### Non-Interventional Study Protocol

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<tr>
<td>Version</td>
<td>Edition 2, incorporates Amendment 1</td>
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**SUPREME-HN**  
A Retrospective Cohort Study of PD-L1 in Recurrent and Metastatic Squamous Cell Carcinoma of Head and Neck (SCCHN)

**Sponsor:** AstraZeneca AB, 151 85 Södertälje, Sweden.  
This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

The following Amendment(s) have been made to this protocol since the date of preparation:

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<tr>
<td>Amendment 1</td>
<td>19 February 2016</td>
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<th>Explanation</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>Assessment</td>
<td>An observation made on a variable involving a subjective judgment (assessment)</td>
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<tr>
<td>CD137</td>
<td>A member of the tumor necrosis factor receptor family</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (electronic/paper)</td>
</tr>
<tr>
<td>CRO</td>
<td>Clinical Research Organization</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>Cytotoxic T-Lymphocyte-Associated Protein 4</td>
</tr>
<tr>
<td>CXCL9</td>
<td>Chemokine (C-X-C Motif) Ligand 9</td>
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<td>CXCL10</td>
<td>Chemokine (C-X-C Motif) Ligand 10</td>
</tr>
<tr>
<td>EC</td>
<td>Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report/Record Form</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>FFPE</td>
<td>Formalin-Fixed, Paraffin-Embedded</td>
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<tr>
<td>First line treatment</td>
<td>First treatment line for recurrent or metastatic disease, excluding adjuvant and neo-adjuvant therapy.</td>
</tr>
<tr>
<td>FoxP3</td>
<td>Forkhead Box P3</td>
</tr>
<tr>
<td>FPI</td>
<td>First Patient In</td>
</tr>
<tr>
<td>GITR</td>
<td>Glucocorticoid-Induced Tumor-Necrosis-Factor-Receptor-Related Protein</td>
</tr>
<tr>
<td>GPP</td>
<td>Good Pharmacoepidemiology Practices</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papillomavirus</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD-9-CM</td>
<td>International Classification of Diseases, Ninth Revision, Clinical Modification</td>
</tr>
<tr>
<td>Abbreviation or special term</td>
<td>Explanation</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>ICD-10-CM</td>
<td>International Classification of Diseases, Tenth Revision, Clinical Modification</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Interferon Gamma</td>
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<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>Index Date</td>
<td>Date of diagnosis of recurrent/metastatic SCCHN</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ISH</td>
<td>In Situ Hybridization</td>
</tr>
<tr>
<td>ISPE</td>
<td>International Society for Pharmacoepidemiology</td>
</tr>
<tr>
<td>LAG3</td>
<td>Lymphocyte-Activation Gene 3</td>
</tr>
<tr>
<td>LPI</td>
<td>Last Patient In</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>National Coordinator</td>
<td>The National Coordinator is the main line of contact to coordinate the submissions and responses of the Leading Ethics Committee and of the Ethics Committees related to the other participating sites (Non-Leading Ethics Committees).</td>
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<tr>
<td>NIS</td>
<td>Non-Interventional Study</td>
</tr>
<tr>
<td>ORR</td>
<td>Objective Response Rate</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>OX40</td>
<td>A member of the tumor necrosis factor receptor/ tumor necrosis factor superfamily – also named CD134</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PD-1</td>
<td>Programmed Cell Death Protein 1</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Programmed Death-Ligand 1</td>
</tr>
<tr>
<td>PD-L2</td>
<td>Programmed Death-Ligand 2</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-Free Survival</td>
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<tr>
<td>PI</td>
<td>Principal Investigator responsible for the conduct of a NIS at a site</td>
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<tr>
<td>Q</td>
<td>Quarter</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
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<tr>
<td>RT-qPCR</td>
<td>Quantitative Reverse Transcription Polymerase Chain Reaction</td>
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</table>
### Abbreviation or special term | Explanation
--- | ---
SAE | Serious Adverse Event
SAP | Statistical Analysis Plan
SCC | Squamous Cell Carcinoma
SCCHN | Squamous Cell Carcinoma of Head and Neck
Second line treatment | Second treatment line for recurrent or metastatic disease, excluding adjuvant and neo-adjuvant treatments.
SIR | Standardized Incidence Ratio
TIL | Tumor-Infiltrating Lymphocytes
Tim3 | T-Cell Immunoglobulin Domain and Mucin Domain 3
US | United States [of America]
Variable | A characteristic of a property of a subject that may vary e.g., from time to time or between subjects
WHO | World Health Organization
# RESPONSIBLE PARTIES

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<th>Professional Title</th>
<th>Role in Study</th>
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<td></td>
<td>Sr Global Medical Affairs Leader</td>
<td>Medical Lead</td>
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<td>Regional Operations Leader</td>
<td>AstraZeneca R&amp;D Global Medicines Development Global Medical Affairs Medical Evidence and Observational Research (MEOR)</td>
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<td></td>
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<td>Diagnostic Technical Lead</td>
<td>AstraZeneca R&amp;D PHB</td>
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<td></td>
<td>Professor, Division of Hematology/Oncology, Department of Medicine</td>
<td>Coordinating Investigator</td>
<td>UC San Diego Moores Cancer Center</td>
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<td>Co-leader, Solid Tumor Therapeutics Program</td>
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<td>Coordinating</td>
<td>Massachusetts</td>
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PROTOCOL SYNOPSIS

SUPREME-HN

A Retrospective Cohort Study of PD-L1 in Recurrent and Metastatic Squamous Cell Carcinoma of Head and Neck (SCCHN)

Background/Rationale:

Programmed cell death protein 1 (PD-1) is an immune inhibitory receptor that interacts with two ligands, programmed death ligand 1 (PD-L1) and ligand 2 (PD-L2). PD-1 pathway is a major immune checkpoint which has been implicated in adaptive immune resistance of squamous cell carcinoma of the head and neck (SCCHN) tumors, particularly in those associated with human papillomavirus (HPV) infection. Based on an internal analysis performed by AstraZeneca, it is reported that approximately 25% of cases of SCCHN express PD-L1. Tumoral PD-L1 expression status correlates closely with response to anti-PD-1/anti PD-L1 antibodies.

Durvalumab (MEDI4736) is an immunoglobulin G1 kappa monoclonal antibody with high affinity and selectivity for PD-L1 and no binding to PD-L2, which is in development for the treatment of patients with recurrent or metastatic SCCHN.

This non-interventional study (NIS) aims to generate and provide data on the prognostic value of PD-L1 status in patients with recurrent/metastatic SCCHN.

Objectives and Hypotheses:

Primary objective:

To determine the prognostic value of PD-L1 status in terms of overall survival (OS) in patients with recurrent/metastatic SCCHN. Overall survival after diagnosis of recurrent/metastatic SCCHN will be assessed in PD-L1 positive and PD-L1 negative patients and in predefined sub-groups (e.g., HPV status, HIV status, smoking history, heavy alcohol use, anatomical sub-site of primary tumor, and prior exposure to radiation therapy).

Secondary objectives:

1. To describe the relevant demographic and clinical characteristics of patients, stratified by PD-L1 status
2. To describe first line treatment choices, and where available, subsequent treatment choices

3. To describe investigator-assessed tumor response for first line and second line of therapy (if any), including: best response, duration of response where applicable, and objective response rate (ORR)

4. To describe investigator-assessed progression-free survival (PFS) for first line and second line of therapy (if any).

Exploratory objectives:

1. To perform additional biomarker research on tumor samples (depending on tissue availability and volume).

2. If feasible, to assess agreement of PD-L1 status in samples obtained at different time points (e.g., before and after chemotherapy or radiation therapy).

