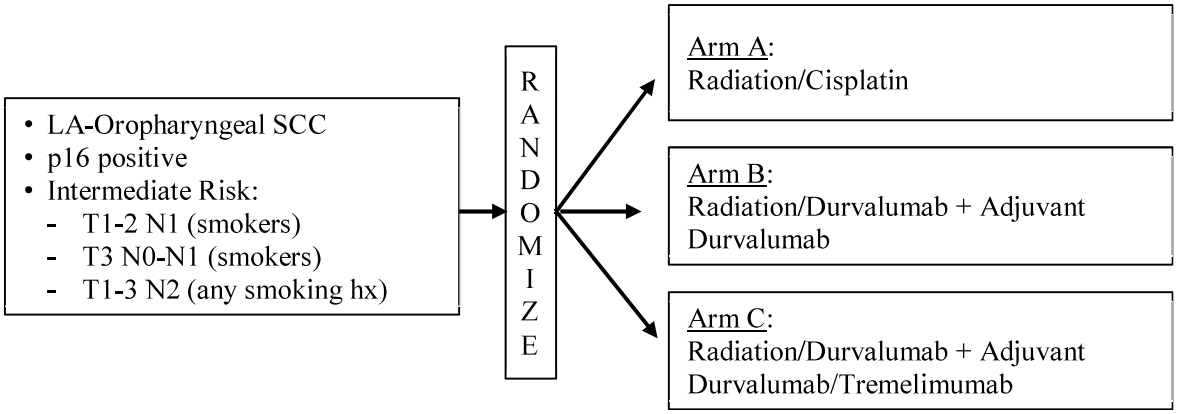
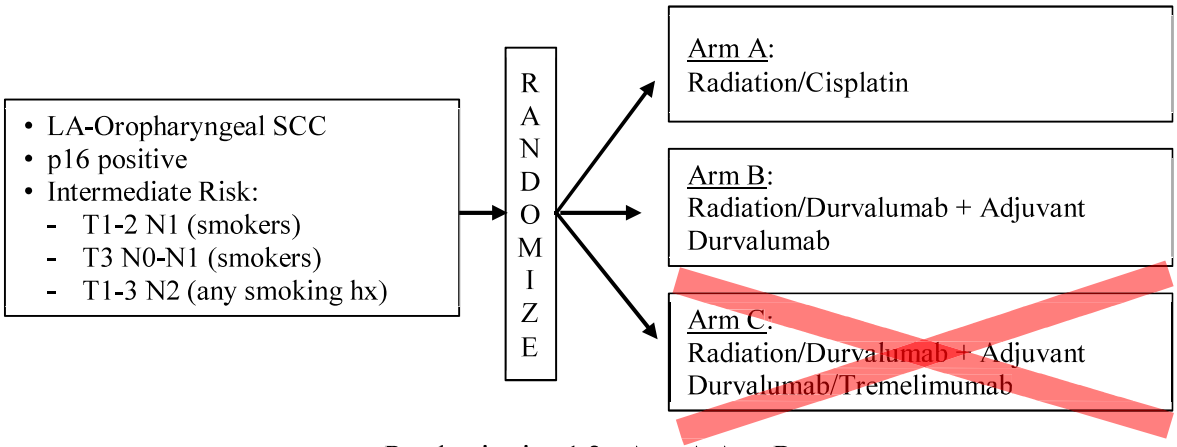
TREATMENT SCHEMA

This is a non-comparative, randomized, phase II study of cisplatin plus radiotherapy or durvalumab plus radiotherapy followed by adjuvant durvalumab or durvalumab plus radiotherapy followed by adjuvant tremelimumab and durvalumab in intermediate risk, HPV-positive, locoregionally advanced oropharyngeal squamous cell cancer (LA-OSCC) of the head and neck.



Sample Size: 240

Update as Per Amendment #1:



Randomization 1:2 - Arm A:Arm B

Sample Size: 180

Dosing:

All patients will receive standard fractionation radiation therapy (RT) scheme: 70 Gy in 35 fractions over 7 weeks (i.e. 2 Gy per fraction)

Arm A: Cisplatin IV 100 mg/m^2 days 1, 22, 43 concurrently with RT

Arm B: *Concurrent Phase:* Durvalumab IV 1500 mg, days -7 and 22 (the second dose is given concurrently with RT).

