Tumor Immune Microenvironment Characterization from Pre- and Post-Dose Tumors Collected from a Phase 1/2 Study of NDI-101150, a Hematopoietic Progenitor Kinase 1 (HPK1) Inhibitor

Scott R. Daigle[1,a]; GiNell Elliott[1]; Scott Boiko[1]; David Sommerhalder[2]; Marcus S. Noel[3]; Sunil Sharma[4]; Rama Balaraman[5]; Martin Gutierrez[6]; Kurt Demel[7]; Ryan H. Moy[8]; David Ciccone[1]; Xinyang Zhang[1]; Anita Scheuber[1]; Pavan Kumar[1]

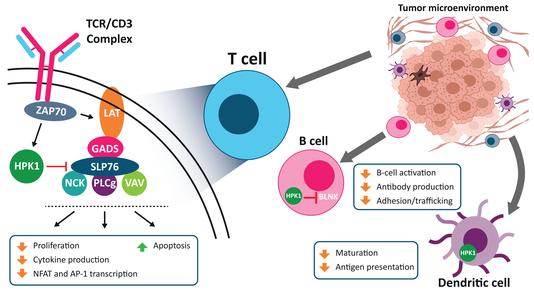
[1]Nimbus Therapeutics, Boston, MA, USA; [2]NEXT Oncology, San Antonio, TX, USA; [3]Georgetown University Medical Center – Lombardi Comprehensive Cancer Center, Washington, DC, USA; [4]Honor Health Research Institute, Scottsdale, AZ, USA; [5]Florida Cancer Affiliates-US Oncology, Ocala, FL, USA; [6]Hackensack University Medical Center – John Theurer Cancer Center, Hackensack, NJ, USA; [7]HealthPartners, Frauenshuh Cancer Center, St. Louis Park, MN, USA; [8]Columbia University Irving Medical Center, New York, NY, USA

[a]Presenting author: Scott R. Daigle (scott.daigle@nimbustx.com)

BACKGROUND

- NDI-101150 is a potent, selective, oral inhibitor of hematopoietic progenitor kinase 1 (HPK1; **Fig. 1**), with an immunotherapy mechanism distinct from checkpoint inhibitors. Preclinical data demonstrate NDI-101150 activates the anti-tumor activity of T cells, B-cells, and dendritic cells, even under immunosuppressive conditions[1]

Figure 1. HPK1 is a compelling immuno-oncology target

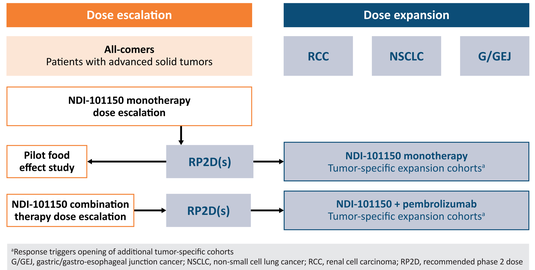


AP-1, activator protein 1; BLNK, B-cell linker protein; GADS, GRB2-related adaptor protein downstream of Shc; HPK1, hematopoietic progenitor kinase 1; LAT, linker for activation of T cells; NCK, non-catalytic region of the tyrosine kinase; NFAT, nuclear factor of activated T-cells; PLCg, phospholipase 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[2] (**Fig. 2**)
- Utilizing ex-vivo stimulated (anti-CD3/CD28) whole blood collected on treatment, proximal pharmacodynamic (PD) target engagement of HPK1 was measured by flow cytometry to quantitate phosphorylated SLP76 (pSLP76) in CD8+ cells
- 4 µm formalin-fixed paraffin-embedded tissue sections from pre- and post-treatment (Day 28 ± 7 days) patient samples were evaluated with Ultivue's InSituPlex® multiplex immunofluorescence assays, using custom 12-plex (Ki67, GrzB, Lag3, CD8, PD-1, FoxP3, CD11c, CD3, CD4, CD20, pan-CK), and 2-Plex (CD3, pSLP76) U-VUE® panels

