



**Prospective Non Interventional Study  
Evaluating Prognostic and Predictive  
Value of PDL-1 Expression and Associated  
T-cell Infiltration in Primary Laryngeal  
Squamous Cell Carcinoma**

*Thesis*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

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## *List of Abbreviations*

Abb.	Full term
A/E .....	Adverse events
ADH.....	Alcohol dehydrogenase
ALDH .....	Aldehyde dehydrogenase
APC.....	Antigen presenting cells
CAFs .....	Carcinoma-associated fibroblasts
CCRT .....	Concurrent chemoradiotherapy
Chth .....	Chemotherapy
CPS .....	Combined positive score
CRT.....	Chemoradiation
CT .....	Computed Tomography
CTLA-4.....	Cytotoxic T lymphocytes associated protein-4
CTLs .....	Cytotoxic T lymphocytes
DNA .....	Deoxyribonucleic acid
EBV.....	Epstein bar virus
ECOG.....	Eastern Cooperative Oncology Group
EGF.....	Epidermal growth factor
EGFR.....	Epidermal growth factor receptor
ENE.....	Extra nodal extension
EORTC .....	European Organization for Research and Treatment of Cancer
FDG PET/CT .....	<sup>18</sup> F fluorodeoxyglucose positron emission tomography/computed tomography
FISH .....	Fluorescence in situ hybridization
FNA .....	Fine needle aspiration
GETTEC .....	Groupe d'Etude des Tumeurs Tete et Cou
GORTEC.....	Groupe d'Oncologie Radiotherapie Tete et Cou
GRB .....	Guanine Nucleotide Releasing Proteins
Gy.....	Grey
HDAC .....	Histone Deacetylase

## *List of Abbreviations Cont...*

Abb.	Full term
HIF-1 .....	Hypoxia inducible factor 1
HIV .....	Human immunodeficiency virus
HNC .....	Head and Neck Cancer
HNSCC .....	Head and neck squamous cell carcinoma
HPV .....	Human papilloma virus
HR.....	Hazard ratio
HSV.....	Herpes simplex virus
IC .....	Immune cells
IL.....	Interleukin
IMRT.....	Intensity-modulated Radiotherapy
LFS .....	Laryngectomy free survival
M.....	Metastasis
MACHNC .....	Meta-Analysis of Chemotherapy on Head and Neck Cancer
miRNAs .....	MicroRNAs
MRI .....	Magnetic Resonance Imaging
MTV .....	Metabolic tumor volume
N.....	Node
NICD.....	NOTCH intracellular domain
NKs .....	Natural killer cells
NO.....	Nitric oxide
NSCLC.....	Non-small-cell lung cancer
OR.....	Odds ratio
OS .....	Overall survival
OSCC .....	Oral squamous cell carcinoma
pAKT.....	Phosphorylated AKT
PD-1 .....	Programmed death-1
PDL-1 .....	Programmed death ligand-1
PET .....	Positron emission tomography

## *List of Abbreviations Cont...*

Abb.	Full term
PFS .....	Progression free survival
QOL .....	Quality of life
Rb.....	Retinoblastoma gene
RFS .....	Relapse-free survival
RR .....	Relative risk
RT .....	Radiation therapy
RTOG.....	Radiation Therapy Oncology Group
SBRT.....	Stereotactic body radiation therapy
SCC .....	Squamous cell carcinoma
SOS .....	Son of Sevenless
STAT3.....	Signal transducer and activator of transcription 3
SUV <sub>max</sub> .....	Standardized uptake value
T.....	Tumor
TC .....	Tumor cells
TCR.....	T cell receptor
TF.....	Transcription factors
Th .....	T helper
TILs .....	Tumor infiltrating lymphocytes
TLG.....	Total lesion glycolysis
TLM .....	Transoral laser microsurgery
TLS .....	Transoral laser surgery
TME .....	Tumor micro environment
TOLM .....	Transoral laser microsurgery
TPF .....	Taxotere /platinum/fluorouracil
Tregs.....	T regulatory cells
UADT.....	Upper aerodigestive tract
VEGF .....	Vascular Endothelial Growth Factor
VEGFR .....	Vascular endothelial growth factor receptor
WHO .....	World Health Organization

## INTRODUCTION

The immune system can have an important role in eliminating tumor cells, although the immune microenvironment may enable malignant cells to become more aggressive and escaping immunological surveillance (*Lee et al., 2011*).

As the tumors cause immunosuppression, the human immune reactivity against solid tumors becomes ineffective. Current cancer immunotherapies focus on overcoming this inhibition, either by activation of the immune system in general or by local manipulation of immunoregulatory molecules in the tumor microenvironment, including what is called immune checkpoints (*Hodi et al., 2010*).

Recently, evaluation of PDL-1 status in tumor specimens could guide in selection of patients for treatment with PD1 checkpoint inhibitors. But accurate measurement of PDL-1 protein levels in tumor samples is limited by the absence of reliable antibodies and uncertain positive cutoff value (*Maria et al., 2016*).

The immune suppressive molecule programmed death-1 (PD-1) is upregulated in activated T lymphocytes and inhibits T-cell function by binding to its ligands. PD-1/PDL-1 interactions are a major mechanism of immune suppression within the tumor microenvironment. Antibodies directed against PD-1 and B7-H1