Sitravatinib and Glesatinib May Enhance the Activity of Checkpoint Inhibitors by Modulating Key Immunologic Pathways

**Background**

- Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy (CIT) is a rational approach to restoring or improving the efficacy of CIT in patients with immunotherapy-resistant NSCLC.
- Glesatinib, a tyrosine kinase inhibitor (TKI), which targets Axl, MER and MET receptor tyrosine kinases (RTKs) expressed on macrophages and antigen-presenting cells (APCs) within the tumor microenvironment (TME), may reverse the immunosuppressive TME and enhance anti-tumor T and natural killer (NK) cell responses by enhancing antigen presentation and T-cell effector function.
- Sitravatinib, also a TKI, which targets vascular endothelial growth factor receptor (VEGFR) family-2 and -3, as well as Axl, MER and MET, may further enhance anti-tumor activity by VEGFR2 and MET inhibition mediated reduction of regulatory T cells (Tregs) within the TME and myeloid-derived suppressor cells (MDSCs).

**Methods**

Given these pleiotropic immune activating effects, the combination of glesatinib or sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of CIT in patients with immunotherapy-resistant NSCLC.

**Key inclusion criteria:**
- Histologically confirmed non-squamous NSCLC with metastatic or unresectable, locally advanced disease, not amenable to treatment with curative intent.
- ECOG performance status of 0, 1 or 2.
- At least one prior treatment in the advanced disease setting.
- Two-stage Simon Optimal Design.
- Modified Toxicity Probability Interval (m TPI) design method for dose escalation decisions.

**Summary**

The combination of glesatinib or sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of CIT in patients with immunotherapy-resistant NSCLC. The pleiotropic effects of both immunotherapeutic agents, which target key nodes in the tumor immune cycle, may both reduce inhibition of immune recognition and promote antitumor immunity.

**Key exclusion criteria:**
- Prior therapies: immunotherapies not previously specified including anti-CTLA-4 and anti-PD-1/PD-L1 antibodies.
- Combination therapy with checkpoint inhibitor and cancer therapy having same mechanism of action as investigational agent.
- Unacceptable toxicity on prior CIT.
- Active or prior documented autoimmune disease.
- Active or prior immunocompromising conditions.
- Unstable angina pectoris, CHF ≥ NYHA Class 3, QRS ≥ 480 msec.

**Dosing regimen and assessments:**
- Patients receive oral glesatinib twice daily (BID) or oral sitravatinib once daily (QD) in combination with nivolumab 240 mg intravenously every 2 weeks, as continuous 28-day cycles.
- Routine safety assessments performed throughout the study.
- Disease assessments using RECIST version 1.1.
- Other assessments include safety, tolerability, PK, and changes in PD-L1 expression, circulating and tumor infiltrating immune cell populations, cytokines and gene expression signatures.

**Enrollment**

Enrollment is anticipated to begin in November 2016. The US IND opened in June 2016.

Clinical Trial Information: NCT02954991