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

M. Oliva[1], D. Chepeha[2], A. Prawira[3], A. Spreafico[1], S. Bratman[4], T. Shek[5,6], J. de Almeida[2], I. Yeung[5,6], A. Hansen[1], A. Hope[4], D. Goldstein[2], R. Gilbert[2], D. Vines[5,6], P. Gullane[2], D. Brown[2], I. Weinreb[7], B. Perez-Ordoñez[7], T. Pugh[8,9], P. Ohashi[9], B. Wang[9], J. Irish[2], P. Olson[10], H. Der-Torossian[10], I. Chen[10], L.L. Siu[1]

[1]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University of Toronto, Canada;[2]Department of Otolaryngology- Head & Neck Surgery/Surgical Oncology, Princess Margaret Cancer Centre, University of Toronto, Canada; [3]Department of Medical Oncology, The Kinghorn Cancer Centre, St Vincent's Hospital Sydney, Australia; [4]Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, Canada; [5]Department of Radiation Physics, Princess Margaret Cancer Centre, University of Toronto, Canada; [6] Quantitative Imaging for Personalized Cancer Medicine, TECHNA Institute, University Health Network, Canada;[7] Department of Pathology, Princess Margaret Cancer Centre, University of Toronto, Canada; [8]Department of Computer Science, University of Toronto, Toronto, Canada; [9]Department of Immunology, University of Toronto, Toronto; [10]Mirati Therapeutics.

UHN Princess Margaret Cancer Centre

marc.oliva@uhn.ca

NCT03575598

Tumor Immunotherapy Program

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 safe toxicity profile and promising antitumor activity in non-small cell lung cancer patients progressing on anti-PD-1 agents [1]. In the CheckMate-358 study, preoperative 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 sitravatanib and nivolumab when given in combination.

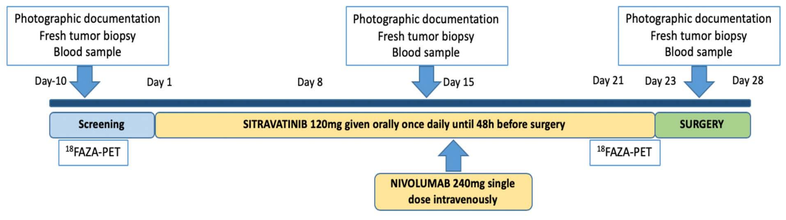
Secondary objectives:

(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 pathologic responses; rate of pathological extranodal extension (ENE) and positive margins.
(c) pharmacokinetics of stravatinib 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 ^{18}FAZA-PET.

STUDY DESIGN



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.

PRELIMINARY RESULTS

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-hypertensive medication.
- **Most common G1/2 TRAEs pre-surgery**: dysphonia (62.5%), ALT/AST elevation (62.5%), fatigue (62.5%), hypertension (50%), mucositis (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.

ANTITUMOR ACTIVITY

Tumor reduction by investigator's assessment was observed in all 8 pts, with pathological downstaging in 7 pts, including 1 complete response (**Table 1**); all pts had clear margins (>5mm) and no pathological ENE. All received postoperative radiotherapy based on clinical stage. None required postoperative chemotherapy. With a median follow-up of 31.4 weeks, all pts are alive with no disease recurrence to date.

Table 1: Pt characteristics and tumor downstaging following study treatment intervention

ID[1]	Age	Gender	Smoking status	HPV status[2]	PD-L1[3]	Primary tumor	Clinical stage	Pathological stage	Margins
S-001	58	Male	Never	Negative	>20	Alveolus	cT4aN2b	ypT0N0	Negative
S-002	58	Female	Never	Negative	>20	Alveolus	cT4aN2b	ypT4aN0*	Negative
S-004	59	Male	Current	Negative	>20	Tongue	cT3N1	ypT2N0	Negative
S-006	59	Male	Former	Negative	>20	Tongue	cT3N1	ypT3N1	Negative
S-007	63	Male	Current	Negative	<1	Floor of mouth	cT4aN2c	ypT4aN0	Negative
S-008	60	Male	Former	Negative	1-20	Tongue	cT2N0	ypT1pN0	Negative
S-009	71	Female	Never	Negative	>20	Alveolus	cT4aN1	ypT3pN0	Negative
S-010	68	Male	Former	Negative	UK[4]	Alveolus	cT2N2b	ypT1pN2a**	Negative

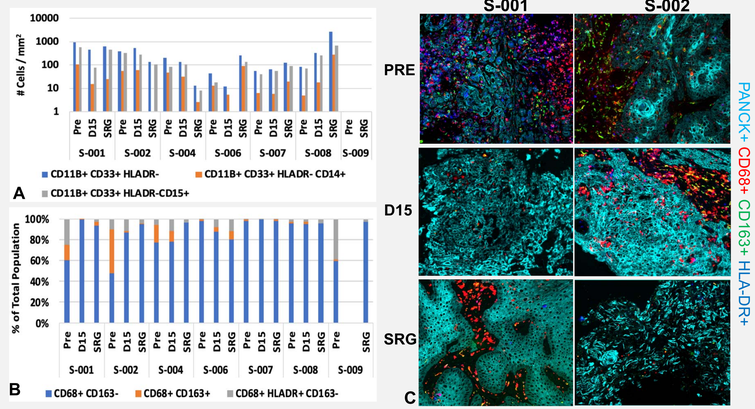
[1] Patient study identification. [2] Human Papillomavirus determined by DNA-PCR. [3] PD-L1 expression by combined positive score (CPS). [4]Unknown: pending to be analyzed. * No tumor in the mucosa, only residual SCC focis in the bone.** No extranodal extension

Figure 1: Tumor response and changes in intratumoral hypoxia by FAZA-PET in pts S-001 and S-002.

IMMUNE BIOMARKER ANALYSES

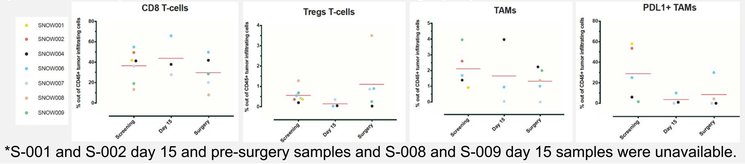
Sitravatinib led to a reduction of intratumoral MDSCs and a trend towards increased percent of M1-type macrophages and M1 to M2-type ratio in several pts, with a stronger effect seen in major responders, S-001 and S-002 (**Figure 2**).

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



Multiplexing IF staining was performed and quantified in tumor biopsies at screening (Pre), day 15 (D15) and surgery (SRG) using NeoGenomics MultiOmyx™ panels. Macrophage data shown as a percent of the total macrophage population. IF overlays show macrophages subpopulations in tumor and residual tissue over time (M1-type=magenta; M1-intermediate=red; M2-type=yellow).

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



*S-001 and S-002 day 15 and pre-surgery samples and S-008 and S-009 day 15 samples were unavailable.

CONCLUSIONS

- Preliminary results suggest the preoperative sitravatinib and nivolumab is a safe and active combination in OCSCC.
- Most pts had clinical benefit and tumor downstaging, with none requiring post operative chemotherapy.
- Sitravatinib led to a decrease in MDSCs and a shift towards M1-type macrophages in the tumor microenvironment.

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