SNOXA12C601/KN559 Collaboration Study

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Abstract Category: Trials in Progress

Evaluation of tumor biomarkers in patients with microsatellite-stable, metastatic colorectal or pancreatic cancer treated with the CXCL12 inhibitor NOX-A12 and preliminary safety in combination with PD-1 checkpoint inhibitor pembrolizumab

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BACKGROUND. NOX-A12 (olaptesed pegol) is a novel inhibitor of the chemokine CXCL12, ligand for CXCR4 and CXCR7, for treatment of solid tumors. Binding of the CXCL12 ligand by NOX-A12 prevents receptor engagement and also blocks the ability of CXCL12 to create a chemotactic concentration gradient by neutralization of the anchor domain. CXCL12 in complex with NOX-A12 has an increased half-life relative to unbound CXCL12, and as such increased CXCL12 levels are a marker of inhibition. The OPERA study (NCT03168139) is a Phase 1/2 open label clinical study to evaluate pharmacodynamic effects and safety of monotherapy with NOX-A12 and safety and efficacy of a combination of NOX-A12 with pembrolizumab in advanced MSS, metastatic colorectal and pancreatic cancer with liver metastasis. The study comprises two weeks of NOX-A12 monotherapy followed by repeated 21-day cycles of NOX-A12 plus pembrolizumab. Here we present pharmacodynamic biomarker data from for monotherapy phase with NOX-A12 as well as safety for the combination with pembrolizumab.

METHODS. Patients received 300 mg NOX-A12 by i.v. infusion on days 1, 4, 8, and 11 of the monotherapy phase. Needle biopsies were taken from suitable liver metastases before treatment and on day 14, peripheral blood was drawn at the same time points. Collected tumor samples were assessed for immune cell infiltration by IHC and cytokine signature using multiplex protein analysis.

RESULTS. At the time of abstract submission, 19 out of 20 patients have been recruited, thereof 10 with colorectal and 9 with pancreatic cancer. Serial biopsies at baseline and end of monotherapy suitable for immunohistochemistry (IHC) and cytokine analysis were obtained from 12 out of 19 patients. CXCL12 levels were found to be increased in blood, but also in post-treatment tumor biopsies, suggesting penetration of NOX-A12 into the tumor. The comparison of cytokine levels in the currently available baseline tumor biopsies with those taken after two weeks of NOX-A12 monotherapy revealed changes in markers that are consistent with a Th1 like immune response in multiple patients. In particular IFN-γ, IL-2 and TNF-β were increased accompanied by an increase of CXCL9 and/or CXCL10 indicating simultaneous T cell attraction which indicate a tissue response to treatment with NOX-A12. However, there were also increased levels of IL-1α, IL-1β and IL-6 in a number of patients indicating potential myeloid counter regulation. IHC analysis is ongoing, and results for all patients will be presented. Treatment with NOX-A12 monotherapy and in combination with pembrolizumab was generally safe and well tolerated (139 AEs in total, thereof 45% grade 1; 37% grade 2; 17% grade 3; no grade 4 and 1 % grade 5).

CONCLUSIONS. NOX-A12 penetrates into the tumor where it binds and neutralizes CXCL12. Changes in the cytokine signature suggest that NOX-A12 modulates the tumor microenvironment and induces an immune-stimulatory Th1-like signature in multiple patients. The safety profile of NOX-A12 combined with pembrolizumab is consistent with that of pembrolizumab in advanced cancer patients.