Figure 2. Overall study schema

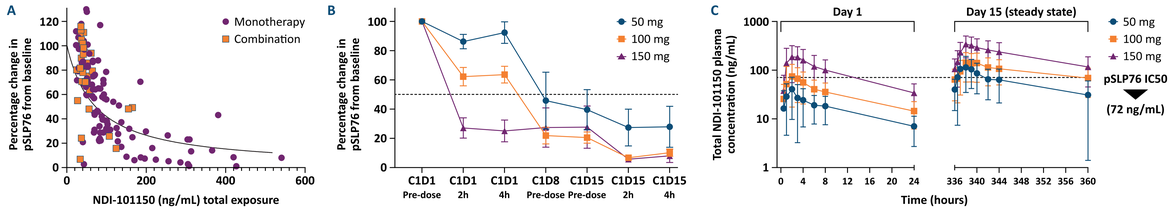


[a]Response triggers opening of additional tumor-specific cohorts
G/GEJ, gastric/gastro-esophageal junction cancer; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose

RESULTS

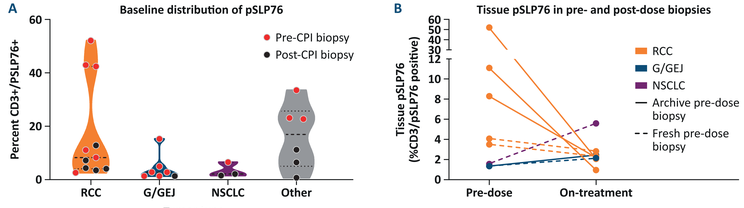
- As of August 12, 2024, 53 patients had been dosed in the dose escalation cohorts (41 receiving NDI-101150 monotherapy and 12 receiving NDI-101150 + pembrolizumab) and 35 patients had been dosed in the dose expansion cohorts (NDI-101150 monotherapy)
- NDI-101150 appears to be well tolerated; emergence of immune-related adverse events supports the proposed mechanism of action of HPK1 inhibition, which results in immune activation[2,3]
- In NDI-101150 monotherapy-treated RCC patients with ≥1 post-baseline assessment, clinical benefit (CR + PR + SD ≥6 months) was observed in 5/17 (29%), including three with objective responses (CR + PR)[2]
- A PK/PD relationship on day 1 of cycle 1 has been established, with an IC_{50} of 72 ng/mL (**Fig. 3A**), with all doses achieving pSLP76 inhibition >50% by day 8 (**Fig. 3B**)
- NDI-101150 plasma concentrations had a near dose-proportional increase, with steady-state plasma concentrations at all doses sufficient to cover the pSLP76 IC_{50} (**Fig. 3C**)

Figure 3. pSLP76 and NDI-101150 PK/PD relationship (C1D1) (A), pSLP76 by cohort (B), and NDI-101150 total exposure (ng/mL) (C)



C, cycle; CR, complete response; D, day; h, hour; IC50. half maximal inhibitory concentration PD, pharmacodynamic; PK, pharmacokinetic; PR, partial response; pSLP76, phosphorylated SLP76; SD, stable disease

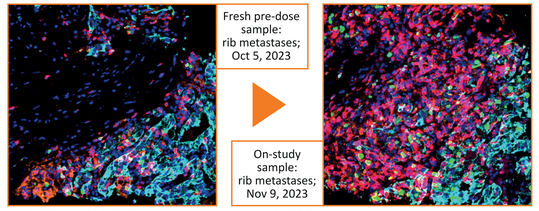
Figure 4. Baseline distribution of pSLP76 in tumor biopsies (A) and inhibition of pSLP76 observed in paired on-study tumor biopsies (B)



CPI, checkpoint inhibitor; G/GEJ, gastric/gastro-esophageal junction; NSCLC, non-small cell lung cancer; pSLP76, phosphorylated SLP76; RCC, renal cell carcinoma

