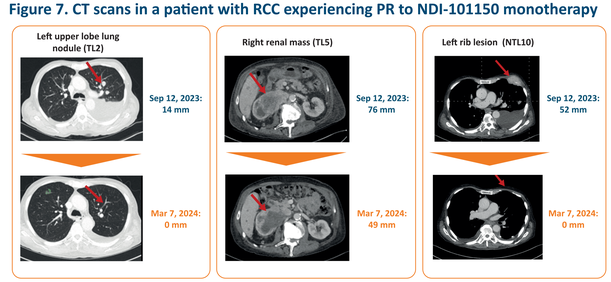
Figure 6. On-treatment increase in activated CD8+ T cells and dendritic cells in a patient with RCC experiencing SD[a]



Key: DAPI (blue); CD8 (red); granzyme B (magenta); Ki67 (green); CD11c (orange); CK (cyan)

[a]Patient was receiving NDI-101150 monotherapy (100 mg)
C, cycle; CK, cytokeratin; D, day; DAPI, 4',6-diamidino-2-phenylindole; RCC, renal cell carcinoma; SD, stable disease

Figure 7. CT scans in a patient with RCC experiencing PR to NDI-101150 monotherapy



CT, computed tomography; NTL, non-target lesion; PR, partial response; RCC, renal cell carcinoma; TL, target lesion

CONCLUSIONS

- NDI-101150 monotherapy appears to be generally well tolerated; emergence of immune-related adverse events supports the proposed mechanism of action of HPK1 inhibition, resulting in immune activation
- Clinical benefit was observed in five (16.7%) patients receiving NDI-101150 monotherapy, including a CR, a PR, and three patients with durable SD; six of eight response-evaluable patients with RCC had a best overall response of SD or better
- NDI-101150 showed increases in CD8+ T cells and dendritic cells in on-treatment biopsies, consistent with preclinical observations
- At steady state, all NDI-101150 doses tested achieved exposures above the pSLP76 half maximal inhibitory concentration
- The observed clinical benefit and safety profile support HPK1 as a differentiated next-generation immunotherapy target as well as continued clinical evaluation of NDI-101150 in tumor-specific expansion cohorts (NCT05128487)

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