Methods:

Study design:

This is a retrospective international, multi-center, non-interventional cohort study based on use of data derived from established medical records and secondary analysis of archival tumor samples. The study will collect data on patient and tumor characteristics, PD-L1 status, patterns of treatment, and clinical outcomes in up to 600 adult patients with recurrent/metastatic SCCHN (falling into specific International Classification of Diseases, Tenth Revision [ICD-10] or International Classification of Diseases, Ninth Revision [ICD-9] codes). For patient selection, the date of diagnosis of recurrent/metastatic disease will be used as the index date. The patient selection period extends from the 1st March 2011 to the 30th June 2015. This allows the inclusion of patients with tumor samples of approximately ≤ 5 years age, and ensures approximately 10 months follow-up for living patients recruited at last day of the enrollment window. All patients with a diagnosis of recurrent/metastatic squamous cell carcinoma (SCC) of oral cavity (tongue, gum, floor of mouth, and other/unspecified part of the mouth), oropharynx, hypopharynx, or larynx during that period will be considered for inclusion in the study. Patients will be identified and followed up through their medical records until death or end of data collection (approximately Q4 2016).

Patients’ demographic and clinical characteristics and medical history will be described. Clinical outcomes including PFS, best response, duration of response, and ORR will be described for the first and second lines of therapy (if any), and OS will be collected. A mandatory archived tumor sample will be used to determine PD-L1 status. If a patient has more than one suitable tissue sample, the most recent sample will be used as the mandatory tissue sample. Where available, additional tumor samples obtained at any other time points of the disease will be also collected (optional).
Statistical analyses will be performed for the whole cohort, per PD-L1 status and for predefined subgroups.

**Data Source(s):**

The study will be implemented in a total of approximately 20 sites in the US, Asia and Europe. Data will be abstracted from patient’s hospital medical records until death, or end of data collection. Archival tumor samples will be retrieved and tested by immunohistochemistry to assess the PD-L1 status of the tumor. Where there is sufficient tissue quantity, the expression of other biomarkers will also be evaluated.

**Study Population:**

Inclusion criteria:

1. Provision of subject informed consent (or consent from next of kin/legal representative if applicable) for use of the data and retrieval of tumor sample, according to local regulations
2. Adult patient (≥ 18 years old)
3. Patient with histologically confirmed SCCHN of oral cavity (tongue, gum, floor of mouth, other/unspecified part of the mouth), oropharynx, hypopharynx or larynx
4. Patient with recurrent or metastatic SCCHN diagnosed between 01 March 2011 and 30 June 2015
5. Mandatory archival tissue sample (most recent) from the primary site, a lymph node or a distant metastatic site:
   - Tissue sample less than 5 years old (compared to date of retrieval) if provided as complete block (preferred option) or as section cut within 60 days of shipment from site prior to testing
6. Optional archival tissue samples taken at other time points of the disease from the primary site, a lymph node or a distant metastatic site (where available):
   - Tissue sample less than 5 years old (compared to date of retrieval) if provided as complete block (preferred option) or as section cut within 60 days of shipment from site prior to testing.

Exclusion criterion:

1. Treatment for SCCHN with anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies, or any other antibody with known immunomodulatory effect.

**Exposure(s):**

The primary variable is the PD-L1 status (positive or negative) in the overall patient population. Archived tissue samples, including samples from the primary site, lymph nodes or distant metastatic sites, will be used to determine PD-L1 status. PD-L1 status will be determined by immunohistochemistry (IHC) using a validated assay.
Outcome(s):

Overall survival will be assessed. Additionally, the following clinical outcomes will be described for first line and second line treatments for recurrent and/or metastatic disease: investigator-assessed best tumor response, duration of response where applicable, and investigator-assessed PFS. ORR (sum of complete and partial responses) will be derived from investigator-assessed best responses and described for first line and second line therapies (if any).

Patient characteristics, disease characteristics, and patterns of treatment will be captured and described.

Sample Size Estimation:

The primary objective of this study is to estimate the prognostic value of PD-L1 status in terms of OS in patients with recurrent/metastatic SCCHN. The available sample size is not known a priori and will be driven by the number of patients at selected sites with available tissue. However, assuming that PD-L1 status distribution is approximately 25% positive and 75% negative status, that the median OS in these patients is 10 months, that the study will accrue uniformly over 52 months with 10 months follow-up from the last patient entering and that survival times are exponentially distributed, the illustrations of hazard ratios it would be possible to detect with 80% power (2-sided alpha 0.05) over various sample sizes are given in the table below.

<table>
<thead>
<tr>
<th>HR to detect</th>
<th>Number of deaths</th>
<th>Number of patients (Total)</th>
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<tr>
<td>0.3</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>0.4</td>
<td>51</td>
<td>68</td>
</tr>
<tr>
<td>0.5</td>
<td>74</td>
<td>112</td>
</tr>
<tr>
<td>0.6</td>
<td>136</td>
<td>196</td>
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<tr>
<td>0.7</td>
<td>278</td>
<td>396</td>
</tr>
</tbody>
</table>

HR: Hazard ratio

These illustrations do not take account of the fact that the binary prognostic factor of interest (PD-L1 status) may be correlated with other covariates and hence could over-estimate the power of the various sample sizes (Bernardo et al, 2000). The sample size (number of events) required when no correlation is assumed should be multiplied by 1/(1-R²) to account for an R² > 0 (Hsieh and Lavori, 2000). The correlation is not currently known. Additionally, a proportion of patients will not have PD-L1 status available. Given these uncertainties, a sample size of up to 600 patients is felt to be adequate.
**Statistical Analysis:**

Descriptive analyses on patient characteristics, treatment choices and treatment outcomes will be conducted.

Time to event data (OS, PFS) including rates of affected patients will be described using the Kaplan-Meier method. Two-sided 95% CIs will be provided for the main statistical estimators.

OS and PD-L1 status will be described in subgroups, including but not limited to the following:

- Per anatomical sub-site of primary tumor
- Per HPV status
- Per HIV status
- Per smoking history
- Per alcohol consumption history
- Per prior exposure to radiation therapy
- Per types of treatment regimens
- By performance status at diagnosis of recurrent/metastatic disease.

The prognostic value of PD-L1 status will be investigated using a Cox proportional hazards model. Additional covariates to be included in the model will be described in the statistical analysis plan.
### AMENDMENT HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Brief description of change</th>
<th>Administrative Change / Amendment / New Protocol Version.</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2016</td>
<td>Primary objective modified to evaluate the prognostic value of PD-L1 positive or negative status in terms of overall survival. Patient population and eligibility criteria modified to include patients diagnosed with recurrent/metastatic squamous cell carcinoma of head and neck (SCCHN) with mandatory tumor sample (most recent tissue sample) obtained anytime during the disease history (no treatment condition). Index date changed to date of diagnosis of recurrent/metastatic SCCHN. Patient selection period changed to 01 March 2011-30 June 2015, to allow mandatory tumor samples of &lt; 5 years of age and approximately 10 months follow-up for living patients recruited at last day of the window. Sample size changed to up to 600 patients, with tumor samples obtained anytime during the disease history, providing that they are of &lt; 5 years of age.</td>
<td>Amendment #1</td>
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## MILESTONES

<table>
<thead>
<tr>
<th>Date</th>
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<td>Protocol edition 1</td>
<td>June 2015</td>
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<tr>
<td>First patient in (FPI)</td>
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1. BACKGROUND AND RATIONALE

1.1 Background

Head and neck cancers are a diverse group of malignancies originating from the nasopharynx, oropharynx, larynx, hypopharynx, oral cavity, nasal cavity, paranasal sinuses, cervical lymph nodes, and salivary glands, including virally mediated cancers in addition to tumors caused by tobacco and alcohol use. Over 650,000 new cases of head and neck cancer are diagnosed each year worldwide, placing them collectively sixth in terms of global incidence (Schoenfeld, 2015). In Europe alone, it is estimated that there are around 143,000 new cases and more than 68,000 deaths due to the disease each year.

