NT219, a Novel Dual Inhibitor of STAT3 and IRS1/2, Demonstrates Anti-Tumor Activity With and Without Cetuximab in Pembrozilumab-Resistant Head and Neck Cancer PDX Models

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Introduction
- Pembrolizumab (Keytruda, an α-PD-1 antibody) with chemotherapy is approved as first line therapy for recurrent and metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Patients refractory to this regimen are often treated with cetuximab. Historically, cetuximab monotherapy resulted in a median response rate of ~13% and an overall survival of ~6 months in patients with platinum-resistant R/M HNSCC. Better therapies for this population are therefore highly warranted.
- Insulin Receptor Substrate 1 and 2 (IRS1/2) and STAT3 are major signaling junctions regulated by various oncogenes and altered during epithelial-to-mesenchymal transition and drug resistance. Feedback activation of STAT3 and IGF1R/IRS plays a prominent role in mediating drug resistance to EGFR blockers.
- STAT3 has also been demonstrated to play an active role in tumor’s immune evasion.
- NT219 is a novel small molecule dual inhibitor of IRS1/2 and STAT3. The purpose of this study was to evaluate NT219 anti-tumor activity with and without cetuximab in chemo- and/or pembrolizumab-resistant head and neck cancer PDX models.

Conclusions
NT219 induced tumor regression in R/M HNSCC and sensitized resistant tumors to cetuximab and pembrolizumab in various preclinical models. The unique mechanism of NT219, targeting two central mechanisms involved in cancer drug resistance, supports further clinical development of NT219 which may present an attractive 2nd and 3rd line therapy.

Efficacy of NT219 as a Monotherapy and in Combination with Cetuximab or α-PD1 in Autologous PBMCs-Injected Patient-Derived Xenograft (PDX) Models

The PDX model originated from a color metastasis-derived biopsy of an HNSCC patient previously treated and progressed on radiation, various chemotherapies and pembrolizumab.

Mice were treated on Days 0, 3, 10 and autologous PBMCs from the same patient were injected on Day 6 (Graph A).

Patient’s bone marrow-isolated CD34+ cells were co-injected 6 weeks before treatment initiation, and mice were treated twice a week when tumors were established (Graph B).

A. Administration of NT219 as a monotherapy resulted in a statistically significant tumor growth inhibition (TGI) of ~60% (p-value<0.001).

In combination with cetuximab, NT219 induced regression of all tumors. When cetuximab alone showed almost no activity, the addition of NT219 showed synergistic effects and complete TGI (p-value<0.001).

NT219 converted non-responsive tumors to responders to cetuximab (TGI=65%*) and Pembrolizumab / Keytruda (TGI=65%**).

FACS analysis of the tumors at the end of the study revealed enhanced levels of CD8, CD20 and CD45 immune cells following treatment with NT219 and the combinations with NT219.

Efficacy of NT219, a Dual Inhibitor of IRS and STAT3, as a Monotherapy and in Combination with Cetuximab and α-PD1 in PBMCs-Injected HNSCC Xenograft Model

A. A Dose Dependent Effect of NT219

NT219 Leads to IRS1 Elimination and STAT3 Dephosphorylation, Inducing HNSCC Cell Apoptosis

B. NT219 induces sustained tumor regression and extends survival

C. NT219 potentiates the anti-cancer effect of cetuximab and anti-PD1

Approved Therapies

- NOD scid gamma (NSG)* mice were injected SC with SCC-9 cells.
- PBMCs from a healthy human volunteer (3*10^6 cells per mouse) administered 4 weeks prior to first treatment.
- NT219, α-PD1, and cetuximab were administered IV (NT219) and IP (α-PD1, and cetuximab) twice a week for 24 days.
- A cumulative dose escalation response of NT219 plasma levels and therapeutic effect was demonstrated.
- Statistical analysis for all studies was performed using one way ANOVA with a post hoc Tukeys HSD test.

NT219 Phase 1/2 Study Design

Title: A phase 1/2 study with open-label, dose escalation phase followed by single-arm expansion to assess the safety, tolerability, PK, PD and efficacy of NT219, alone and in combination with Erbitux* (cetuximab) in adults with recurrent or metastatic solid tumors and Head and Neck cancer

- Primary endpoint: Safety, pharmacokinetics and to determine the MTD
- Secondary endpoint: Obtain preliminary efficacy data

- Dose Escalation
  - NT219 q4W, 180 & 240 mg
  - NT219 180 mg q4W with or without Erbitux

- Expansion
  - NT219 q4W + cetuximab 1000 mg q3W + Erbitux

* Colorectal adenocarcinomas pts will be recruited in the Dose Escalation phase
** Indication TBD (expansion not part of the study protocol)