



HAL
open science

Facteurs biologiques prédictifs de réponse au nivolumab dans les carcinomes épidermoïdes de la tête et du cou

Jonathan Wong Chong

► **To cite this version:**

Jonathan Wong Chong. Facteurs biologiques prédictifs de réponse au nivolumab dans les carcinomes épidermoïdes de la tête et du cou. Human health and pathology. 2021. dumas-03597278

HAL Id: dumas-03597278

<https://dumas.ccsd.cnrs.fr/dumas-03597278v1>

Submitted on 4 Mar 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

WONG CHONG Jonathan

Présentée et soutenue publiquement le 27 avril 2021

FACTEURS BIOLOGIQUES PRÉDICTIFS DE RÉPONSE AU NIVOLUMAB
DANS LES CARCINOMES ÉPIDERMOÏDES DE LA TÊTE ET DU COU

Directeur de thèse : Madame **BERNADACH Maureen**, Docteur, Centre Jean Perrin, Clermont-Ferrand

Président du jury : Monsieur **DURANDO Xavier**, Professeur, UFR de Médecine et des Professions paramédicales de Clermont-Ferrand

Membre(s) du jury : Monsieur **BIAU Julian**, Docteur, Centre Jean Perrin, Clermont-Ferrand

UNIVERSITÉ CLERMONT AUVERGNE
UFR DE MÉDECINE ET DES PROFESSIONS PARAMÉDICALES

THÈSE D'EXERCICE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

par

WONG CHONG Jonathan

Présentée et soutenue publiquement le 27 avril 2021

FACTEURS BIOLOGIQUES PRÉDICTIFS DE RÉPONSE AU NIVOLUMAB
DANS LES CARCINOMES ÉPIDERMOÏDES DE LA TÊTE ET DU COU

Directeur de thèse : Madame **BERNADACH Maureen**, Docteur, Centre Jean Perrin, Clermont-Ferrand

Président du jury : Monsieur **DURANDO Xavier**, Professeur, UFR de Médecine et des Professions paramédicales de Clermont-Ferrand

Membre(s) du jury : Monsieur **BIAU Julian**, Docteur, Centre Jean Perrin, Clermont-Ferrand

UNIVERSITÉ CLERMONT AUVERGNE

PRESIDENTS HONORAIRES
UNIVERSITE D'AUVERGNE

: **JOYON** Louis
: **DOLY** Michel
: **TURPIN** Dominique
: **VEYRE** Annie
: **DULBECCO** Philippe
: **ESCHALIER** Alain

PRESIDENTS HONORAIRES
UNIVERSITE BLAISE PASCAL

: **CABANES** Pierre
: **FONTAINE** Jacques
: **BOUTIN** Christian
: **MONTEIL** Jean-Marc
: **ODOUARD** Albert
: **LAVIGNOTTE** Nadine

PRESIDENT DE L'UNIVERSITE et
PRESIDENT DU CONSEIL ACADEMIQUE PLENIER : **BERNARD**
Mathias PRESIDENT DU CONSEIL ACADEMIQUE RESTREINT : **DEQUIEDT**
Vianney VICE-PRESIDENTE DU CONSEIL D'ADMINISTRATION : **FOGLI** Anne
VICE-PRESIDENT DE LA COMMISSION DE LA RECHERCHE : **HENRARD**
Pierre VICE PRESIDENTE DE LA COMMISSION DE LA
FORMATION ET DE LA VIE UNIVERSITAIRE : **PEYRARD** Françoise
DIRECTEUR GENERAL DES SERVICES : **PAQUIS** François

□□□□□
UFR DE MEDECINE
ET DES PROFESSIONS PARAMEDICALES

DOYENS HONORAIRES

: **DETEIX** Patrice
: **CHAZAL** Jean

DOYEN

: **CLAVELOU** Pierre

RESPONSABLE ADMINISTRATIVE

: **ROBERT** Gaëlle

Secrétariat Doyen / Scolarité – Mise à jour septembre 2020

LISTE DU PERSONNEL ENSEIGNANT

PROFESSEURS HONORAIRES :

MM. BACIN Franck - BEGUE René-Jean - BEYTOUT Jean - BOMMELAER Gilles - BOUCHER Daniel - BUSSIERE Jean-Louis - CANO Noël - CASSAGNES Jean - CATILINA Pierre - CHABANNES Jacques - CHAZAL Jean - CHIPPONI Jacques - CHOLLET Philippe - CITRON Bernard - COUDERT Jean - DASTUGUE Bernard - DAUPLAT Jacques - DECHELOTTE Pierre - DEMEOCQ François - DE RIBEROLLES Charles - DETEIX Patrice - ESCANDE Georges - Mme FONCK Yvette - MM. GENTOU Claude - Mme GLANDDIER Phyllis - MM. IRTIUM Bernard - JACQUETIN Bernard - Mme LAVARENNE Jeanine - MM. LAVERAN Henri - LESOURD Bruno - LEVAI Jean-Paul - MAGE Gérard - MARCHEIX Jean- Claude - MICHEL Jean-Luc - MONDIE Jean-Michel - PHILIPPE Pierre - PLAGNE Robert - PLANCHE Roger - PONSONNAILLE Jean - REY Michel - Mme RIGAL Danièle - MM. ROZAN Raymond - SCHOEFFLER Pierre - SIROT Jacques - RIBAL Jean-Pierre - SOUTEYRAND Pierre - TANGUY Alain - TERVER Sylvain - THIEBLOT Philippe - TOURNILHAC Michel - VANNEUVILLE Guy - VIALLET Jean-François - Mlle VEYRE Annie

PROFESSEURS EMERITES :

MM. AUMAITRE Olivier - BOITEUX Jean-Paul - CHAMOIX Alain - DUBRAY Claude - ESCHALIER Alain - KEMENY Jean-Louis - LABBE André - Mme LAFEUILLE Hélène - MM. LEMERY Didier - LUSSON Jean-René

PROFESSEURS DES UNIVERSITES-PRATICIENS HOSPITALIERS

PROFESSEURS DE CLASSE EXCEPTIONNELLE

M. VAGO Philippe	Histologie-Embryologie Cytogénétique
M. AVAN Paul	Biophysique et Traitement de l'Image
M. DURIF Franck	Neurologie
M. BOIRE Jean-Yves	Biostatistiques, Informatique Médicale et Technologies de Communication
M. BOYER Louis	Radiologie et Imagerie Médicale option Clinique
M. POULY Jean-Luc	Gynécologie et Obstétrique
M. CANIS Michel	Gynécologie-Obstétrique
Mme PENAULT-LLORCA Frédérique	Anatomie et Cytologie Pathologiques
M. BAZIN Jean-Etienne	Anesthésiologie et Réanimation Chirurgicale
M. BIGNON Yves Jean	Cancérologie option Biologique
M. BOIRIE Yves	Nutrition Humaine
M. CLAVELOU Pierre	Neurologie
M. GILAIN Laurent	O.R.L.
M. LEMAIRE Jean-Jacques	Neurochirurgie
M. CAMILLERI Lionel	Chirurgie Thoracique et Cardio-Vasculaire
M. DAPOIGNY Michel	Gastro-Entérologie

M.	LLORCA Pierre-Michel	Psychiatrie d'Adultes
M.	PEZET Denis	Chirurgie Digestive
M.	SOUWEINE Bertrand	Réanimation Médicale
M.	BOISGARD Stéphane	Chirurgie Orthopédique et Traumatologie
Mme	DUCLOS Martine	Physiologie
M.	SCHMIDT Jeannot	Médecine d'Urgence
M.	BERGER Marc	Hématologie
M.	GARCIER Jean-Marc	Anatomie-Radiologie et Imagerie Médicale
M.	ROSSET Eugénio	Chirurgie Vasculaire
M.	SOUBRIER Martin	Rhumatologie
M.	ABERGEL Armando	Hépatologie
Mlle	BARTHELEMY Isabelle	Chirurgie Maxillo-Faciale
M.	RUIVARD Marc	Médecine Interne