The World Health Organization’s (WHO) International Agency for Research on Cancer provided incidence and prevalence for cancers of the lip and oral cavity, other pharynx and larynx in their GLOBOCAN 2012 analysis tool (Globocan 2012). Taken together, their collective age-standardized incidence in the most developed regions of the world was 10.0 per 100,000 inhabitants for both sexes, and the estimated mortality rate was 3.7 per 100,000.

In the European Union (EU) in 2012, the age-standardized incidence of new cancers was estimated to be 18.3 and 5.5 per 100,000 male and female individuals respectively (altogether, 11.6 per 100,000) for cancers of the oral cavity and pharynx (International Classification of Diseases 10th revision [ICD-10] codes C00-C14), and 8.3 and 0.9 per 100,000 male and female individuals respectively (altogether, 4.4 per 100,000) for cancer of the larynx (ICD-10 code C32) (Ferlay et al, 2013). Age-related incidence peaks in the 55-64 years decade (Binder-Foucard et al, 2013), and the vast majority of these cancers are diagnosed in the 50-74 age group (Cancer Research UK, Statistics by cancer type).

In the United States (US), it is estimated that 45,780 new cases of cancers of the oral cavity and pharynx will be diagnosed in 2015 (2.8% of all cancer cases), and that these cancers will cause 8,650 deaths (1.5% of all cancer-related deaths) (SEER Stat Fact Sheets: oral cavity and pharynx cancer). The corresponding figures for cancer of the larynx are 13,650 new diagnoses, (0.8% of all new cancer cases) and 3,640 deaths (0.6% of cancer-related deaths) (SEER Stat Fact Sheets: larynx cancer).

Squamous cell carcinoma (SCC) is the most common histology. Squamous cell carcinomas of head and neck (SCCHN) frequently spread to the lymph nodes of the neck, and this is often the first sign of the disease at the time of diagnosis. Tumors are often located within or in close proximity of structures that are vital to speak, breathe and swallow (Schoenfeld, 2015). The management of SCCHN is complex and requires a multidisciplinary approach involving medical oncologists, radiation oncologists, head and neck surgeons, pathologists, radiologists, plastic and/or reconstructive surgeons. The majority of patients develop local and/or regional recurrences and distant metastases occur in 20%–30% of patients after front line treatment. Most patients with recurrent and/or metastatic disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, or in addition single-agent
chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents. In the metastatic setting, despite use of aggressive treatment regimens, the outcome remains poor with median survival generally less than one year (Schoenfeld, 2015).

Tobacco and alcohol use is the predominant risk factor for the development of carcinomas across all anatomical sites of SCCHN; however, oncogenic viruses are recognized to play an increasing role in tumor development (Schoenfeld, 2015). Infection with human papillomavirus (HPV), particularly strain HPV-16, is deemed a risk factor for development of SCCHN, particularly for oropharyngeal (palatine and lingual tonsil) carcinomas (Andersen et al, 2014). According to existing literature on head and neck cancers it is estimated that 25-30% of the cases are HPV positive (Weinberger et al, 2010; Sethi et al, 2012; Deng et al, 2011). In particular, it is estimated that HPV is responsible for up to 80% of oropharyngeal cancers in the US (Lyford–Pike et al, 2013).

HPV status and lifetime tobacco smoking are major independent prognostic factors for overall survival and risk of relapse among patients with oropharyngeal SCC (Ang et al, 2010). A retrospective analysis of the association between tumor HPV status and survival among patients with stage III or IV oropharyngeal squamous cell carcinoma who were enrolled in a randomized trial comparing accelerated-fractionation radiotherapy showed, after adjustment for age, race, tumor and nodal stage, tobacco exposure, and treatment assignment, a 58% reduction of the risk of death (hazard ratio, 0.42; 95% confidence interval [CI], 0.27 to 0.66) and a 51% reduction in the risk of relapse or death (hazard ratio, 0.49; 95% CI, 0.33 to 0.74) for HPV-positive (HPV+) patients, compared to their HPV negative (HPV-) counterparts (Ang et al, 2010). Recurrent and/or metastatic SCHHN are more commonly associated with tobacco and alcohol exposure. It has been hypothesized that the worse prognosis in HPV-unrelated oropharyngeal carcinomas is due to the larger number of mutations on average in HPV negative tumors as compared to HPV+ tumors (Andersen et al, 2014).

Individuals infected with human immunodeficiency virus (HIV) are at greater risk for oral HPV infection and therefore HPV-associated head and neck cancers (Beachler et al, 2013). A recent retrospective study pooling data from 17 prospective studies carried out between 1996 and 2009 in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) showed that standardized incidence ratios (SIRs) were 3.0 times greater for HPV- SCCHN and 3.2 times greater for HPV+ SCCHN in this HIV-infected population than in the general US population. Lower CD4 cell count prior to cancer diagnosis was significantly associated with increased HPV-related and HPV-unrelated SCCHN risk (Beachler et al, 2014). These findings indicate that HIV infection (and immunosuppression at large) may be a risk factor for SCCHN, independent of HPV infection.

1.2 PD-L1 Pathway

Programmed cell death protein 1 (PD-1) is an immune inhibitory receptor that interacts with two ligands, programmed death ligand 1 (PD-L1) and ligand 2 (PD-L2). PD-L1 is widely expressed on antigen presenting cells and other immune cells (Kim and Eder, 2014). PD-L1 is
up-regulated on tumor cells from a broad range of human cancers including SCCHN. The expression of PD-L1 may be modified by the treatments received by the patient.

The PD-1/PD-L1 pathway is a major immune checkpoint which has been implicated in adaptive immune resistance of SCCHN, particularly in those associated with HPV infection. The mechanism of PD-1 activation in HPV+ SCCHN lesions begins with the activation of CD8+ T cells to the initial HPV infection and the associated secretion of inflammatory cytokines such as interferon gamma (IFN-γ). The local secretion of IFN-γ upregulates tumoral PD-L1 expression, which then engages the PD-1 receptor expressed on the activated T cells to render the tumor-infiltrating lymphocytes (TILs) functionally anergic, or unable to combat tumor proliferation and growth. This inflammatory response allows HPV+ SCCHN tumors to effectively evade the immune system in the absence of therapeutic intervention (Pai, 2013; Lyford-Pike et al, 2013; Pitprajak et al, 2015).

Results from a small scale analysis of SCCHN biopsies suggest that a greater proportion of metastatic tumors had elevated levels of both PD-1 and PD-L1 compared to non-metastatic tumors, independent of HPV status. These results suggest the PD-1/PD-L1 pathway involvement in all SCCHN, not only HPV+ tumors, as well as a potential association between elevated PD-1/PD-L1 expression and advanced disease (Feldman et al, 2014).

