# Nivolumab (Nivo) and ipilimumab (Ipi) combined with radiotherapy (RT) in patients with locally advanced squamous cell carcinoma of the head and neck (LA SSCHN): updated results of a pilot study

Abstract 869P

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## Background

- Definitive treatment of LA SCCHN often relies on concurrent chemotherapy and radiation.
- Platinum agents have been the backbone of systemic therapy in combined modality approaches. However, the addition of cisplatin to radiotherapy results in a modest survival benefit and is associated with multiple acute and late toxicities.
- Nivolumab (nivo), a fully human anti-programmed cell death-1 (PD-1) monoclonal antibody, has demonstrated a survival advantage when compared with standard treatment in patients with platinum-refractory recurrent or metastatic SCCHN[1].
- Combination of nivo with the CTLA-4 directed antibody ipilimumab (ipi) has yielded improvements in antitumor activity in melanoma and is under investigation in multiple other solid tumor types including SCCHN in the CheckMate 651 Trial NCT02741570[2].
- Nivo and Ipi have shown promising antitumor activity in the neoadjuvant setting for LA SCCHN in the IMCISION trial NCT03003637[3].
- The combination of RT and immunotherapy leads to synergistic effects in the laboratory and has promise in early phase clinical trials[4,5,6].
- This clinical trial combines immunotherapy and RT to build upon these observations for the treatment of LA SCCHN.

## Key Inclusion Criteria

Disease:
- Newly Diagnosed and Untreated AJCC 8th Edition SCCHN
- Stage III-IVB of the Oral Cavity, Hypopharynx, Larynx, p16- Oropharynx
- Stage II-III p16+ Oropharynx; Stage II OPSCC must have N2 disease, if T3N0 or T3N1 must have 20 pack year smoking history
- Nasopharyngeal is excluded

Patient:
- ECOG PS 0-1
- Adequate tumor available for PD-L1 testing
- Adequate Organ Function as determined by WBC, ANC, platelets, hemoglobin, total bilirubin, AST, ALT, and creatinine
- HIV, Hepatitis B, Hepatitis C negative
- No history of autoimmune disease
- No concurrent malignancies

## Objectives

Primary Objective:
- To investigate the safety of the combination of nivolumab and ipilimumab with radiation treatment for definitive management of patients with locally advanced squamous cell carcinoma of the head and neck

Secondary Objectives:
- To estimate 1 year PFS in all patients treated
- To assess overall response rate
- To assess overall survival

Exploratory Objectives:
- To explore whether PD-L1 expression is associated with treatment response.
- To explore whether there is an association of the Th1/Th2 ratio (IFN-λ, IL-4, IL10) or cell subset frequencies (M2 monocytes, myeloid-derived suppressor cells) in a patient's peripheral blood at baseline or a change these values in response to treatment that is associated with treatment response
- To explore whether exosomes or other immune related serum biomarkers change after combination therapy

## Statistical Considerations

- Goal Enrollment of 24 patients was met.
- Designed in 2 stages with safety stopping rules.
  - First stage= 12 patients. Enrollment was suspended until all 12 patients completed radiotherapy and toxicities assessed 2 weeks after radiotherapy completion
  - For the stopping rules, we considered grade 4-5 in-field toxicities DURING radiation treatment and the two week period after the completion of radiation treatment
- Safety requirements were met and accrual was completed in 7/2019.

## Trial Schema and Completion Rates

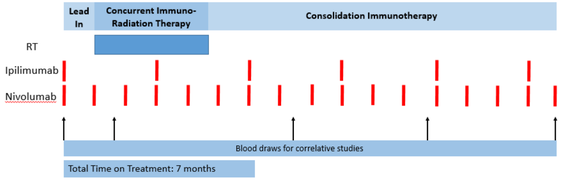


**Figure 1. Trial Schema**

- 100% of patients completed all planned radiation therapy (RT)
- 0 treatment delays
- 0 patients experienced grade 4/5 AEs during RT

- Immunotherapy was discontinued in 7 patients > 3 months after RT
  - 1 Grade 3 immune colitis
  - 5 in field ulcerations, developed 3 months post RT
  - 1 persistent mucositis without ulceration

## Demographics

| | | |
|---|---|---|
| Age | Median | 60 |
| | Range | 44 - 77 |
| Sex | M : F | 20 : 4 |
| Site of Tumor | Oral Cavity | 0 |
| | Oropharynx | 16 |
| | p16+ | 14 |
| | p16- | 2 |
| | Hypopharynx | 2 |
| | Larynx | 6 |
| AJCC 8th Edition Stage | II | 8 |
| | III | 6 |
| | IVA | 10 |
| 8th Edition T Stage | T1 | 1 |
| | T2 | 7 |
| | T3 | 9 |
| | T4 | 4 |
| | T4a | 3 |
| 8th Edition N Stage | N0 | 1 |
| | N1 | 2 |
| | N2 | 12 |
| | N2b | 4 |
| | N2c | 4 |
| | N3b | 1 |