**PROFESSEURS DE
1ère CLASSE**

M.	CAILLAUD Denis	Pneumo-physiologie
M.	VERRELLE Pierre	Radiothérapie option Clinique
M.	D'INCAN Michel	Dermatologie -Vénérologie
Mme	JALENQUES Isabelle	Psychiatrie d'Adultes
M.	GERBAUD Laurent	Epidémiologie, Economie de la Santé et Prévention
M.	TAUVERON Igor	Endocrinologie et Maladies Métaboliques
M.	MOM Thierry	Oto-Rhino-Laryngologie
M.	RICHARD Ruddy	Physiologie
M.	SAPIN-DEFOUR Vincent	Biochimie et Biologie Moléculaire
M.	BAY Jacques-Olivier	Cancérologie
M.	COUDEYRE Emmanuel	Médecine Physique et de Réadaptation
Mme	GODFRAIND Catherine	Anatomie et Cytologie Pathologiques
M.	LAURICHESSE Henri	Maladies Infectieuses et Tropicales
M.	TOURNILHAC Olivier	Hématologie
M.	CHIAMBARETTA Frédéric	Ophthalmologie
M.	FILAIRE Marc	Anatomie – Chirurgie Thoracique et Cardio-Vasculaire
M.	GALLOT Denis	Gynécologie-Obstétrique
M.	GUY Laurent	Urologie
M.	TRAORE Ousmane	Hygiène Hospitalière
M.	ANDRE Marc	Médecine Interne
M.	BONNET Richard	Bactériologie, Virologie
M.	CACHIN Florent	Biophysique et Médecine Nucléaire
M.	COSTES Frédéric	Physiologie
M.	FUTIER Emmanuel	Anesthésiologie-Réanimation
Mme	HENG Anne-Elisabeth	Néphrologie
M.	MOTREFF Pascal	Cardiologie
Mme	PICKERING Gisèle	Pharmacologie Clinique
M.	RABISCHONG Benoît	Gynécologie Obstétrique
M.	CHABROT Pascal	Radiologie et Imagerie Médicale
M.	DESCAMPS Stéphane	Chirurgie Orthopédique et Traumatologique
Mme	HENQUELL Cécile	Bactériologie Virologie
M.	POMEL Christophe	Cancérologie – Chirurgie Générale

**PROFESSEURS DE
2ème CLASSE**

Mme CREVEAUX Isabelle

Biochimie et Biologie Moléculaire

M. FAICT Thierry	Médecine Légale et Droit de la Santé
Mme KANOLD LASTAWIECKA Justyna	Pédiatrie
M. TCHIRKOV Andréï	Cytologie et Histologie
M. CORNELIS François	Génétique
M. LESENS Olivier	Maladies Infectieuses et Tropicales
M. AUTHIER Nicolas	Pharmacologie Médicale
M. BROUSSE Georges	Psychiatrie Adultes/Addictologie
M. BUC Emmanuel	Chirurgie Digestive
M. LAUTRETTE Alexandre	Néphrologie Réanimation Médicale
Mme BRUGNON Florence	Biologie et Médecine du Développement et de la Reproduction
M. ESCHALIER Romain	Cardiologie
M. MERLIN Etienne	Pédiatrie
Mme TOURNADRE Anne	Rhumatologie
M. DURANDO Xavier	Cancérologie
M. DUTHEIL Frédéric	Médecine et Santé au Travail
Mme FANTINI Maria Livia	Neurologie
M. SAKKA Laurent	Anatomie – Neurochirurgie
M. BOURDEL Nicolas	Gynécologie-Obstétrique
M. GUIEZE Romain	Hématologie
M. POINCLOUX Laurent	Gastroentérologie
M. SOUTEYRAND Géraud	Cardiologie
M. EVRARD Bertrand	Immunologie
M. POIRIER Philippe	Parasitologie et Mycologie
Mme PHAM DANG Nathalie	Chirurgie Maxillo-Faciale et Stomatologie
Mme SARRET Catherine	Pédiatrie

PROFESSEURS DES UNIVERSITES

M. CLEMENT Gilles	Médecine Générale
Mme MALPUECH-BRUGERE Corinne	Nutrition Humaine
M. VORILHON Philippe	Médecine Générale

PROFESSEURS ASSOCIES DES UNIVERSITES

Mme BOTTET-MAULOUBIER Anne	Médecine Générale
M. CAMBON Benoît	Médecine Générale
M. TANGUY Gilles	Médecine Générale

MAITRES DE CONFERENCES DES UNIVERSITES

PRATICIENS HOSPITALIERS

**MAITRES DE CONFERENCES
HORS CLASSE**

Mme CHAMBON Martine
Mme BOUTELOUP Corinne

Bactériologie Virologie
Nutrition

**MAITRES DE CONFERENCES DE 1^{ère}
CLASSE**

M. MORVAN Daniel	Biophysique et Traitement de l'Image
Mle GOUMY Carole	Cytologie et Histologie, Cytogénétique
Mme FOGLI Anne	Biochimie Biologie Moléculaire
Mle GOUAS Laetitia	Cytologie et Histologie, Cytogénétique
M. MARCEAU Geoffroy	Biochimie Biologie Moléculaire
Mme MINET-QUINARD Régine	Biochimie Biologie Moléculaire
M. ROBIN Frédéric	Bactériologie
Mle VERONESE Lauren	Cytologie et Histologie, Cytogénétique
M. DELMAS Julien	Bactériologie
Mle MIRAND Audrey	Bactériologie Virologie
M. OUCHCHANE Lemlih	Biostatistiques, Informatique Médicale et Technologies de Communication
M. LIBERT Frédéric	Pharmacologie Médicale
Mle COSTE Karen	Pédiatrie
Mle AUMERAN Claire	Hygiène Hospitalière
Mme CASSAGNES Lucie	Radiologie et Imagerie Médicale
M. LEBRETON Aurélien	Hématologie
M. BUISSON Anthony	Gastroentérologie

**MAITRES DE CONFERENCES DE 2^{ème}
CLASSE**

Mme PONS Hanaë	Biologie et Médecine du Développement et de la Reproduction
M. JABAUDON-GANDET Matthieu	Anesthésiologie – Réanimation Chirurgicale
M. BOUVIER Damien	Biochimie et Biologie Moléculaire
M. COLL Guillaume	Neurochirurgie
M. MAQDASY Salwan	Endocrinologie, Diabète et Maladies Métaboliques
Mme NOURRISSON Céline	Parasitologie - Mycologie
M. GODET Thomas	Anesthésiologie-Réanimation et Médecine Péri-Opératoire
M. LACHAL Jonathan	Pédopsychiatrie
M. MOUSTAFA Farès	Médecine d'Urgence

MAITRES DE CONFERENCES DES UNIVERSITES

Mme VAURS-BARRIERE Catherine	Biochimie Biologie Moléculaire
M. BAILLY Jean-Luc	Bactériologie Virologie
Mlle AUBEL Corinne	Oncologie Moléculaire
M. BLANCHON Loïc	Biochimie Biologie Moléculaire
Mlle GUILLET Christelle	Nutrition Humaine
M. BIDET Yannick	Oncogénétique
M. MARCHAND Fabien	Pharmacologie Médicale
M. DALMASSO Guillaume	Bactériologie
M. SOLER Cédric	Biochimie Biologie Moléculaire
M. GIRAUDET Fabrice	Biophysique et Traitement de
l'Image Mme VAILLANT-ROUSSEL Hélène	Médecine Générale
Mme LAPORTE Catherine	Médecine Générale
M. LOLIGNIER Stéphane	Neurosciences – Neuropharmacologie
Mme MARTEIL Gaëlle	Biologie de la Reproduction
M. PINEL Alexandre	Nutrition Humaine
M. PIZON Frank	Santé Publique

MAITRES DE CONFERENCES ASSOCIES DES UNIVERSITES

M. BERNARD Pierre	Médecine Générale
Mme ESCHALIER Bénédicte	Médecine Générale
Mme RICHARD Amélie	Médecine Générale
M. TESSIERES Frédéric	Médecine Générale
Mme ROUGE Laure	Médecine Générale

Remerciements

A mon jury de thèse

Monsieur le **Professeur Xavier DURANDO**, Président du Jury,

Je vous remercie de nous faire l'honneur de présider ce jury et d'avoir accepté de juger ce travail de thèse. Je vous prie d'accepter l'expression de toute ma considération et mon profond respect.

Madame le **Docteur Maureen BERNADACH**, Directeur de thèse,

Merci pour ton soutien et pour toutes les connaissances que tu m'as transmises au cours de ces années d'internat. Merci pour tous ces bons conseils prodigués lorsque l'hésitation était à son apogée concernant les choix qui s'offraient à moi. Ce fut un honneur de bénéficier de ton encadrement et de tes enseignements; je souhaite à tous les internes d'avoir cette chance. Encore merci pour la confiance que tu m'as accordée pour ce travail. J'espère qu'il sera à la hauteur de tes attentes.