1.3 Rationale

Blocking anti-PD-L1 antibodies have shown durable, single-agent anti-tumor activity across multiple tumor types. Tumoral PD-L1 expression status correlates closely with response to anti-PD-1/ anti-PD-L1 antibodies. Based on an internal analysis performed by AstraZeneca, approximately 25% of cases of SCCHN express PD-L1.

Durvalumab (MEDI4736) is an immunoglobulin G1 kappa monoclonal antibody with high affinity and selectivity for PD-L1 and no binding to PD-L2, which is in development for the treatment of patients with recurrent and/or metastatic SCCHN and has shown promising results in early phase studies (Fury et al, 2014).

This non-interventional study (NIS) aims to describe the patient characteristics, patterns of treatment, overall survival and other clinical outcomes in association with PD-L1 status in a retrospective cohort of patients with recurrent/metastatic SCCHN treated according to the current clinical practice. This study will utilize data abstracted from patient’s medical records and biochemical determinations on archival tumor samples.

1.4 Limitations

Given the observational and retrospective nature of the study, data collection will be limited to the extent of data available in the medical records. The patients may have been diagnosed more than 5 years before those involved in the present durvalumab clinical trials.

Treatments prescribed in clinical practice may vary across countries and be dependent on certain patient characteristics, some of which may not be known. However, globally the
available treatment options in this patient segment have not changed recently and this study should provide a good overview of the target population treated in real world conditions, and therefore the patients enrolled in this study should be comparable to ongoing trial populations.

2. OBJECTIVES AND HYPOTHESES

2.1 Primary Objective
The primary objective of this NIS is to determine the prognostic value of PD-L1 status in terms of overall survival (OS) in patients with recurrent/metastatic SCCHN. Overall survival after diagnosis of recurrent/metastatic SCCHN will be assessed for PD-L1 positive and PD-L1 negative patients and in predefined sub-groups (e.g., HPV status, HIV status, smoking history, heavy alcohol use, anatomical sub-site of primary tumor, and prior exposure to radiation therapy).

2.2 Secondary Objectives
1. To describe the relevant demographic and clinical characteristics of patients, stratified by PD-L1 status
2. To describe first line treatment choices, and, where available, subsequent treatment choices
3. To describe investigator-assessed tumor response for first line and second line of therapy (if any) including: best response, duration of response where applicable, objective response rate (ORR)
4. To describe investigator-assessed progression-free survival (PFS) for first line and second line of therapy.

2.3 Exploratory Objectives
1. To perform additional biomarker research on tumor samples (depending on tissue availability and volume)
2. If feasible, to assess agreement of PD-L1 status in samples obtained at different time points (e.g., before and after chemotherapy or radiation therapy).

3. METHODOLOGY

3.1 Study Design – General Aspects
This is a retrospective international, multi-center, non-interventional cohort study based on use of data derived from established medical records and secondary analysis of archival tumor samples. The study will collect data on patient and tumor characteristics, PD-L1 status,
patterns of treatment, and clinical outcomes in up to 600 adult patients with recurrent/metastatic SCCHN. SCCHN of interest for this study are defined as the diseases falling into specific ICD-10 or International Classification of Diseases, Ninth Revision (ICD-9) codes (Table 1), depending on anatomical sub-site of the primary tumor.

For patient selection, the date of diagnosis of recurrent/metastatic disease will be used as the index date. The patient selection period extends from 01 March 2011 to 30 June 2015. This allows for the inclusion of patients with tumor samples of approximately ≤ 5 years age, and ensures approximately 10 months follow-up for living patients recruited at last day of the enrollment window. All patients with a diagnosis of recurrent/metastatic SCC of the oral cavity (tongue, gum, floor of mouth, and other/unspecified part of the mouth), oropharynx, hypopharynx, or larynx during that period will be considered for inclusion in the study (Figure 1). Patients will be identified and followed up through their medical records until death or end of data collection in approximately 20 centers in the US, Asia and Europe.

Patients’ demographic, clinical characteristics and medical history will be described. Clinical outcomes including PFS, best response, duration of response, and ORR will be described for the first line and second line of therapy (if any), and OS will be collected.

A mandatory archived tumor sample will be used to determine PD-L1 status. If a patient has more than one suitable tissue sample, the most recent sample will be used as the mandatory tissue sample. Where available, additional tumor samples obtained at any other time points of the disease will be also collected (optional).

The enrolment target is up to 600 patients.

Statistical analyses will be performed for the whole cohort, per PD-L1 status and for predefined subgroups.

Figure 1  Schematic Representation of Study Periods.
3.1.1 Data Sources

Data from the date of diagnosis of recurrent/metastatic SCCHN until death, or end of data collection (planned by Q4 2016) will be abstracted from patient’s hospital medical records. Archival tumor samples will be retrieved and tested by immunohistochemistry to assess the PD-L1 status of the tumor. Where there is sufficient tissue quantity, the expression of other biomarkers will also be evaluated.

The study will be implemented in a total of approximately 20 sites in the US, Asia and Europe. Investigators will be selected through a site-level feasibility process assessing the number of patients available, treatment patterns, and availability of archival tumor tissue samples.

The sites selected will be a convenience sample and may not be representative of the geographic distribution or the hospital type or size in each of the participating countries. However, there may be capping at site or country level to ensure that all countries and sites are represented and one site/country does not dominate.

3.2 Study Population

This NIS will provide information about PD-L1 status, patterns of treatment and outcomes in an unselected patient population representative of patients who may receive durvalumab post-licensure.

Patients diagnosed with recurrent/metastatic SCCHN between 01 March 2011 and 30 June 2015 will be identified through review of established medical records. The index date will be the date of diagnosis of recurrent/metastatic disease.

3.3 Inclusion Criteria

The subject population that will be selected and observed in the study must fulfill all of the following criteria:

1. Provision of subject informed consent (or consent from next of kin/legal representative if applicable) for use of the data and retrieval of tumor sample, according to local regulations
2. Adult patient (≥ 18 years old)
3. Patient with histologically confirmed SCCHN of the oral cavity (tongue, gum, floor of mouth, other/unspecified part of the mouth), oropharynx, hypopharynx or larynx
4. Patient with recurrent or metastatic SCCHN diagnosed between 01 March 2011 and 30 June 2015
5. Mandatory archival tissue sample (most recent) from the primary site, a lymph node, or a distant metastatic site:

- Tissue sample less than 5 years old (compared to date of retrieval) if provided as complete block (preferred option) or as section cut within 60 days of shipment from site prior to testing

6. Optional archival tissue samples taken at other time points of the disease from the primary site, a lymph node or a distant metastatic site (if available):

- Tissue sample less than 5 years old (compared to date of retrieval) if provided as complete block (preferred option) or as section cut within 60 days of shipment from site prior to testing.

The applicable ICD-10 and ICD-9 codes are provided in Table 1 to assist in the patient selection process.