Adjuvant Phase (to start 4 weeks after completion of concurrent phase): Durvalumab IV 1500 mg q4 weekly for 6 doses.

Arm C: *Concurrent Phase:* Durvalumab IV 1500 mg, days -7 and 22 (the second dose is given concurrently with RT).

Adjuvant Phase (to start 4 weeks after completion of concurrent phase): Tremelimumab IV 75 mg q4 weekly for 4 doses + Durvalumab IV 1500 mg q4 weekly for 6 doses

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Stratification:

- Smoking status (< 10 pack-years vs ≥ 10 pack years)
- Age (≤ 60 years vs > 60)
- ECOG (0 vs 1)
- TNM classification (T1-2, N1 vs T3, N0-2 or T1-2, N2)

All patients will be followed for event-free survival.

1.0 OBJECTIVES

1.1 Primary Objective

To estimate the efficacy (in terms of event-free survival) of 3 treatment Arms: (A) radiotherapy (RT) and cisplatin; (B) RT and durvalumab followed by adjuvant durvalumab; and (C) RT and durvalumab followed by adjuvant durvalumab and tremelimumab in patients with intermediate risk, HPV-positive, locally advanced oropharyngeal squamous cell carcinoma of the head and neck (LA-OSCC).

Updated Primary Objective as Per Amendment #1:

To estimate the efficacy (in terms of event-free survival) of 2 treatment Arms: (A) radiotherapy (RT) and cisplatin; (B) RT and durvalumab followed by adjuvant durvalumab in patients with intermediate risk, HPV-positive, locally advanced oropharyngeal squamous cell carcinoma of the head and neck (LA-OSCC).

1.2 Secondary Objectives

- To assess differences between arms in change in FACT-HN score from baseline to 36 months post-RT.
- To estimate and describe the following in each of the 3 treatment arms:
  - Locoregional control (LRC);
  - Distant metastasis-free survival (DMFS);
  - Overall survival (OS);
  - Toxicity;
  - Incidence of second cancer;
  - Dysphagia: PSS-HN swallowing subscale and MDADI Global at 36 months from the end of RT;
  - PRO-CTCAE baseline, last week of treatment, 3 months, 6 months and 12, 24 and 36 months from the end of RT;
  - Radiation related late toxicity at 3 months, 6 months and 1 year from the end of RT;
  - Cost effectiveness of the 2 immunotherapy-based experimental treatment arms vs. the standard of RT and cisplatin in patients with intermediate risk LA-OSC using the EQ-5D-5L;
  - Cost utility and lost productivity.

Updated Secondary Objectives as Per Amendment #1:

- To assess differences between arms in change in FACT-HN score from baseline to 36 months post-RT.
- To estimate and describe the following for Arms A and B:
  - Locoregional control (LRC);
  - Distant metastasis-free survival (DMFS);
  - Overall survival (OS);

- Cost effectiveness of the immunotherapy-based experimental treatment arm vs. the standard of RT and cisplatin in patients with intermediate risk LA-OSC using the EQ-5D-5L;
- Cost utility and lost productivity

- To estimate and describe the following for Arms A, B and C:
  - Toxicity;
  - Incidence of second cancer;
  - Dysphagia: PSS-HN swallowing subscale and MDADI Global at 36 months from the end of RT;
  - PRO-CTCAE baseline, last week of treatment, 3 months, 6 months and 12, 24 and 36 months from the end of RT;
  - Radiation related late toxicity at 3 months, 6 months and 1 year from the end of RT

1.3 Tertiary Objectives

- To perform exploratory correlative studies such as immunophenotyping, radiomics and microbiome studies to understand mechanisms of sensitivity or resistance to systemic therapy given with radiotherapy and prognostic/predictive biomarkers in this population.
- Event free survival as defined by iRECIST.

Updated Tertiary Objectives as per Amendment #1:

- To perform exploratory correlative studies such as immunophenotyping, radiomics and microbiome studies to understand mechanisms of sensitivity or resistance to systemic therapy given with radiotherapy and prognostic/predictive biomarkers in this population.
- Event free survival as defined by iRECIST in Arm B.