Monsieur le **Docteur Julian BIAU**, Membre du Jury,

Je vous remercie d'avoir accepté de faire partie de mon jury de thèse et d'y apporter votre expertise clinique. Veuillez accepter l'expression de ma profonde gratitude.

Table of contents

Tables and Figures	10
Abbreviations	11
Peripheral blood biomarkers as predictor of response to nivolumab in recurrent or metastatic squamous cell carcinoma of head and neck (HNSCC)	12
Section 1: Introduction	12
1.1 Epidemiology	12
1.2 Immune checkpoint inhibitors and PD-L1 expression	12
1.3 Evaluation of response to immunotherapy	14
1.4 Pharmaco-economics of treatment of HNSCC.....	14
1.5 Background: White-blood cells , platelets and antitumoral activity.	15
1.5.1 Lymphocytes.....	15
1.5.2 Neutrophils.....	15
1.5.3 Eosinophils.....	16
1.5.4 Monocytes/Macrophages	16
1.5.5 Basophils	16
1.5.6 Platelets	16
1.6 Primary and secondary objectives	16
Section 2: Methods	17
2.1 Patients and Study design.....	17
2.2 Endpoints	19
2.3 Statistical analysis	19
Section 3: Results	20
3.1 Baseline characteristics	20
3.2 Treatment	22
3.3 Response to nivolumab and predictive factors	24
3.4 Progression-Free Survival and predictive factors	25
3.5 Overall survival and predictive factors	28
3.6 Time-to-treatment failure and predictive factors (response or tolerance).....	30
Section 4: Discussion	33
Section 5: Conclusion (EN)	39
Section 6: References	41
Section 7: Appendix and Supplementary material	45

Tables and Figures

Table I : Baseline Characteristics.....	21
Table II : Treatment - Qualitative variables.....	23
Table III: TNM ⁱ staging according to primary tumor location.....	46
Table IV : Immune-related adverse effects.....	47
Figure 1: Kaplan-Meier curve of Progression-Free-Survival (PFS).....	25
Figure 2: Kaplan-Meier curve of Progression-Free-Survival (PFS) (NLR=5).....	26
Figure 3: Kaplan-Meier curve of Progression-Free-Survival (PFS) (PLR=150).....	26
Figure 4: Kaplan-Meier curve of Overall Survival (OS).....	28
Figure 5: Kaplan-Meier curve of Overall Survival (OS) (NLR=5).....	29
Figure 6 : Kaplan-Meier curve of Overall Survival (OS) (PLR=150).....	29
Figure 7: Kaplan-Meier curve of Time-to-treatment failure (TTF).....	30
Figure 8: Kaplan-Meier curve of Time-to-treatment failure (TTF) (NLR=5).....	31
Figure 9: Kaplan-Meier curve of Time-to-treatment failure (TTF) (PLR=150).....	31
Figure 10: Kaplan-Meier curve of Time-to-treatment failure (TTF) (LWR2=0.12).....	33

Abbreviations

AEC: Absolute Eosinophil Count

ABC: Absolute Basophil Count

AMC: Absolute Monocyte Count

ALC: Absolute Lymphocyte Count

ANC: Absolute Neutrophil Count

CTCAE: Common Terminology Criteria for Adverse Events

CT: Computed tomography

ECOG PS: Eastern Cooperative Oncology Group
Performance Status

G-CSF: Recombinant human granulocyte-colony
stimulating factor

HNSCC: Head and neck squamous-cell carcinoma

HPD: Hyperprogressive disease

HPV: Human Papillomavirus

ICI: Immune checkpoint inhibitors

iCPD: Immune confirmed progressive disease

iUPD: Immune unconfirmed progressive disease

irAE: Immune-related Adverse Event

iRECIST: Immune related RECIST criteria

LWR : Lymphocyte-to-white blood cell ratio

NLR: Neutrophil-to-Lymphocyte Ratio

ORR: Objective response rate

PD1: Programmed Cell Death Protein 1

PD-L1: Programmed Death-Ligand 1

PET: Positron emission tomography

PFS: Progression-Free Survival

PLR: Platelet-to-Lymphocyte Ratio

R/M HNSCC: Recurrent and/or Metastatic Head and
Neck Squamous Cell Carcinoma

RECIST: Response Evaluation Criteria in Solid Tumors

TME : Tumor microenvironment

Peripheral blood biomarkers as predictor of response to nivolumab in recurrent or metastatic squamous cell carcinoma of head and neck (HNSCC)

Section 1: Introduction

1.1 Epidemiology

Head and neck squamous-cell carcinoma (HNSCC) is the seventh most common cancer worldwide and accounts for approximately 700 000 diagnosed cases annually. Prognosis remains poor with a mortality rate of more than 330 000 deaths per year (1). In France, the incidence rate is about 10 000 cases per year and the mortality rate is of 3 000 deaths annually. Both rates have been steadily declining since 1998 (2) mainly due to the decrease in alcohol consumption (3,4).

1.2 Immune checkpoint inhibitors and PD-L1 expression

Immune checkpoint inhibitors, such as anti-PD1/PDL1 antibodies, are becoming a cornerstone of cancer therapy. Promising antitumoral responses have been obtained with such treatment across several cancer types such as melanoma (5), non-small-cell lung cancer (6), urothelial carcinoma (7), renal-cell carcinoma (8,9), gastric and gastro-oesophageal junction cancer (10), hepatocellular carcinoma (11), Hodgkin's lymphoma (12), colorectal cancer (13) and head and neck squamous cell carcinoma (14,15). Nivolumab, an anti-PD1 antibody, has been approved for reimbursement in France in January 2018 in platinum-refractory, recurrent or metastatic squamous-cell carcinoma of head and neck in monotherapy, regardless of PD-L1 status. It has since then been considered as standard of care as second line of treatment, in patients who did not receive first-line immunotherapy-based treatment, based on the results of the CHECKMATE-141 trial, a randomized, open-label, phase 3 trial (16). Median overall survival increased from 5

to 7.5 months in the treatment arm and response rates were 13.3% in the nivolumab group against 5.8% in the standard treatment group. Even with such significant results, the majority of patients do not respond to immunotherapy.

There is currently no definite predictive biomarker to select patients most likely to benefit from immunotherapy. In a subgroup analysis (16), PD-L1 expressors (PDL \geq 1%) seemed to be correlated with better response rates in HNSCC [ORR=17.7% (10.7–26.8)]. However, responses were also observed in PD-L1 negative patients [ORR=11.8% (5.6–21.3)]. PD-L1 expression is thus an imperfect predictor of response notably because of increased risk of false negatives in case of insufficient tumor sample, focal heterogeneity of PD-L1 expression, variation of PD-L1 expression according to metastatic sites, potential immunomodulatory effect of prior chemotherapy on the tumor microenvironment (TME) and lack of standardization in the evaluation of the PD-L1 score (several antibodies used, variable positivity thresholds)(17). Therefore, PD-L1 score is neither used for selection nor reimbursement of nivolumab in France.

The implication of the TME in providing antitumoral responses and constraining tumor growth (18,19) is currently being actively investigated. The recent development of the Combined Positive Score (CPS-score) (20) which takes into account PD-L1 positive lymphocytes and macrophages in the vicinity of infiltrating tumor cells reflects this logic.

1.3 Evaluation of response to immunotherapy

Evaluation of response to immunotherapy is challenging in HNSCC since there is no reliable assessment tool that can be used in clinical practice to differentiate pseudo-progression from true progression (21). Pseudo-progression is defined as an increase in the size of the primary tumor or the appearance of a new lesion followed by tumor regression, confirmed by two consecutive imaging analysis, set at a minimum of 4 weeks apart. Immune related RECIST criteria (iRECIST) (22) was thus developed to identify such responses in clinical trials involving immunotherapy and defined immune unconfirmed progressive disease (iUPD) and immune confirmed progressive disease (iCPD). Although no consensual definition has been adopted, hyperprogressive disease (HPD) is also a significantly recognized phenomenon under ICI in HNSCC (about 30%) (23) that has been described as an acceleration in tumor growth kinetics (24). Continuing immunotherapy in case of iUPD in head and neck cancer can rapidly lead to dyspnea, pain, dysphagia, or speech disorders. Such clinical manifestations can be life-threatening and lead to discontinuation of immunotherapy, especially in case of HPD. Few cases of pseudo-progression are thus reported in head and neck cancers. It is therefore essential to develop new tools to differentiate pseudoprogessions from hyperprogressions and confirmed progressions in order to avoid pursuing an ineffective treatment that would expose patients to life-threatening risks.