**Table 1. Demographics**

## Immune AEs

| AE | Grade 1-2 n (%) | Grade 3 n (%) | Grade 4-5 |
|---|---|---|---|
| Dermatitis | 5 (21) | 2 (8) | 0 |
| Pruritus | 5 (21) | 0 | 0 |
| Elevated Lipase | 0 | 1 (4) | 0 |
| Colitis | 0 | 1 (4) | 0 |
| Hyperglycemia | 0 | 1 (4) | 0 |
| Hypothyroidism | 1 (4) | 0 | 0 |
| Hyperthyroidism | 2 (8) | 0 | 0 |

**Table 2. Immune adverse events** (CTCAE v5)

- Grade 3 dermatitis was managed with oral and topical steroids. The patients were rechallenged and able to continue immunotherapy.
- Grade 3 elevated lipase was asymptomatic, observed, and resolved without intervention.
- Grade 3 colitis was managed with oral steroids. The patient was 3 months post-radiation therapy and discontinued treatment.
- Grade 3 hyperglycemia was noted after the patient completed immunotherapy.

## In-Field Toxicities During Concurrent Immuno-Radiation Therapy

| AE | Grade 1-2 n (%) | Grade 3 n (%) | Grade 4-5 |
|---|---|---|---|
| Dysgeusia | 19 (79) | 0 | 0 |
| Dysphagia | 14 (58) | 6 (25) | 0 |
| Odynophagia | 21 (88) | 3 (13) | 0 |
| Dysphonia | 6 (25) | 1 (4) | 0 |
| Radiation Mucositis | 15 (63) | 10 (42) | 0 |
| Radiation Dermatitis | 19 (79) | 5 (21) | 0 |
| Hemorrhage (Upper Airway) | 3 (13) | 0 | 0 |
| Xerostomia | 19 (79) | 0 | 0 |
| Increased Secretions | 3 (13) | 0 | 0 |
| Oropharyngeal or Laryngeal Edema | 3 (13) | 0 | 0 |
| Thrush | 6 (25) | 0 | 0 |
| Trismus | 1 (4) | 0 | 0 |
| Esophagitis | 1 (4) | 0 | 0 |
| Neck Stiffness | 2 (8) | 0 | 0 |
| Facial Pain | 1 (4) | 0 | 0 |
| Salivary Duct Inflammation | 1 (4) | 0 | 0 |

**Table 3. In-field toxicities during combination immunotherapy and radiation.** (CTCAE v5)
This includes 2 weeks prior to radiation and two weeks after the last fraction of radiation given.

- 16/24 (67%) patients experienced at least 1 grade 3 in field toxicity during concurrent immuno-radiation therapy. No patients experienced grade 4 or 5 in field toxicities during this time.

- 5 patients developed soft tissue ulceration at the primary tumor site at a mean of 86 days post- RT completion
  - 1 of these patients declined evaluation and treatment for the ulcer leading to fatal carotid rupture
- 2 patient experienced osteoradionecrosis at sites of prior teeth extraction
- 2 patients experienced persistent mucosal inflammation without ulceration

- 8/24 patients require PEG tube placement during Immuno-RT due to toxicities; 5 were still present at 6 months and 2 were present at 1 year

## Survival Data

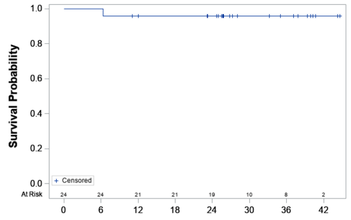


**Figure 2. Overall Survival (months)**
- OS at 1 year 95.8% (95% CI: 78.3, 99.9%)
- OS at 2 years 95.8% (95% CI: 74.7&, 100.0%)

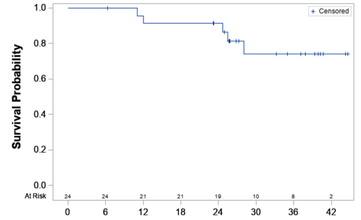


**Figure 3. Progression Free Survival (months)**
- PFS at 1 year 91.3% (95% CI: 70.7%, 99.1%)
- PFS at 2 years 86.5% (95% CI: 62.3%, 97.8%)

- **Range of follow-up:** 7.03 – 46.82 months, median 31.52 months

- **Sites of Failure:**
- 4 patients progressed distantly and for these patients DFS ranged from 9 to 26 months: 3 in the lungs- 2 treated with RT and 1 treated with resection and 1 in the mediastinal lymph nodes treated with chemo-RT
- 1 patient progressed regionally in cervical lymph nodes at 23.39 months: considered unresectable, planned to return to immunotherapy
- Within the limits of this small sample size there was no correlation between PDL1 status of the primary tumor and recurrence

## Conclusions

- RT plus dual PD-1 and CTLA-4 blockade resulted in excellent locoregional control with 1 year PFS of 91.3% in high risk locally advanced HNSCC.
- While there were no grade 4/5 toxicities observed during concurrent immuno-radiation, a high rate of in-field ulceration/necrosis was observed.
- Further exploration of this combined therapy is warranted with careful monitoring and intervention for delayed toxicities.

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