### Table 1: Definition of SCCHN of interest using ICD-9 and ICD-10 codes.

<table>
<thead>
<tr>
<th>Malignant Neoplasm Site</th>
<th>ICD-9-CM</th>
<th>ICD-10-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>141</td>
<td>C01 - C02</td>
</tr>
<tr>
<td>Gum</td>
<td>143</td>
<td>C03</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>144</td>
<td>C04</td>
</tr>
<tr>
<td>Other / unspecified parts of the mouth</td>
<td>145</td>
<td>C05 - C06</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>146</td>
<td>C09 - C10</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>148</td>
<td>C12 - C13</td>
</tr>
<tr>
<td>Larynx</td>
<td>161</td>
<td>C32</td>
</tr>
</tbody>
</table>

### 3.4 Exclusion Criteria

The patient should not be selected if the following exclusion criterion is met:

1. Treatment for SCCHN with anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies or any other antibody with known immunomodulatory effect.

### 3.5 Criteria for Discontinuation

Subjects may be discontinued from the NIS at any time. Specific reasons for discontinuing a subject from this NIS are:

1. Withdrawal of consent by the subject who is at any time free to discontinue his/her participation in the NIS, without prejudice to further treatment
2. Withdrawal of consent by next of kin/legal representative if applicable (for patients who are deceased at study entry)

3. Violation of eligibility criteria.

The reason for subject discontinuation will be recorded in the electronic case record form (eCRF).

Any data collected before consent withdrawal will remain in the dataset.

4. VARIABLES AND EPIDEMIOLOGICAL MEASUREMENTS

4.1 Exposures

4.1.1 PD-L1 Status

The primary variable is the PD-L1 status (positive or negative) in the overall patient population. PD-L1 status will be assessed for prognostic value of OS after diagnosis of recurrent/metastatic SCCHN.

A mandatory archived tissue sample from the primary site, a lymph node or a distant metastatic site will be used to determine PD-L1 status, preferably provided as formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks. If a patient has more than one tissue sample meeting the study requirements, the most recent sample will be used as the mandatory tissue sample. Where available, additional tumor samples obtained at any other time points of the disease will be also collected if they fall within the 5 year window (optional). If feasible, these samples will be used to explore the agreement of PD-L1 status across samples obtained at different time points during treatment.

PD-L1 status will be determined by immunohistochemistry (IHC) using the Ventana PD-L1 (SP263) validated assay (Rebelatto et al, 2015). PD-L1 IHC analysis will be performed at an approved testing laboratory.

Patients will be described as having positive, negative or unknown/undetermined PD-L1 status. The scoring algorithm for interpretation of the test is presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>PD-L1 (SP263) Scoring Algorithm.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interpretation</strong></td>
<td><strong>Staining Description</strong></td>
</tr>
<tr>
<td>Positive for PD-L1</td>
<td>≥ 25% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative isotope control</td>
</tr>
<tr>
<td>Negative for PD-L1</td>
<td>&lt; 25% of tumor cells with membrane positivity for PD-L1 at any intensity above background staining as noted on the corresponding negative isotope control</td>
</tr>
</tbody>
</table>
4.1.2 Other Biomarkers

Tissue obtained for establishing PD-L1 expression status may be analyzed for additional markers by IHC. If the quantity of tissue is sufficient, CD8 and CD4/FoxP3 measures will be completed in an effort to enumerate cytotoxic versus regulatory T (Tregs) cells.

Based on availability of tissue, a panel of additional, immune-relevant markers expressed on TILs or on tumor cells may be assessed. Markers of special interest include but are not limited to OX40, GITR, PD-1, PD-L2, CTLA-4, Tim-3, CD137, and LAG-3. Tissues obtained at screening may be assessed also for an IFN-γ gene expression signature (e.g. IFN-γ, CXCL9, CXCL10) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), in situ hybridization (ISH), and/or by NanoString technology.

The results of this biomarker research will be reported either in the Clinical Study Report itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies to generate hypotheses to be tested in future research.

4.2 Outcomes

4.2.1 Patient Characteristics, Risk Factors and Medical History

Patient characteristics will be described, including socio-demographic variables and performance status at index date, smoking habits (lifetime consumption, if available), alcohol consumption history, HPV status and method of testing, HIV status, medical history and major co-morbidities, and history of chronic steroid use (if available). Variables captured are detailed in Section 6.1.1.

4.2.2 Tumor Characteristics

Disease characteristics will be described including date of initial diagnosis and date of diagnosis of recurrent/metastatic disease, primary tumor sub-site, stage and grade, and number and sites of metastases (see Section 6.1.1).

4.2.3 Treatment Patterns

The complete treatment history will be captured and described, including surgery, radiation therapy and adjuvant therapy where applicable, and all chemotherapy/systemic treatment lines (including targeted therapies, if relevant) for recurrent/metastatic disease.

Regarding chemotherapies, description will encompass the drug regimen, number of cycles and duration of therapy (estimated from dates of initial and last cycle).
4.2.4 Treatment Outcomes

Overall survival will be assessed. Additionally, the following clinical outcomes will be described for first line and second line treatments (if any) for recurrent and/or metastatic disease: investigator-assessed best tumor response, duration of response where applicable, and investigator-assessed PFS. ORR (sum of complete and partial responses) will be derived from investigator-assessed best responses and described for first line and second line therapies.

In this regard, the following will be collected from medical records:

- Date of death: OS will be calculated from the date of diagnosis of recurrent/metastatic disease to date of death of any cause.
- Treatment duration per line of therapy, based on recorded dates of initial and last cycle of each treatment line.
- Best response for first line and second line of therapy as defined by the physician, date of assessment and measure of response utilized.
- Date of progression for first line and second line of therapy, as defined by the physician, and measures of progression utilized (radiological progression, symptomatic progression, death). Where the assessment was performed according to Response Evaluation Criteria In Solid Tumors (RECIST) guidelines, date of progression completed in the eCRF will be determined based on the earliest of the assessment dates of the component that triggered the progression.
- PFS will be assessed for first line and second line therapies (if any):
  - From start of first line therapy to progression on or after therapy
  - From start of second line therapy to progression on or after therapy or death of any cause.

4.3 Other Variables and Covariates

Sub-group analyses will be undertaken depending on availability of covariates. In this regard, covariates of interest include (but are not limited to) the following:

- Anatomical sub-site of primary tumor
- HPV status
- HIV status
- Smoking history (lifetime consumption, if available)
Non-Interventional Study Protocol
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Version Edition 2, incorporates Amendment 1
Date 19 February 2016

- Alcohol consumption history
- Types of treatment regimens
- Exposure to radiation therapy
- Performance status at diagnosis of recurrent/metastatic disease.

5. STATISTICAL ANALYSIS PLAN

5.1 Statistical Methods – General Aspects

An observational study is a study in which epidemiologic methods are used to analyze human population health data.

A comprehensive Statistical Analysis Plan (SAP) will be prepared before the first data cut-off, (if an interim analysis is performed) and will be amended as needed for subsequent and final analyses.

Descriptive analyses on patient characteristics, treatment choices, and treatment outcomes will be conducted:

- For the overall patient population, defined as all patients meeting the eligibility criteria
- Per PD-L1 status (positive, negative, unknown/not done). PD-L1 status is defined as unknown/not done for patients whose PD-L1 testing has failed.

Categorical variables will be summarized by absolute and relative frequencies. Continuous variables will be summarized by descriptive statistics (number of valid and missing observations, mean, and standard deviation, median, minimum, and maximum). All percentages, means and medians are reported to one decimal place, standard deviation reported to two decimal places and minimum and maximum values to the same decimal places as the original data are recorded.

Time to event data (OS, PFS) including rates of affected patients will be described using the Kaplan-Meier method. Two-sided 95% CIs will be provided for the main statistical estimators.