1.4 Pharmaco-economics of treatment of HNSCC

The economic and clinical burden of immunotherapy in HNSCC is substantial even for developed countries and is not currently cost-effective (25–28). Routinely available full blood counts could provide effective, widely available and inexpensive, surrogate biomarkers to predict response to immunotherapy and thus allow to maximize treatment benefits for patients.

1.5 Background: White-blood cells , platelets and antitumoral activity.

The different subtypes of white blood cells, whose functions are deeply intricated, have diverse functions ranging from protection against infectious diseases to antitumoral activity. However, their role in cancer progression is complex since they can both promote and suppress tumor growth depending on their activation and subtypes.

1.5.1 Lymphocytes

Lymphocytes, and more specifically T cell lymphocytes, are the target effectors of immune checkpoint inhibitors such as anti PD-1/PD-L1 inhibitors and play a critical role in antitumoral activity (29). New emerging cancer immunotherapeutics are being actively developed, with novel targets such as lymphocyte activation gene 3 (LAG3), T cell immunoglobulin 3 (TIM3), V-domain immunoglobulin suppressor of T cell activation (VISTA), B7-H3 and T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) (30). Tumor-infiltrating lymphocytes CD8+ T cells (TILs) have been found to be independent factor of good prognosis in HNSCC in a metanalysis (31). Low pretreatment absolute lymphocyte count (ALC) (32) and severe lymphopenia (33) have been found to be of poorer prognosis in HNSCC.

1.5.2 Neutrophils

Neutrophils are known to favor angiogenesis, metastatic processes as well as immunosuppression but can also provide antitumoral activity depending on their subtypes (34). High neutrophil to lymphocyte ratio (NLR) is a biomarker of poor prognosis in many cancer types (35–39), including HNSCC (40).

1.5.3 Eosinophils

Eosinophils are capable of synthesizing and secreting molecules that can promote as well as hinder tumor growth (41). The prognostic value of hypereosinophilia differs across cancer type and is thus not consensual. In melanoma, absolute eosinophil count correlates to response and overall survival in patients treated with anti-CTLA4 antibody but seems to be a biomarker of poor prognosis in HNSCC (42).

1.5.4 Monocytes/Macrophages

Macrophages are also involved in the different steps of primary tumor initiation, promotion, angiogenesis and immunoregulation (43), but can also provide antitumoral activity.

1.5.5 Basophils

Basophils can be implicated in hematologic malignancies but have also been found in the TME of lung adenocarcinoma, pancreatic cancer and inflammation-driven skin tumors (44) (45). Their role in cancer progression is not completely elucidated.

1.5.6 Platelets

Platelets play a major role as first responders to wound and cancer (46). They are involved in metastatic processes by shielding metastatic cells from immune peripheral NK T lymphocytes and mechanical constraints of the bloodstream (47). They also recruit other immune cells via different inflammatory pathways (47) and form neutrophil extracellular traps (NETs) (48), known to favor metastasis.

1.6 Primary and secondary objectives

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte-to-monocyte ratio (LMR) correlate to poor prognosis in many cancer types (35,36,49–54), including

HNSCC (37,55). The variation of such peripheral blood parameters over time could potentially be more adequate to avoid confounding factors such as infections and act as a surrogate biomarker to confirm iUPD or pseudo-progression along with imaging data for patients under treatment by nivolumab for recurrent/metastatic HNSCC.

The primary objective of our study is to determine the correlation between variations of peripheral blood parameters and response to nivolumab in HNSCC. As secondary objectives, we analyzed the correlation between pretreatment values and variations of those peripheral blood parameters, with respectively, response, progression-free survival (PFS), overall survival (OS) and time-to-treatment failure (TTF) of nivolumab.

Section 2: Methods

2.1 Patients and Study design

We analyzed retrospectively registered data of 44 patients with recurrent or metastatic head and neck squamous cell carcinoma who received anti-PD-1 based treatment regimens with at least one prior line of systemic treatment at Centre Jean Perrin, France (CJP) from March 2018 to December 2020. Nivolumab was administered at a single dose of 240mg as an intravenous infusion every 2 weeks. Eligible patients were ≥ 18 years of age, received at least two injections of nivolumab, and had at least one imaging or clinical assessment confirming disease progression. We excluded patients with tumor histology other than squamous cell carcinoma, prior exposure to nivolumab and active brain metastases. No recombinant human granulocyte-colony stimulating factor (G-CSF) were administered 2 weeks prior or while on treatment by nivolumab. The Institutional Review Board of Centre Jean Perrin approved this study. According to French legislation, the database has been declared to the French National Commission on Informatics

and Liberty (CNIL). All patients have been informed about the research by a non-opposition letter. They were free to oppose the use of their personal data for this study.

Hemoglobin, white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute eosinophil count (AEC), absolute monocyte count (AMC), absolute basophile count (ABC), absolute platelet count (APC) were collected from peripheral blood samples at baseline and before each subsequent administration cycle of nivolumab. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), monocyte to basophil ratio (MBR), lymphocyte to total white blood cell (LWR), neutrophil to total white blood cell (NWR) were derived from these data. We also calculated rates of change of NLR, PLR and LWR with initial pretreatment values and between consecutive blood samples (*cf* Appendix I). Demographic and clinical data such as Performance-Status (PS), Body-mass index (BMI), alcohol consumption, smoking habit and history, primary tumor location, TNM staging at initial diagnosis and upon recurrence, site of metastasis, the number of prior and subsequent systemic therapy regimen were also collected.

2.2 Endpoints

Best treatment response was assessed by CT-TDM and/or PET-TDM and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as compared to the baseline imaging on the primary and on metastatic sites. Imaging was performed every 6 to 12 weeks, or at least 4 weeks apart when iUPD was suspected. Progression of disease was defined by documentation of new clinical manifestation, new biopsy-proven disease, or unequivocal progression (iCPD). Hyperprogression was defined by clinical progression of disease with life-threatening consequences within 2 weeks of administration of nivolumab.

2.3 Statistical analysis

Categorical variables, such as patient and disease characteristics, were described using absolute frequencies and percentages. Continuous variables were presented as means, medians, standard-deviations, interquartile intervals and ranges. PFS was defined as the time from the introduction of nivolumab and radiographic or clinical progression or death, whichever came first, censored at last follow-up. Time to treatment failure (TTF) was defined as the time from the first dose of nivolumab to the last administered dose of nivolumab due to radiographic or clinical progression, death, or early discontinuation of immunotherapy. Overall survival (OS) was defined as the time from introduction of nivolumab and date of death or last follow-up. Wilcoxon-Mann-Whitney U test was used to compare quantitative variables with respect to response to nivolumab. Cox proportional hazards model was used for univariate and multivariate analyses of OS and PFS. Fisher's exact test was used to analyze the association between response to immunotherapy and qualitative variables. Kaplan-Meier survival curves were plotted according to the cutoff values of NLR (< 5 or ≥ 5) and PLR (< 150 or ≥ 150). Multivariable regressions (logistic

and Cox) were applied on variables with (non-adjusted) p -value less than 0.1 in the univariate analysis, and using a LASSO penalization method. Statistical significance was considered at $p < 0.05$ with a confidence interval of 95% (CI 95%), and was also adjusted according to Benjamini-Hochberg procedure. Statistical analysis was performed using software R, version 3.6.1 (R-Project, GNU GPL, <http://cran.r-project.org/>).

Section 3: Results

3.1 Baseline characteristics

Forty-four patients were included in our study. Demographic and clinical characteristics are summarized in Table I. Most patients were men (86.4%) with an ECOG PS ≤ 1 (68.1%). All patients had a histology of squamous cell carcinoma. The mean age was 63.5 ± 11.0 years. Mean BMI was 21.67 kg/m² at initiation of nivolumab. Concerning smoking habit, sixteen patients were active smokers at diagnosis (36.4%), eighteen (40.9%) had stopped smoking and ten (22.7%) had never smoked.

