NDI-101150 IS A POTENT AND HIGHLY SELECTIVE
HEMATOPOIETIC PROGENITOR KINASE 1 (HPK1)
INHIBITOR THAT PROMOTES A ROBUST AND BROAD
ANTI-TUMOR IMMUNE RESPONSE

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Background HPK1 is a member of the MAP4K family of protein serine/threonine kinases that negatively regulates activation signals in multiple immune cells and is an attractive therapeutic target for many cancers. Using structure-based drug design, we developed a highly selective HPK1 inhibitor, NDI-101150, with nanomolar potency and physicochemical properties suitable for once daily oral administration.

Methods Biochemical and cell-based assays were used to characterize the potency and selectivity of NDI-101150, respectively. Mechanistic activity was studied in vitro across lymphoid and myeloid cell populations. Anti-tumor efficacy and pharmacodynamic immune modulatory effects of NDI-101150 were analyzed in vivo across multiple murine syngeneic tumor models and benchmarked against programmed cell death-1 (PD-1) antibody administration.

Results NDI-101150 demonstrated single-digit nanomolar HPK1 enzymatic IC50 potency with >300-fold selectivity against MAP4K family kinases. In vitro NDI-101150 treatment dose-dependently activated multiple primary human immune cells as evidenced by pro-inflammatory cytokine secretion in human CD8+ T-cells, increased IgG antibody secretion in CD19+ B-cells and enhanced antigen presentation capacity of CD11C+ dendritic cells (DCs). Similarly, HPK1 inhibition overcame adenosine and prostaglandin E2 tumor-mediated suppression of effector T-cells.

In vivo once daily oral administration of NDI-101150 caused significant tumor growth inhibition (TGI) in CT26 and EMT-6 murine syngeneic models (50% and 85% TGI, respectively). Strikingly, in the EMT-6 model, 7/10 mice receiving NDI-101150 exhibited complete tumor regressions, compared to only 1/10 from a benchmark PD-1 antibody cohort. Furthermore, NDI-101150 established a robust immune memory response as 100% of treated mice showed complete rejection of tumor growth upon subsequent re-challenge. Immunophenotyping of EMT-6 bearing mice revealed NDI-101150 administration significantly enhanced the number of CD45+ leukocytes in the tumor, while having no significant effect in neighboring tissue compartments including the spleen and lymph node. Tumor-centric pharmacodynamic effects of NDI-101150 administration included an increased adaptive immune cell transcriptional signature (T- and B-cells) and increased number of infiltrating effector T-cells and CD11C+ DCs.

Conclusions Pharmacological inhibition of HPK1 with NDI-101150 represents a powerful system-wide immunomodulatory approach for enhancing anti-tumor immunity in patients failing to respond to currently approved immune checkpoint therapies. NDI-101150 is currently being tested in a Phase 1 trial in patients with advanced recurrent or metastatic solid tumors.

REFERENCES

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