Abstract 6556

SNOW: Sitravatinib and Nivolumab in Oral Cavity Cancer (OCC) Window of Opportunity Study

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STUDY RATIONALE

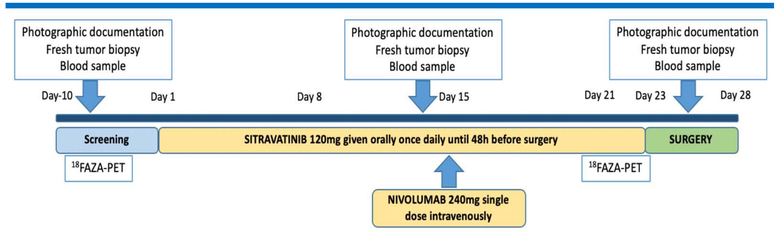
Sitravatinib (TKI receptor against TYRO3, AXL, MERTK and VEGF family of receptors) is predicted to increase M1-type tumor-associated macrophages (TAMs) and decrease MDSCs in the tumor microenvironment (TME). SNOW is a window-of-opportunity study evaluating preoperative sitravatinib and nivolumab in patients (pts) with OCC. Early results showed the combination was safe and active (Oliva et al, SITC 2019).

STUDY OBJECTIVES

Primary objective: to evaluate the immune and pharmacodynamic effects of sitravatanib and nivolumab.

Secondary objectives*: **1. Safety,*** including rate of treatment-related adverse events (TRAEs), surgery completion within the planned window and postoperative complications; ***2. Antitumor activity,*** including clinical and pathologic responses; rate of pathological extranodal extension (ENE) and positive margins.

STUDY DESIGN



Key eligibility criteria: untreated resectable OCC, T2-4a, N0-2 or T1 (>1cm)-N2 tumors as per TNM-AJCC 8th edition, ECOG PS 0-1, adequate organ function and no autoimmune disorders. *Adjuvant Radiotherapy as per standard of care based on clinical staging. **Sample size**: 12 evaluable pts.

ANTITUMOR ACTIVITY

From Aug 30th 2018 to date, 10 pts have been enrolled. All pts had tumor reduction by exam and 9 had pathological downstaging, including 1 complete response (**Table 1, Figure 1**). All had clear margins (>5mm) and no extranodal extension. None required adjuvant chemotherapy.

Take Home Messages

Preoperative sitravatinib and nivolumab showed promising antitumor responses in resectable OCC, with a safe toxicity profile.

Pharmacodynamic analyses revealed a shift towards a less immunosuppressive TME after sitravatinib supporting the immune effects of the combination.

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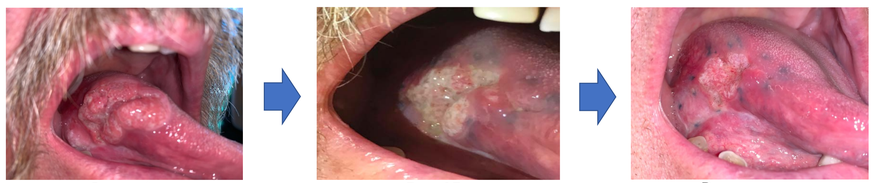
At median follow-up of 52 weeks (21-68), all pts are alive with no recurrence.

Table 1: Pathological downstaging

Pt	Primary tumor	PD-L1 CPS	Clinical stage	Pathological stage
S-01	Alveolus	79	T4aN2b	ypT0N0
S-02	Alveolus[1]	90	T4aN2b	ypT4aN0[2]
S-04	Tongue	34	T3N1	ypT2N0
S-06	Tongue	100	T3N1	ypT3N1
S-07	Floor of the mouth	<1	T4aN2c	ypT4aN0
S-08	Tongue	7	T2N0	ypT1pN0
S-09	Alveolus	27	T4aN0	ypT3pN0
S-10	Tongue	Pending	T2N2b	ypT1pN2a
S-11	Tongue	Pending	T3N0	ypT1pN1
S-13	Gingiva	Pending	T4aN0	ypT2pN0

[1] KRAS G12D mutation found in baseline tumor biopsy; 2. Only residual tumor focis in bone

Figure 1: Right tongue tumor in pt S-10 at screening, day 15 and pre-surgery.



SAFETY

Study treatment was overall well-tolerated:

- **G≥3 TRAEs** pre-surgery occurred only in 1 pt (sitravatinib-related hypertension). **G1/2** TRAEs occurred in all pts. Most common were gastrointestinal disorders (18%), fatigue (14%) and ALT/AST elevation (10%) related to both sitravatinib and nivolumab followed by hypertension (6%) and dysphonia (5%) related to sitravatinib.
- Only 1 pt required surgery delay due to G2 thrombocytopenia.
- None had intraoperative complications. 1 pt had G3 wound infection and tracheostomy bleeding 11 days post-surgery, deemed possibly-related to both study drugs.

IMMUNE/PHARMACODYNAMIC EFFECTS

Sitravatinib led to a reduction of intratumoral MDSCs (**Figure 2A**) and increased M1-intermediate to M2-type ratio (**2B**) in post-treatment biopsies in several pts, with a stronger effect seen in major responders, S-01 and S-02 (**2C**). Flow cytometry showed higher % of PD-L1+ TAMs in baseline tumor biopsies of best responders (S-01 and S-02).

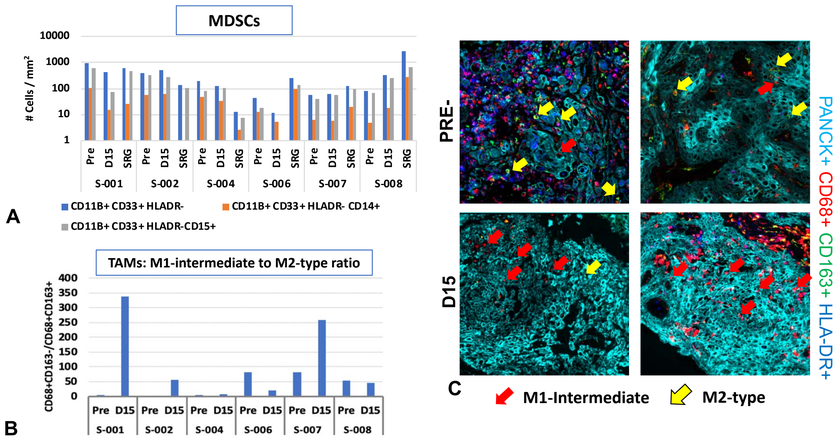


Figure 2. Multiplexing immuno-fluorescence (IF) staining was performed and quantified in tumor biopsies at screening (Pre), day 15 (D15) and surgery (SRG) using NeoGenomics MultiOmyx™ panels. MDSCs determined as number of cells/mm² (A). Ratio of M1-intermediate (CD68+HLADR+CD163-) to M2-type (CD68+CD163+) TAMs based on number of cells/mm² of each type. IF overlays show changes in TAMs in tumor and residual tissue over time: M1-intermediate=red; M2-type= yellow)