At diagnosis, 41 patients (93.2%) had local and/or locally advanced tumors (stage I-IV according to the 8th Edition TNM Classification for Head and Neck Cancer). On administration of ICI, 30 patients were metastatic (68.2%), with lung being the most frequent metastatic site (47.7%).

Baseline NLR was ≤ 5 in 19 patients (43.2%) and $NLR > 5$ in 25 patients (57.8%). Baseline PLR was ≤ 150 in 6 patients (13.7%) and > 150 in 38 patients (86.3%).

TABLE I : BASELINE CHARACTERISTICS

	<i>n</i> total = 44	Number (%)
Gender		
Female		6 (13.6)
Male		38 (86.4)
Age (years)		
<65		21 (47.7)
>65		23 (52.3)
ECOG PS		
0		2 (4.6)
1		28 (63.6)
2		11 (25)
3		3 (6.8)
Smoking habit		
Active		16 (36.4)
Stopped		18 (40.9)
Never		10 (22.7)
Alcohol		
Active		11 (25)
Stopped		26 (59)
Never		6 (16)
Body mass index (kg/m ²)		
<18.5		8 (18.2)
18,5-25		26 (59.1)
> 25		10 (22.7)
> 30		0 (0)
Primary tumor location		
Hypopharyngeal		13 (30)
Oral cavity		13 (30)
Oropharyngeal		12 (27)
Other		6 (14)
TNM ^a staging at diagnosis		
Local		16 (36.4)
Regional		25 (56.8)
Metastatic		3 (6.8)
TNM Staging at initiation of ICI		
Local		3 (6.8)
Regional		11 (25)
Metastatic		30 (68.2)
Metastatic sites		
Lung		21 (47.7)
Bone		13 (29.5)
Liver		4 (9.1)
Lymph nodes		12 (27.3)
Other		2 (4.5)

a: TNM Classification for Head and Neck Cancer, 8th Edition

3.2 Treatment

At initial treatment, 16 patients (37.2%) had surgery, with 10 patients (62.5%) with complete *in sano* resection margins; 10 patients (22.7%) received adjuvant radiotherapy. Twenty-four patients (54.5%) received an exclusive radiochemotherapy with cisplatin, and 6 patients (13.6%) received concurrent radiotherapy with cetuximab. Thirty patients (68.2%) had received cetuximab prior to ICI. (*cf* Table II). Five patients (31.3%) started nivolumab on recurrence after local treatment. Sixteen patients (36.3%) received one prior line of systemic treatment and twenty-three patients (52.3%) received at least two prior systemic treatment before nivolumab.

Best response to nivolumab was stable disease in nine patients (20.5%), partial response in five patients (11.4%) and complete response in two patients (4.5%). Twenty-five patients (56.8%) showed disease progression, two patients (4.5%) experienced hyperprogressive disease.

Best favorable responses to nivolumab (SD, PR and CR) were obtained on local and/or regional recurrence in 7/14 patients (50%) and in metastatic recurrence in 8/30 patients (26.7%).

In patients with both primary and metastatic recurrence (29 patients), 5 patients (17.2%) obtained only local responses, 15 patients (51.7%) responded on metastatic sites only and 9 patients (40.9%) obtained global responses.

TABLE II : TREATMENT - QUALITATIVE VARIABLES

	Number (%)
Surgery	
Yes	16 (37.2)
No	27 (62.8)
Resection margins R0	10 (62.5)
Resection margins R1	6 (37.5)
Local treatment	
No local treatment	4 (9.1)
Radiotherapy (R)	10 (22.7)
R-Cetuximab	6 (13.6)
R-chemotherapy	24 (54.6)
Best local response	
CR	15 (48.4)
DR	1 (3.2)
PR	8 (25.8)
SD	5 (16.1)
PD	2 (6.5)
Prior Cetuximab administration	30 (68.2)
Response to Cetuximab	
CR	1 (6.7)
DR	4 (26.7)
PR	5 (33.3)
SD	5 (33.3)
PD	4 (26.7)
Best overall response to nivolumab	
CR	2 (4.5)
PR	5 (11.4)
SD	9 (20.5)
PD	24 (54.5)
HP	2 (4.5)
No. of prior systemic therapy	
0	5 (31.3)
1	16 (36.3)
≥2	23 (52.3)
No. of subsequent systemic therapy regimens	
0	20 (45.5)
1	18 (40.9)
≥2	6 (13.6)

CR : Complete response, DR : Dissociated response, PR : Partial response, SD : Stable disease, PD : Progressive disease , HP : Hyperprogression

During nivolumab treatment, reported grade ≥ 2 irAES concerned 6 patients (12.8 %) and 38 patients (84.6%) reported grade ≤ 1 irAES (*cf* Appendix III). We report a case of grade 3 hypophysitis and grade 3 dermatitis.

3.3 Response to nivolumab and predictive factors

Best response to nivolumab (SD, PR, CR) was 16/44 patients (36.3%). Objective response rate (PR and CR) was 7/44 patients (15.9%).

Primary tumor location was not significantly correlated with response in univariate and multivariate analysis.

In univariate analysis, pretreatment values and variations of LWR and PLR were not significantly associated with response.

In multivariate analysis, metastatic lymph nodes were significantly associated with progression [OR= 4.404, CI95% (1.085-20.266), $p=0.013$], while NLR at 2 cycles of nivolumab was significantly associated with response [OR=0.897 (0.770-0.992), $p=0.013$].

3.4 Progression-Free Survival and predictive factors

Median PFS was 3 months [(0-28), (CI95% 2-4)], as shown in Figure 1.

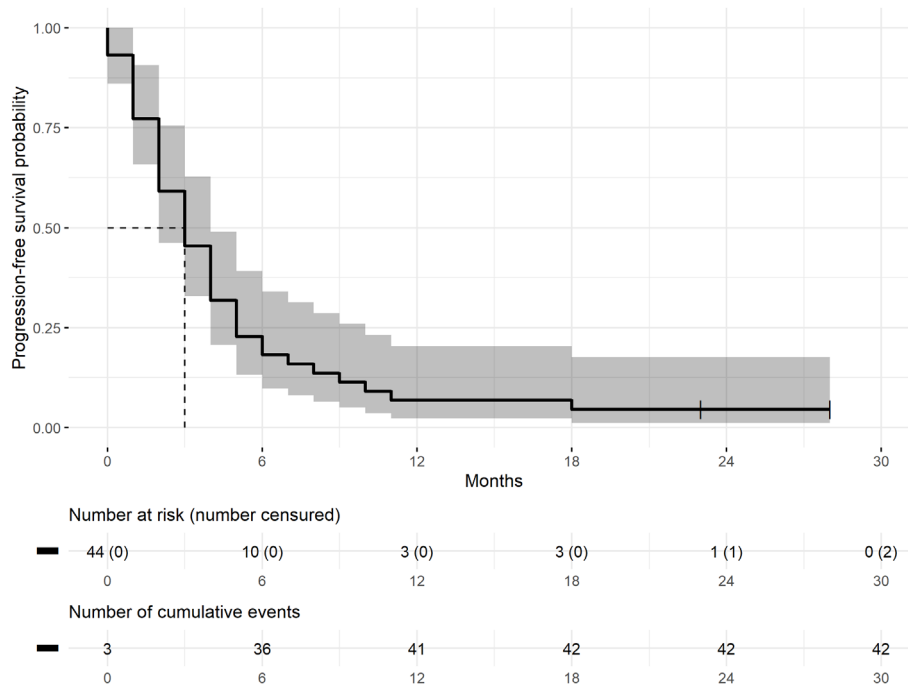


FIGURE 1: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS)

With thresholds of $NLR \leq 5$ and $PLR \leq 150$, median PFS increased from 2 to 4 months ($p=0.11$), and from 3 to 5 months ($p=0.13$) respectively but did not reach significance (Figure 2 and Figure 3).

