SITRAVATINIB and NIVOLUMAB in Oral Cavity Cancer Window of Opportunity Study


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BACKGROUND

• Sitravatinib is a receptor tyrosine kinase inhibitor that blocks TAM and VEGF family of receptors. Based on non-clinical findings, it is predicted to increase M1 tumor-associated macrophage (TAM) response and decrease myeloid-derived suppressor cells (MDSCs) and immunosuppressive regulatory T-cells (Tregs) in the tumor microenvironment.

• Sitravatinib combined with nivolumab showed a safely toxic profile and promising antitumor activity in non-small cell lung cancer patients progressing on anti-PD-1 agents [1]. In the CheckMate-358 study, the combination of nivolumab was safe and active in oral cavity squamous cell carcinoma (OCSCC) [2]. We hypothesize that preoperative sitravatinib and nivolumab have synergistic immunogenic and antitumor effects in OCSCC.

STUDY OBJECTIVES

Primary objective: to evaluate the immune and pharmacodynamic effects of sitravatinib and nivolumab when given in combination.

Secondary objectives:
(a) safety, including rate of treatment-related adverse events (TRAEs), surgery completion within the planned window and postoperative complications.
(b) antitumor activity, including clinical and radiological responses; rate of pathological extranodal extension (ENE) and positive margins.
(c) pharmacokinetics of sitravatinib alone and when combined with nivolumab.

Exploratory objectives:
(a) dynamic changes in immune cell activation and/or suppression including immune biomarkers by multiplex immunofluorescence (IF), tumor and blood immunophenotyping; tumor genome and transcriptome analyses.
(b) dynamic changes in intratumoral hypoxia using 18FAZA-PET.

STUDY DESIGN

Photograph documentation fresh tumor biopsy Blood sample

PHOTOGRAPHIC DOCUMENTATION SHOWS COST EFFECTIVE DELIVERY OF BOTH THERAPIES

Investigator-initiated, single-center, non-randomized window of opportunity study of preoperative sitravatinib and nivolumab in patients (pts) with previously untreated resectable OCSCC.

Key eligibility criteria: T2-4a, N0-2 or T1 (>1cm)-N2 tumors as per AJCC 8th edition, ECOG PS 0-1, adequate organ function and no autoimmune disorders. Sample size: 12-15 patients evaluable for correlative studies. Statistical considerations: SNOW is a proof-of-concept study with no specific statistical assumptions at trial onset.

SAFETY DATA

As of October 9th, 2019, a total of 9 pts have been enrolled: 1 active and 8 in follow-up. Safety data on the 8 pts who have completed treatment are presented:
- 7 pts (88%) completed study treatment and had surgery within the planned window. One pt (S-009) had 2-week delayed surgery due to Sitravatinib-related G2 thrombocytopenia.
- G3/4 TRAEs pre-surgery: 1/8 pts (S-009) had asymptomatic G3 hypertension (known baseline hypertension) resolved 48 hours after adjusting anti-hypertensives.
- Most common G3/4 TRAEs pre-surgery: dysphonia (62.5%), ALTAST elevation (62.5%), fatigue (62.5%), hypertension (50%), mucosis (50%), diarrhea (37.5%) and skin rash (37.5%).
- Post-operative complications: 1 pt (S-004) had G3 neck infection and G3 bleeding from the tracheostomy site day 11 post-surgery, both resolved and deemed possibly related to study drugs.

IMMUNE BIOMARKER ANALYSES

• Preliminary results suggest the preoperative sitravatinib and nivolumab is a safe and active combination.
• Most pts had clinical benefit and tumor downsizing, with non-require post operative chemotherapy.
• Sitravatinib led to a reduction of intratumoral MDSCs and a trend towards increased percent of M1-type macrophages and M1 to M2 type ratio in several pts, with a stronger effect seen in major responders. S-001 and S-002 (Figure 2).

Figure 2. Multiplex IF analyses for MDSCs and macrophages subpopulations. (A) Decreased MDSCs and (B) decreased percent of M2-type (CD163+CD68+) relative to M1-type (CD163+CD68+) and M1-M2 intermediate (CD163+CD68+) in day 15 biopsies. (C) Changes in macrophage subpopulations in pts S-001 and 002.

Figure 3: Tumor flow cytometry analyses. Low Treg-infiltration was observed in most pts at all timepoints. Pts 001 and 002 had a high proportion of PD-L1+ TAMs.

CONCLUSIONS

• Preliminary results suggest the preoperative sitravatinib and nivolumab is a safe and active combination.
• Most pts had clinical benefit and tumor downsizing, with non-require post operative chemotherapy.
• Sitravatinib led to a decrease in intratumoral MDSCs and a trend towards increased percent of M1-type macrophages in the tumor microenvironment.