633 A PHASE 1A/1B, DOSE-ESCALATION/DOSE-EXPANSION STUDY OF NPX267 IN SUBJECTS WITH SOLID TUMORS KNOWN TO EXPRESS HHLA2

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Background HHLA2 (B7H7) is a B7 family member which suppresses T and NK cell activation through an inhibitory receptor, KIR3DL3,[1 2] and stimulates activation through a distinct receptor, TMIGD2. HHLA2 is expressed on tumor cells of many histologic subtypes and is frequently associated with poor prognosis. As HHLA2 expression appears independent of PD-L1 expression, this may represent a novel checkpoint axis for therapeutic targeting. NPX267 is a monoclonal antibody (IgG4) directed against KIR3DL3 which blocks the interaction of KIR3DL3 with HHLA2 to enhance NK cell-mediated tumor cell killing *in vitro* and reduce tumor cell growth *in vivo*.

Methods NPX267 is being studied in a phase 1a/1b dose-escalation, dose expansion study in solid tumors where HHLA2 is known to be expressed including non-small cell lung carcinoma (NSCLC), renal cell carcinoma (RCC), colorectal carcinoma, cholangiocarcinoma (CCA), pancreatic adenocarcinoma, urothelial carcinoma, gastric/gastro-esophageal carcinoma, triple negative breast carcinoma, endometrial cancer, cervical carcinoma, osteosarcoma, and prostate cancer. The primary objective is evaluation of the safety and tolerability of NPX267 at different dose levels and preliminary efficacy in dedicated phase 1b cohorts. Secondary objectives include characterization of pharmacokinetics (PK), pharmacodynamics (PD) (including dose-dependent changes in the tumor microenvironment reflective of T/NK cell activation or proliferation), and immunogenicity of NPX267.

Dose escalation is being conducted utilizing an accelerated titration design for the first two dose levels followed by a Bi3 +3 design for subsequent dose levels.[3] This design permits enrollment of three tumor types–lung adenocarcinoma, RCC, and CCA–into backfill cohorts while dose-escalation is ongoing at up to 3 dose levels to better characterize PK/PD relationships in determining dose(s) and tumor types to move forward into phase 1b. At least two dose expansion cohorts are planned, including EGFR-mutant NSCLC, based on high levels of HHLA2, infiltrating KIR3DL3+ immune cells, and lack of benefit to existing immune checkpoint inhibitors. Dose expansion cohorts will initially enroll 20 subjects, followed by randomization to different doses if indicated, following a multi-arm, two-stage (MATS) design.[4] Key eligibility criteria include histologic diagnosis of tumor types known to express HHLA2, refractory metastatic or locally advanced disease and the absence of autoimmune disease or history of colitis or pneumonitis.

HHLA-2 expression will be assessed by immunohistochemistry from archival tissue and fresh biopsies to assess correlation with pharmacodynamic and clinical activity to determine the potential use of HHLA2 expression as a prospective selection marker.

REFERENCES

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Ethics Approval This study has been approved by the Institutional Review Boards at NEXT Oncology and Sarah Cannon Research Institute and is being reviewed the institutional review boards at the remaining institutions (JHU, MGH, MDACC, and AECOM).

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0633