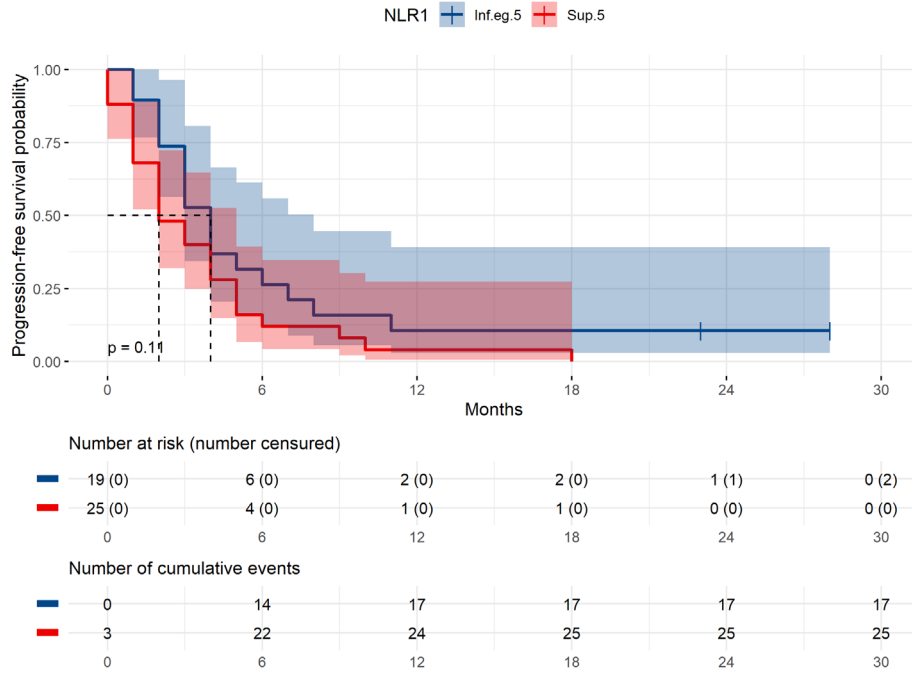


FIGURE 2: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS) (NLR=5)

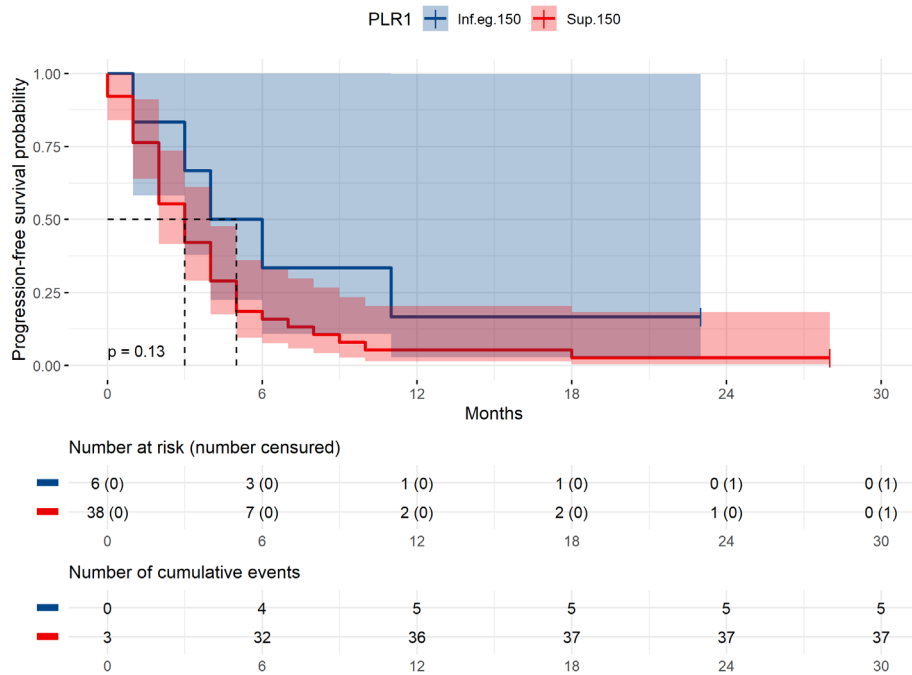


FIGURE 3: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS) (PLR=150)

In univariate analysis, favorable response on primary tumor [HR=0.148 (0.063-0.348), p-adjusted<0.001] and on metastatic sites [HR=0.250 (0.098-0.640), p-adjusted=0.026], pretreatment LWR [HR=0.006 (0.000-0.266), p-adjusted=0.028] and LWR at 2 cycles of nivolumab [HR=0.002 (0.000-0.195), p-adjusted=0.026] were significantly associated with longer PFS. LWR at 4, 6 and 8 cycles and prior administration of cetuximab was not significantly associated with increase in PFS.

PFS was significantly associated with poorer outcomes in patients with pretreatment NLR [HR=1.080 (1.031-1.131), p-adjusted=0.026], NLR at 2 [HR= 1.075 (1.038-1.112), p-adjusted=0.015] and 4 cycles of nivolumab [HR= 1.069 (1.029-1.111), p-adjusted=0.026].

In multivariate analysis, PFS was significantly associated with better prognosis in patients with favorable response on primary tumor [HR=0.124 (0.048-0.323), p-adjusted<0.001], while variation of PLR from baseline to 6th cycle (PLRdi3) of nivolumab was significantly correlated to worse prognosis [HR= 1.752 (1.028-2.984), p=0.039].

Primary tumor location was not significantly correlated to PFS in univariate and multivariate analysis. Metastatic lymph nodes were not significantly associated with PFS.

3.5 Overall survival and predictive factors

Median overall survival time was 17 months (CI95%14-28) as shown in Figure 1.

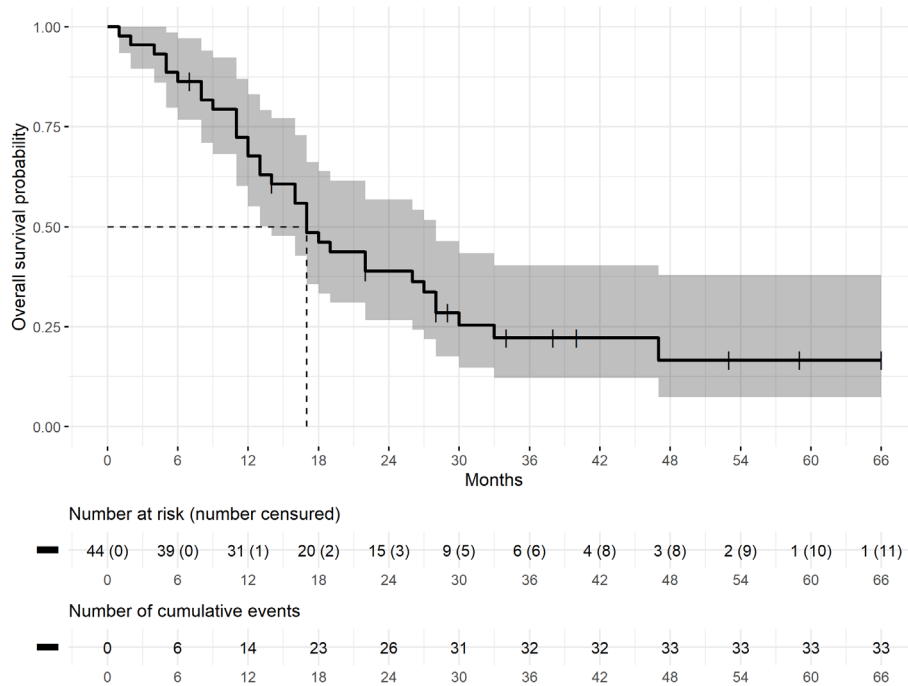


FIGURE 4: KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS)

OS was significantly longer in patients with pretreatment NLR ≤ 5 with a median of 22 months ($p=0.046$) as opposed to 17 months for patients with NLR > 5 , as shown in Figure 5. OS did not increase significantly according to pretreatment PLR at a threshold of 150 ($p=0.89$), as shown in Figure 6.

In multivariate analysis, the relative rate of change of LWR (LWRdR4) between the 6th and 8th cycle of was significantly associated with better prognosis [HR=0.091 (0.017-0.479), p -adjusted=0.001]. Lung metastases, regardless of type of recurrence or other metastatic sites, were however significantly associated with poorer outcomes [HR=7.195 (1.821-28.421), $p=0.005$].

Neither primary tumor location nor presence of lymph node metastases was significantly correlated to overall survival.