5.1.1 Primary Objective: Prognostic Value of PD-L1 Status

OS will be defined as the time from the date of diagnosis of recurrent/metastatic SCCHN until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. OS will
be presented descriptively by the Kaplan Meier curve together with a 95% CI, stratified according to PD-L1 status.

Besides the stratification by the PD-L1 status, this analysis will be run separately in subgroups, including but not limited to the following:

- Per anatomical sub-site of primary tumor
- Per HPV status
- Per HIV status
- Per smoking history (lifetime history, if available)
- Per alcohol consumption history
- Per prior exposure to radiation therapy
- Per types of treatment regimens
- By performance status at diagnosis of recurrent/metastatic disease.

In cases where a prognostic factor affecting treatment decision has been potentially affected by the previous treatment, a weighted (by inverse of the probability of the treatment) Kaplan Meier estimate of OS and PFS will be used.

The prognostic value of positive or negative PD-L1 status in terms of OS will be investigated using a Cox proportional hazards model. Additional covariates to be included in the model will be described in the statistical analysis plan.

5.1.2 Secondary Objectives

Descriptive analyses will be conducted to evaluate the distribution of the following variables for the overall cohort and per PD-L1 status:

- Demographic and other patient characteristics
- Tumor primary site, grading and staging at initial diagnosis, number and sites of metastases
- Risk factors (smoking history, alcohol consumption, HPV status, HIV status)
- Treatment history, treatment regimens per treatment line
- Investigator-assessed treatment outcomes and their criteria of evaluation
- Distribution of other biomarkers, as available.
ORR (best overall complete and partial responses) will be summarized for first line and second line therapies (if any), using frequency tables, with their associated two-sided exact 95% CIs (Clopper-Pearson method).

Duration of response will be evaluated for first line and second line therapies (if any). It will be assessed from start of therapy line (start date of first cycle) to date of acknowledged disease progression, as completed in the eCRF. Median duration of response and time to response will be summarized, where possible, by PD-L1 status. In addition, duration of response may be summarized graphically as appropriate.

PFS will be assessed for first line and second line therapies (if any): from start of first line therapy to progression on or after therapy, and from start of second line therapy to progression on or after therapy or death. PFS after start of second line treatment will be evaluated based on start date of second line therapy and date of progression or date of death and presented descriptively by the Kaplan Meier curve together with a 95% CI, stratified according to PD-L1 status. Weighted survival curves will be presented for all patients, and stratified according to PD-L1 status, as well as by treatment.

5.2 Bias

5.2.1 Methods to Minimize Bias

Given the descriptive purpose of study, no statistical techniques will be implemented to minimize any bias.

5.2.2 Adjustment for Multiple Comparisons

Given the observational and descriptive nature of study no adjustment for multiple comparisons will be performed.

5.2.3 Strengths and Limitations

This study will use retrospective longitudinal patient data that are collected during the standard clinical care. Variable misclassification may occur, and it is not known if this misclassification will be random. Additionally, the study may be limited with respect to statistical power for some of the patient segments, particularly when studying sub-groups.

5.3 Interim Analyses

An interim analysis may be performed. The analysis will use data from all patients available in the database at the time of data cut-off.
5.4 Sample Size and Power Calculations

The primary objective of this study is to estimate the prognostic value of PD-L1 status in terms of OS in patients with recurrent/metastatic SCCHN. The available sample size is not known a priori and will be driven by the number of patients at the selected sites with available tissue. However, assuming that PD-L1 status distribution is approximately 25% positive and 75% negative status, that the median OS in these patients is 10 months, that the study will accrue uniformly over 52 months with 10 months follow-up from the last patient entering and that survival times are exponentially distributed, the illustrations of hazard ratios it would be possible to detect with 80% power (2-sided alpha 0.05) over various sample sizes are given in Table 3.

Table 3 Illustrations of Hazard Ratios for Various Sample Sizes.

<table>
<thead>
<tr>
<th>HR to detect</th>
<th>Number of deaths</th>
<th>Number of patients (Total)</th>
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</thead>
<tbody>
<tr>
<td>0.3</td>
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<td>40</td>
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<tr>
<td>0.4</td>
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<tr>
<td>0.5</td>
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<tr>
<td>0.6</td>
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<td>196</td>
</tr>
<tr>
<td>0.7</td>
<td>278</td>
<td>396</td>
</tr>
</tbody>
</table>

HR: Hazard ratio

These illustrations do not take account of the fact that the binary prognostic factor of interest (PD-L1 status) may be correlated with other covariates and hence could over-estimate the power of the various sample sizes (Bernardo et al, 2000). The sample size (number of events) required when no correlation is assumed should be multiplied by \(1/(1-R^2)\) to account for an \(R^2 > 0\) (Hsieh and Lavori, 2000). The correlation is not currently known. Additionally, a proportion of patients will not have PD-L1 status available. Given these uncertainties, a sample size of up to 600 patients is felt to be adequate.

6. STUDY CONDUCT AND REGULATORY DETAILS

6.1 Data Management

6.1.1 Study Flow Chart and Plan

Data collection will be performed according to the Study Plan presented in Table 4.

Table 4 Study Plan.

<table>
<thead>
<tr>
<th>Type of Measure</th>
<th>Planned Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>Confirmation of inclusion and exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Informed consent</td>
</tr>
</tbody>
</table>
## Type of Measure | Planned Variables
--- | ---
Availability of optional tumor sample(s)

| Socio-Demographics | Age at index date, Gender, Race
| | Height, weight, body surface area
| | Marital status and living conditions

| Risk factors | Smoking status and consumption (lifetime exposure, if available)
| | Alcohol consumption (as available)
| | HPV status and method of testing (p16 IHC, PCR, ISH)
| | HIV status

| Medical history | Past medical history including history of cancer
| | Major co-morbidities and history of systemic steroid use

| Disease history | Date of initial diagnosis
| | Sub-site of primary tumor, stage and grade at diagnosis
| | Number and sites of metastases (including local and distant lymph nodes) at index date
| | Performance status at index date

| Treatment history | Surgeries (date and type)
| | Radiation therapy
| | Neo-adjuvant and adjuvant therapy
| | First line chemotherapy (if any)
| | Subsequent lines of therapy (if any)
| | Best supportive care

| Clinical outcomes | Best response per treatment line
| | Mode of evaluation and response criteria
| | Duration of response
| | Date of progression
| | Date of death, cause of death
| | Date of last information (where alive)

1 According to local regulations.
2 Where permitted per local regulations.
3 IHC: immunohistochemistry; PCR: polymerase chain reaction; ISH: in situ hybridization
4 Gx: undetermined; G1: well differentiated (low grade); G2: moderately differentiated (intermediate grade); G3: poorly differentiated (high grade); G4: undifferentiated (high grade).
5 WHO/ Eastern Cooperative Oncology Group (ECOG) or Karnofsky as available
6 As available: start and stop date, number of sessions, site, and total dose.
7 As available: start and stop date, drug name(s), dose, number of cycles if relevant.
8 As available: drug regimen (drug names, frequency, starting dose, cycle length), number of cycles completed, treatment duration based on initial and last cycle, and reason for treatment discontinuation.
9 According to investigator’s assessment. The mode of evaluation and response criteria will be recorded.
6.1.2 Procedures

6.1.2.1 Selection of Patients

All patients with a diagnosis of SCCHN of the oral cavity, oropharynx, hypopharynx or larynx (anatomical sub-site of the primary tumor corresponding to ICD-9 and ICD-10 codes displayed in Table 1) who have been diagnosed with recurrent/metastatic SCCHN in the period from 01 March 2011 to the 30 June 2015 will be considered for inclusion in the study. The date of diagnosis of recurrent/metastatic disease will be used as the index date. Patients must have an available archival tissue sample of less than 5 years old, obtained from the primary tumor site, a lymph node or a distant metastatic site. Where available, additional tissue samples obtained at any other time points of the disease will be also collected (optional).