- From baseline samples tested to date (N=27), the median percent CD3+/pSLP76+ population was 6.5% (range: 0.73–52%), with early results showing greater tissue pSLP76 distribution in RCC tumors compared with gastric/gastro-esophageal junction and NSCLC tumors (**Fig. 4A**)
- Review of pSLP76 from biopsy tissue collected pre- or post-initial CPI therapy suggests a trend toward higher pSLP76 levels pre-CPI; however, the current sample number is limited and analysis of additional samples is ongoing
- In patients with pre- and post-dose biopsies, pSLP76 reduction was observed in most cases following NDI-101150 treatment, including all RCC patients tested (**Fig. 4B**)
- Regardless of comparator (archive or fresh), an increase in T-cell activation markers (granzyme B and Ki-67) and dendritic cell marker CD11c was observed post-NDI-101150 treatment (**Figs. 5** and **6**)

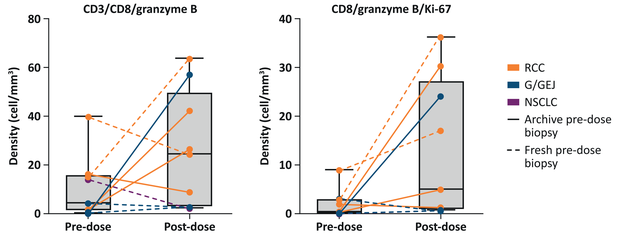
Figure 5. Matched biopsies from an RCC patient show increased infiltration of activated CD8+ T-cells and dendritic cells following NDI-101150 treatment



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

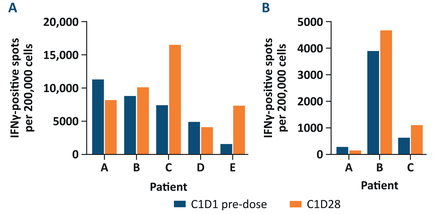
DAPI, 4′,6-diamidino-2-phenylindole; RCC, renal cell carcinoma

Figure 6. Increased activated CD8 T-cells observed following NDI-101150 treatment



G/GEJ, gastric/gastro-esophageal junction; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma

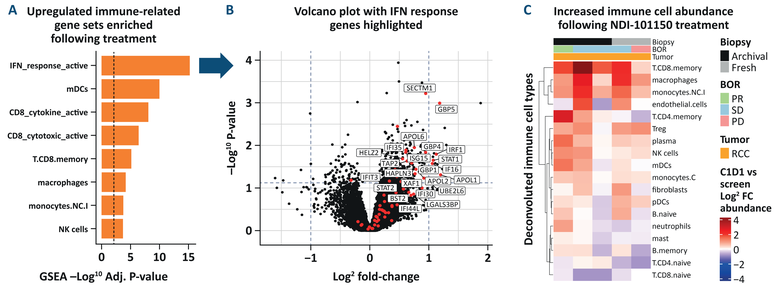
Figure 7. IFNγ ELISpot data using PHA stimulation (A) and CERI stimulation (B) suggest peripheral T-cells are not functionally exhausted following NDI-101150 treatment



C, cycle; CERI, CMV, EBV, RSV, and Influenza virus peptides; D, day; ELISpot, Enzyme-Linked Immunosorbent Spot assay; IFNγ, interferon gamma; PHA, phytohemagglutinin

- Viably frozen peripheral blood mononuclear cells (PBMCs) were collected at baseline and on-treatment during the first 28 days of treatment
- PBMCs were thawed, rested overnight, and then stimulated in separate wells with PHA or a CERI peptide pool for 18 hours
- Utilizing an IFNγ ELISpot assay, results demonstrate no functional T-cell exhaustion through the first 28 days of therapy (**Fig. 7**)
- Matched biopsies were evaluated through the GeoMx whole transcriptome digital spatial profiling assay
- Compared with baseline, upregulation in gene sets corresponding to IFN response, dendritic cells, and CD8 T-cell activation and recruitment (e.g. CXCL9 and CXCL11) was observed in post-NDI-101150 treatment biopsies (**Figs. 8A** and **8B**)
- Consistent with the 12-plex immunophenotyping assay, NDI-101150 treatment led to immune cell enrichment in tumor regions (**Fig. 8C**)