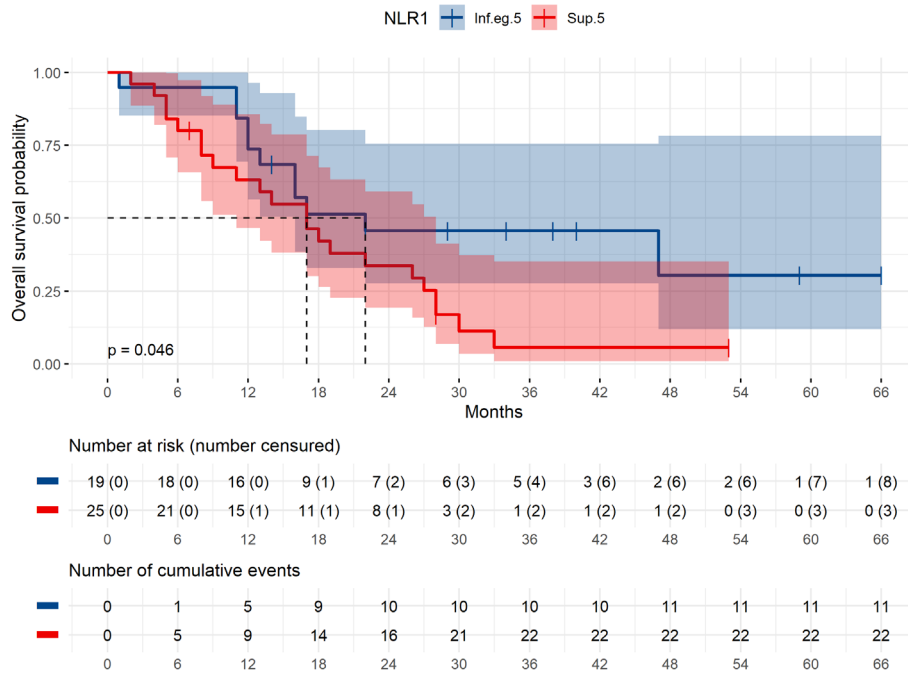


FIGURE 5: KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS) (NLR=5)

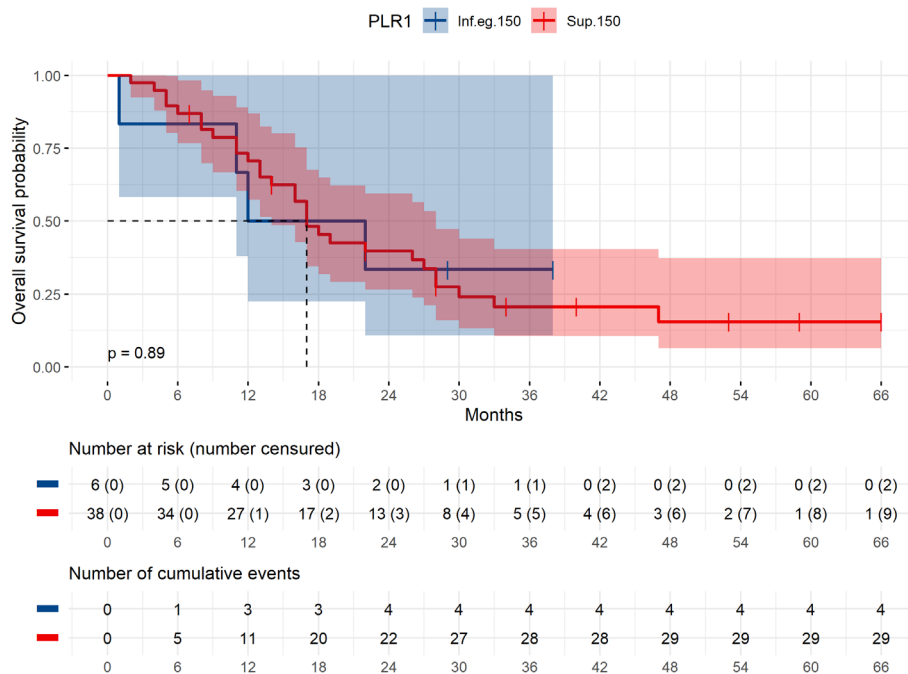


FIGURE 6 : KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS) (PLR=150)

3.6 Time-to-treatment failure and predictive factors (response or tolerance)

Median TTF was 3 months (CI 95% 2-3) as shown in Figure 7.

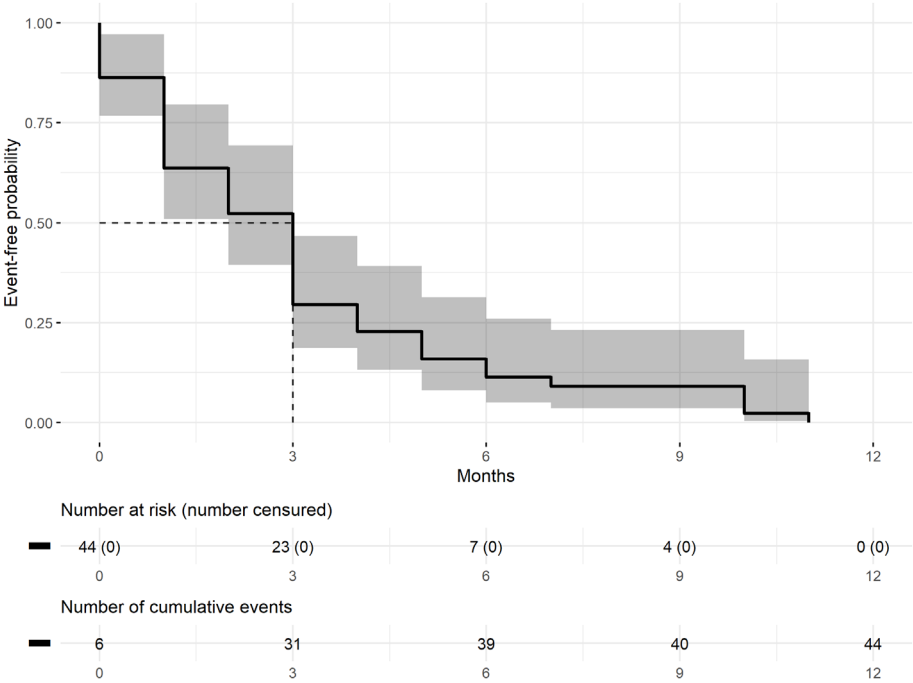


FIGURE 7: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF)

Median TTF increases significantly in patients with NLR ≤ 5 from 1 to 3 months (p=0.012) and PLR ≤ 150 from 3 to 5 months respectively (p=0.027), as shown in Figure 8 and Figure 9.

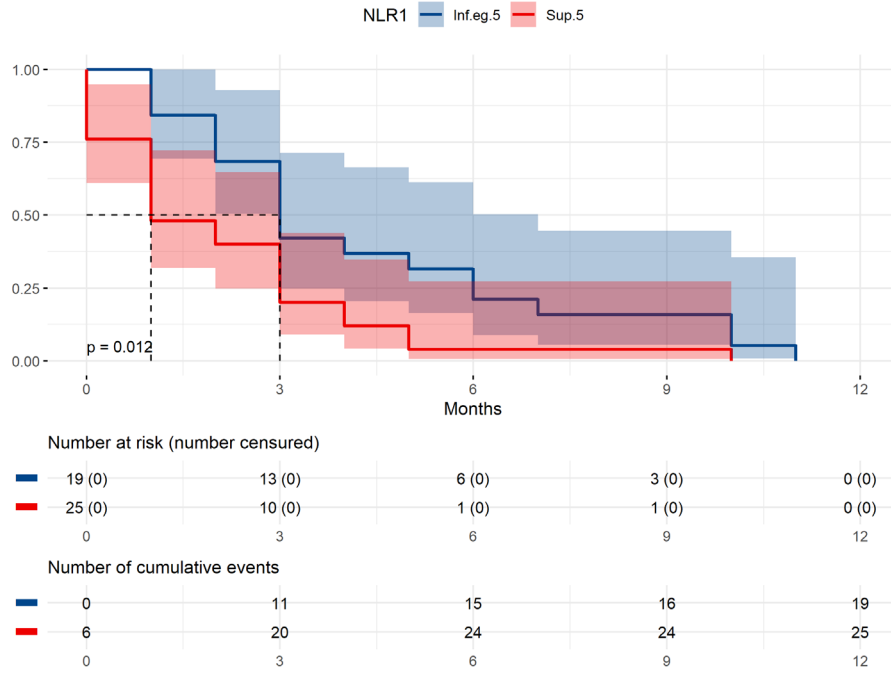


FIGURE 8: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (NLR=5)