The investigator and his/her team will identify all potential patients for inclusion during the patient selection period, obtain the corresponding medical records, and apply the study inclusion and exclusion criteria. They will also verify the availability of additional tumor samples.

A list of available patients will be established, indicating whether the patient is alive or deceased.

Once the list is established the investigator will solicit consent, as needed, from the patient (if alive) or from next of kin/legal representative in line with local regulation requirements (unless a consent waiver is applicable/obtained). Consent will encompass data collection from medical records and the retrieval and donation of archival tumor sample(s) available at the study site, including the mandatory tumor sample and optional tumor samples.

6.1.2.2 Data Abstraction

Once informed consent has been obtained in line with local regulations, the investigator and his/her team will extract from the hospital records the information of interest for each participant patient and enter this information in the eCRF.

6.1.2.3 Collection of Tumor Samples

The investigator and his/her team will retrieve the mandatory archival tumor samples meeting the inclusion criteria and ship them to the designated facility for PD-L1 testing, according to the procedure provided in the Laboratory Manual. Additional tumor samples may be collected and analyzed where a patient has suitable tumor samples at any other time points of the disease.

Labelling and shipment of biological samples

The investigator and his/her team ensure that samples are labeled and shipped in accordance with the Laboratory Manual.
Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle. The investigator at each center keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival. The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca or delegated representatives keep oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers. Samples retained for further use may be registered in the AstraZeneca Biobank or delegate during the entire life cycle.

Storage, re-use and destruction of biological samples

Unused tumor samples will be stored for a maximum of 15 years from the date of database lock (or as per local regulations), unless requested to be repatriated sooner to the study sites. Samples not repatriated will be destroyed.

6.1.2.4 Procedures for Withdrawal of Informed Consent for Donated Biological Samples

At any time, patients are free to withdraw their consent to participate in the study, without prejudice to further treatment. Similarly, next of kin/legal representative (for patients who are deceased at study entry) are free to withdraw consent for deceased patient’s participation. The reason for subject discontinuation will be recorded in the eCRF.

If a patient or next of kin/legal representative withdraws consent to the use of donated biological samples, unused samples will be returned to the study site, and the action will be documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The principal investigator (PI) should:

- Ensure patients’ withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or designated Clinical Research Organization (CRO)
- Along with AstraZeneca, ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are returned to the study site/disposed, the action documented and the signed document returned to the study site
- Ensure that the patient and AstraZeneca are informed about the sample return.
6.1.2.5 Procedures for Study Discontinuation

Should AstraZeneca decide to discontinue the study prior to what was established in this protocol, the investigator, and relevant authorities should receive written notice describing the reasons why the study was terminated at an earlier date.

6.1.3 Quality Control

6.1.3.1 Monitoring

Before the first subject is recruited into the study, AstraZeneca delegated representatives will:

- Establish the adequacy of the facilities and the investigator’s capability to appropriately select the sample
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regards to protocol compliance, and the responsibilities of AstraZeneca and/or its representatives. This will be documented in a NIS Primary Agreement between the CRO and the investigator.

During the study the CRO can implement different activities to assure compliance with AstraZeneca standards of quality. These activities could include but are not limited to:

Contacts with the sites to:

- Provide information and support to the investigator(s)
- Confirm that the research team is complying with the protocol and that data are being accurately recorded in the eCRFs
- Ensure that the Informed Consent Forms (ICFs) from subject or next of kin/legal representative are signed and stored at the investigator’s site (if appropriate)
- Ensure that the eCRFs are completed properly and with adequate quality.

Monitoring activities for:

- Checking a sample of ICFs
- Checking that subjects exist in medical records (a sample).

Different signals (e.g., high rejection rate in a site) should be used as potential identification of low protocol compliance by investigators. If these or any other signal occurs or if the local monitor is suspicious of a potential non-optimal level of protocol compliance by the site investigator, specific measures should be adopted to evaluate the situation, identify the issue and implement specific action plans to correct the situation.

Source data verification will be carried out as appropriate by CRO representatives during in-person monitoring visits to each site, as described in the Monitoring Plan. The Investigator must provide direct access to study documentation, subject medical records and other source document, in compliance with the local regulations. A sample of completed eCRFs will be
compared with the patient medical record for a percentage of patients to assess concordance on key pieces of information relating to study endpoints. Any corrections to the eCRF must be authenticated and explained (if necessary) and should not replace the information originally entered.

**Training of Study Site Personnel:**

The PI will ensure that appropriate training relevant to the NIS is given to investigational staff, and that any new information relevant to the performance of this NIS is forwarded to the staff involved.

6.1.4 **Data Management**

Data will be entered in the eCRF at the Investigator’s site. The Investigator will be responsible for entering data into the electronic data capture (EDC) system according to the eCRF Completion Guidelines.

When data have been entered reviewed and edited, the Investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the Investigator’s site.

Data management will be performed by the CRO, according to the Data Management Plan.

Medical/surgical history will be classified according to the terminology of the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries as specified in the study agreement. Data queries will be raised for inconsistent, improbable, or missing data. The Investigator will ensure resolution of all outstanding data entries, data queries and other action items detailed by the CRO. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**Serious Adverse Event (SAE) reconciliation**

Not applicable

**Data associated with human biological samples**
Data associated with biological samples will be transferred from laboratory(ies) internal or external to AstraZeneca.

**Management of external data**

Data from external providers (e.g. central laboratories) will be validated as appropriate to ensure it is consistent with the clinical data and included in the final database.

Regarding biomarker analyses data, information relating to the processing of the sample, including the original date of biopsy (historical tumor tissue sample and the actual date the sample(s) were collected), treatment setting, type of sample provided (block or slides), and shipment details (date/bar code as appropriate) will be recorded in the eCRF and database by the investigator. The results of the biomarker analyses may either be uploaded to the database before database lock, or provided as a separate file.

**6.1.5 Storage and Retention**

Upon completion of database lock and at the agreed time point, data from the EDC system will be transferred to AstraZeneca via a secure file transfer portal in the pre-agreed format.

All original source documentation is expected to be stored at the site for the longest possible time as required by local applicable regulations or as specified in the contract, whichever is longer. The records must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived following the study conclusion, according to local regulations or as specified in the contract, whichever is longer.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national regulations. Essential documents include:

- IRB approvals for the study protocol and all amendments
- All source documents
- CRF contents
- Patients' or next of kin/legal representative’s ICFs (with study number and title)
- Any other pertinent study document.

AstraZeneca will notify the investigators/institutions when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify AstraZeneca.

**6.2 Protection of Human Subjects**

The NIS will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonization (ICH) guidelines, International Society for Pharmacoepidemiology (ISPE) (2007) *Guidelines for Good Pharmacoepidemiology Practices* (GPP) and the applicable legislation on NISs.
The Investigator will perform the NIS in accordance with the regulations and guidelines governing medical practice and ethics in the country of the NIS and in accordance with currently acceptable techniques and know-how.