Figure 8. GeoMx digital spatial profiling results confirm tumor immune activation (A, B and C) following NDI-101150 treatment in patients with RCC



Adj., adjusted; BOR, best overall response; C1D1, day 1 of cycle 1; GSEA, gene set enrichment analysis; FC, fold change; IFN, interferon; mDCs, myeloid dendritic cells; NK, natural killer; PD, progressive disease; pDC, plasmacytoid dendritic cell; PR, partial response; RCC, renal cell carcinoma; SD, stable disease

CONCLUSIONS

- Objective responses were reported in three (18%) of 17 response-evaluable patients with RCC: including one patient with a complete response and two patients with a partial response (SITC 2024 Poster 682)[3]
- All tested doses achieved steady-state exposures above the whole blood pSLP76 half maximal inhibitory concentration, consistent with preclinical efficacy predictions
- Tumor biopsy immunofluorescence assay confirmed on-treatment inhibition of pSLP76
- Enhanced CD8+ T-cell recruitment and activation, observed via 12-plex tissue immunophenotyping, support NDI-101150's proposed mechanism of action in modulating the tumor immune microenvironment
- GeoMx digital spatial profiling corroborated the 12-plex assay findings, providing additional evidence for tumor immune cell activation and increased dendritic cell recruitment; results also show upregulation of genes involved in immune cell migration and differentiation

References: **1.** Ciccone D, Kuo F-S, Boiko S, et al. *JITC.* 2023;11 (Suppl. 1):1340; **2.** Noel M, Demel K, Srivastava B, et al. *J Clin Oncol.* 2024;42 (Suppl. 16):3083; **3.** Sommerhalder D, Demel K, Noel MB, et al. SITC 2024:P682.

Acknowledgements: Editorial assistance was provided by Melody Watson, Bioscript Group, Macclesfield, UK, and supported by Nimbus Therapeutics (Nimbus Discovery Inc. on behalf of Nimbus Saturn Inc.). This study was funded by Nimbus Therapeutics (Nimbus Discovery Inc. on behalf of Nimbus Saturn Inc.).

Disclosures: **SRD**, **GE**, **SB**, **DC**, **XZ**, **AS**, and **PK** are employees and equity holders of Nimbus Therapeutics (Nimbus Discovery Inc.) on behalf of Nimbus Saturn Inc; **DS** has received honoraria from Syneos, consulting fees from Guidepoint and ongoing or past research funding from AbbVie, ADC Therapeutics, Ascentage Pharma Group, Astellas, Biomea Fusion, Boehringer Ingelheim, BJ Bioscience, BioNTech, Fate Therapeutics, Gilead Sciences, Haihe Pharmaceutical, IconOVir Bio, Immuneering, IMPACT Therapeutics, Kura Oncology, MediLink Therapeutics, Mirati Therapeutics, Monopteros Therapeutics, Navire Pharma Inc., Nimbus Saturn Inc., NGM Biopharmaceuticals, OncoResponse Inc., Parthenon, Pfizer, Revolution Medicines, Symphogen, Tachyon Therapeutics, Teon Therapeutics, Vincerx Pharma, ZielBio Inc. **MSN** has held a consulting or advisory role for Celgene, Ipsen, and Taiho Pharmaceutical, has taken part in speakers' bureaus for Celgene, Daiichi Sankyo/Astra Zeneca, and Taiho Pharmaceutical, has received research funding from ERYTECH Pharma, and has received consulting fees from Pfizer; **SS** has no relationships to disclose; **RB** has received honoraria from Cardinal Health, has held a consulting or advisory role for Bristol Myers Squibb, and has received research funding from Bristol Myers Squibb; **MG** has received consulting fees from Guardant, Cellularity, and Merck, and has taken part in a data safety monitoring board/advisory board for Sanofi.; **KD** has no conflicts of interest to report.; **RHM** has received consulting/advisory fees from Puretech Health, IDEAYA Biosciences, Nimbus Therapeutics; Research Funding: Repare Therapeutics, and Nimbus Therapeutics.