The final protocol of the NIS, including the final version of the subject or next of kin/legal representative ICF, must be approved or given a favorable opinion in writing by the Ethics Committee/Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The Ethics Committee (EC)/IRB/IEC must also approve any amendment to the protocol and all communication to patient or next of kin, according to local regulations.

6.2.1 Subject Informed Consent

The Investigator at each site will ensure, where applicable, that the subject (or next of kin/legal representative for deceased patients) is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the NIS. Subjects or next of kin/legal representative must also be notified that they are free to discontinue from the NIS at any time. The subjects or next of kin/legal representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The signed and dated subject or next of kin/legal representative informed consent must be obtained before any specific procedure for the NIS is performed, as appropriate.

The Investigator must store the original, signed Subject ICF (or next of kin/legal representative ICF, as applicable). A copy of the signed ICF must be given to the subject or next of kin/legal representative, as applicable.

6.2.2 Confidentiality of Study/Subject Data

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subject or next of kin/legal representative will authorize the collection, use and disclosure of their personal data by the Investigator and by those persons who need that information for the purposes of the NIS.

The ICF will explain that NIS data will be stored in a computer database, maintaining confidentiality in accordance with the local law for Data Protection.

The Subject ICF will also explain that for quality check purposes, a monitor of AstraZeneca or a monitor of company representing AstraZeneca, will require direct access to the signed ICFs. In case source data verification will be planned as quality check, the subject (or next of kin/legal representative) ICF will explain that for data verification purposes, a monitor of AstraZeneca or a monitor of company representing AstraZeneca may require direct access to source documents that are part of the hospital or practice records relevant to the NIS.
6.2.3 Restrictions

Given the therapeutic indication and the retrospective nature of the study, it is expected that the majority of patients eligible to the study may be deceased at time of data collection. Hence, the Investigator will obtain informed consent from the patient or from next of kin/legal representative as appropriate, according to local regulations, unless a consent waiver is applicable.

6.3 Changes to the Protocol and Informed Consent Form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also by the national regulatory authority(ies), before implementation. Local requirements are to be followed for revised protocols.

The designated CRO will distribute any subsequent amendments and new versions of the protocol to each PI.

If a protocol amendment requires a change to a center’s ICF, AstraZeneca or delegate and the center’s Ethics Committee are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

6.4 Audits and Inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GPP, ICH guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca or delegate immediately if contacted by a regulatory agency about an inspection at the center.

6.5 Management and Report of Adverse Events/Adverse Drug Reactions

6.5.1 Definition of Adverse Events (AE)

An adverse event (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An
undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.5.2 Definition of Serious Adverse Events (SAE)

A serious adverse event (SAE) is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

6.5.3 Definition of Adverse Drug Reactions (ADR)

An adverse drug reaction (ADR) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a medicinal product, suspected to be causally related to the product.

6.5.4 Collection of Adverse Events

This NIS does not have a specific safety objective and will be using existing medical records as data sources. For NIS designs which are based on existing (secondary) data sets, there is no requirement to actively collect any AE data.

However, investigators will be advised to report any SAE and ADR to an AstraZeneca drug, according to the standard spontaneous reporting procedures for marketed products in their country. The investigator is responsible for ensuring compliance with these reporting procedures.

Adverse reactions identified for non-AstraZeneca products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder.
6.6 Communication Plan

6.6.1 Publication Plan

AstraZeneca is obliged to analyze and report all NIS data as described in the protocol.

AstraZeneca delegate will prepare a Non-Interventional Study Report within 12 months after database lock. AstraZeneca will communicate the results to all participating investigators. The results of the NIS will be posted at AstraZeneca Clinical Trials portal no later than 12 months after completion of the last patient.

In accordance with the Declaration of Helsinki, both authors and publishers have ethical obligations. In publication of the results of the NIS, the authors are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. AstraZeneca endeavors to publish the results of NIS and is committed to ensure that the data are reported in a responsible and coherent manner.

AstraZeneca seeks to ensure that publications in biomedical journals follow the guidelines established by the International Committee of Medical Journal Editors (ICMJE) and published in its Uniform Requirements of Manuscripts Submitted to Biomedical Journals.

AstraZeneca is committed to ensuring that authorship for all publications should comply with the criteria defined by the ICMJE. These state that: "Each author should have participated sufficiently in the work to take public responsibility for the content."

AstraZeneca believes that participation solely in the collection of data or drafting the manuscript does not justify authorship. These conditions apply equally to external investigators and to AstraZeneca employees.

Other members of the group should be listed in the acknowledgments as appropriate.

Publication of data subsets from individual institutions participating in multicenter studies should not precede the primary manuscript, and when developed should always reference the primary publication of the entire study. All publications should be in line with AstraZeneca’s Publication Policy, available at www.astrazeneca.com.

6.6.2 Compliance with Study Registration and Results Posting Requirements

AstraZeneca is committed to providing full and transparent disclosure of, and open access to, the findings of all AstraZeneca sponsored studies and information on ongoing studies sponsored by AstraZeneca.

AstraZeneca or the delegated CRO must register all qualifying studies prior to enrollment of the first subject, referred to as the First Subject In date. Studies are registered on ClinicalTrials.gov (sponsored by the National Institute of Health) and other country-specific
or regional websites as required by law, with study information set forth on AstraZeneca internal templates. In addition to publicly registering studies on ClinicalTrials.gov and other country specific or regional websites, basic study information is also posted on AstraZenecaClinicalTrials.com.

On first Regulatory Approval for a clinical study in the European Union (EU)/European Economic Area, the concerned National Competent Authority is responsible for publication of study information to the EU Clinical Trial Register. The information posted is extracted from the Clinical Trial Application Approval form (or EudraCT form) submitted by AstraZeneca as the Sponsor.

Once a study is initially registered, any changes related to study status or protocol amendments must be updated to ensure accurate reporting of all required information. By law (Food and Drug Administration [FDA] Amendment Act 2007), any changes in a study’s overall recruitment status must be updated on ClinicalTrials.gov no later than 30 days after the change in status. All other changes to posted information must be updated at least quarterly.

Results for studies of approved medicines must be disclosed within 12 months of study completion, whether the study completed according to the study protocol or was discontinued earlier. Following marketing authorization, results for studies that have already passed 12 months from study completion must be disclosed within 30 days after the first approval by any regulatory authority, for any indication. Results are disclosed on ClinicalTrials.gov, AstraZenecaClinicalTrials.com and on other public websites in a format and to timelines as required by law form) submitted by AstraZeneca as the Sponsor.

6.6.3 Compliance with Financial Disclosure Requirements

Not applicable.
7. LIST OF REFERENCES


8. APPENDICES

Not Applicable.
9. ATTACHMENTS

Not Applicable.
10. SIGNATURES
ASTRAZENECA SIGNATURE(S)

SUPREME-HN
A Retrospective Cohort Study of PD-L1 in Recurrent and Metastatic Squamous Cell Carcinoma of Head and Neck (SCCHN)

This SUPREME-HN D4193R00002 Protocol has been subjected to an internal AstraZeneca review.
I agree to the terms of this Non-Interventional Study protocol edition 2 (incorporates amendment 1).

AstraZeneca representative

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(Day Month Year)

This document contains confidential information, which should not be copied, referred to, released or published without written approval from AstraZeneca. Investigators are cautioned that the information in this protocol may be subject to change and revision.
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