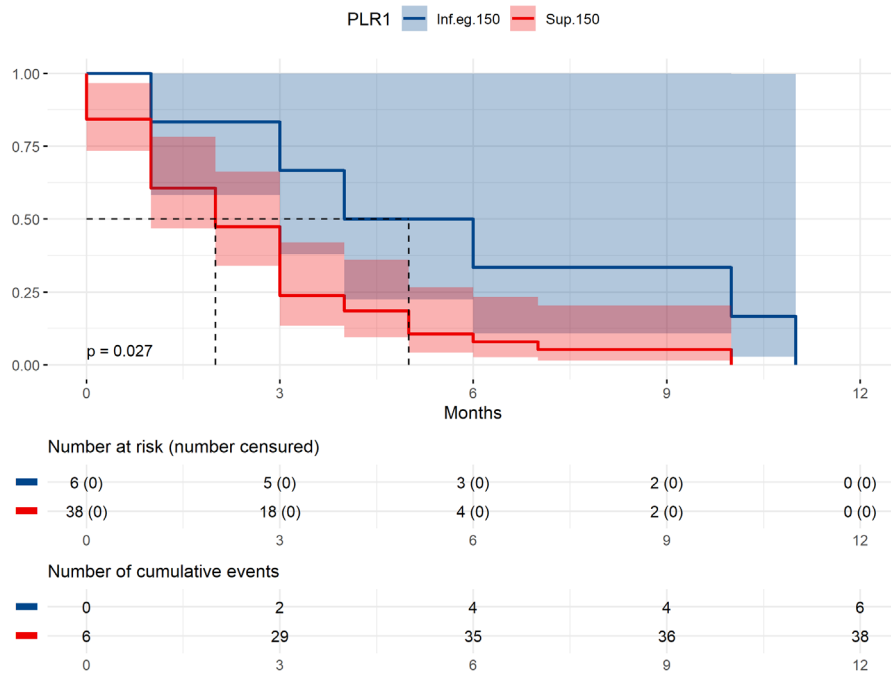


FIGURE 9: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (PLR=150)

Treatment was discontinued due to toxicity in 2 patients (4.5%), disease progression in 33 patients (75%), death in 6 patients (13.6%), transfer to supportive care in 1 patient (2.3%) and complete response in 2 (4.5%) patients.

In univariate analysis, pretreatment LWR [HR= 0.002 (0.000-0.102), p-adjusted=0.006], LWR at 2 cycles [HR= 0.000 (0.000-0.019), p-adjusted= 0.001], 4 cycles [HR= 0.001 (0.000-0.297), p-adjusted= 0.048] and 6 cycles [HR= 0.000 (0.000-0.072), p-adjusted= 0.0017] of nivolumab and relative variations of LWR from the 6th to the 8th cycle of nivolumab [HR=0.142 (0.033-0.604), p-adjusted=0.017] were significantly correlated with longer TTF.

Pretreatment NLR [HR= 1.085 (1.037-1.135), p-adjusted=0.012], NLR at 2 cycles [1.102 (1.061-1.146), p-adjusted < 0.001], 4 cycles [HR= 1.082 (1.040-1.125), p-adjusted=0.007] and 6 cycles of nivolumab [HR= 1.069 (1.026-1.114), p-adjusted=0.039] respectively, were significantly associated with shorter TTF. Variations of PLR between pretreatment values and 2nd and 4th cycle of nivolumab were also correlated, although not significantly, to shorter TTF.

Neither primary tumor location nor presence of lymph node metastases was significantly correlated to TTF.

In multivariate analysis, increase in the rate of LWR from the 6th to the 8th cycle of nivolumab [HR= 0.050 (0.009-0.285), p=0.001] were significantly associated with increase in TTF, whereas PS 2-3 [HR= 11.737 (2.753-50.040), p < 0.001] was associated with shorter TTF. There was also a significant increase in median TTF from 1 to 3.5 months when LWR at 2 cycles of nivolumab was ≥ 0.12 (p<0.0001), as shown in Figure 10.

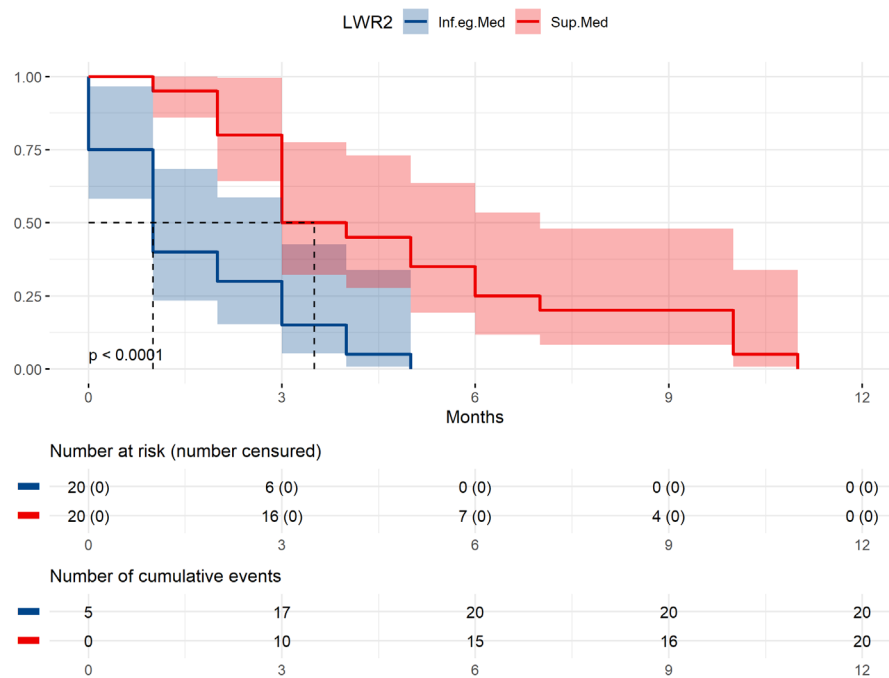


FIGURE 10: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (LWR2=0.12)

Section 4: Discussion

There is currently no proven predictive biomarker of response to nivolumab in non-resectable R/M HNSCC. The search for such biomarkers is justified by the low objective response rates obtained in this indication, the potential life-threatening risks involved in case of tumor progression in the neck area and the high cost of immunotherapy. Identifying pseudo-progression in patients with on-going antitumoral responses would allow to transfer non-responders to subsequent lines of chemotherapy or palliative care instead of pursuing an ineffective treatment. In our study, we performed a dynamic analysis of peripheral blood sample data to predict and assess response to nivolumab.

Low pretreatment absolute lymphocyte count (ALC) (32) and severe lymphopenia (33) are factors of poor prognosis in HNSCC. This may be explained by their important role of lymphocytes in tumor suppression in the TME (56). In our study, pretreatment absolute lymphocyte count was not correlated to response, OS or PFS. However, LWR ≥ 0.12 at 2 cycles of ICI was significantly correlated with an increase in median TTF to 3.5 months ($p < 0.0001$). Additionally, an increase of the rate of LWR between the 6th and 8th cycle of nivolumab was significantly correlated to an increase in both OS and TTF, suggesting that an acceleration in the recruitment of lymphocytes proportional to total white blood cell, after sufficient action by nivolumab, is associated with better overall prognosis. This biomarker variation may provide additional data to reinforce suspicion of pseudo-progression or on the contrary, suspect true progression and lead to anticipated imaging or discuss treatment change.

Our findings are consistent with several studies (35,36,50–54) concerning pre-treatment NLR as biomarkers of poor prognosis in different cancer types and notably in HNSCC (37,40,49,55). OS was significantly higher in patients with pretreatment NLR ≤ 5 with a median of 22 months (vs 17 months for patients with NLR > 5). Other authors such as Matsuki *et al.* used different thresholds (NLR=7) but provide converging data about lower NLR being associated with better prognosis. Additionally, a lower NLR value at 2 cycles of nivolumab has been associated with higher response rates in our study cohort [OR= 0.897 (0.770-0.992), $p=0.013$]. We did not reproduce literature data concerning pretreatment PLR and association with response or OS, as shown in several studies in NSCLC (54), pulmonary large cell neuroendocrine carcinoma (53) or HNSCC (51), probably due to the small number of patients. However, pretreatment PLR ≤ 150 was significantly associated with an increase in TTF compared to PLR > 150 from 3 to 5 months, respectively ($p=0.027$). Additionally, an increase in rate of PLR from baseline PLR to PLR at 6th cycle of

nivolumab was significantly associated with shorter PFS [HR=1.752 (1.028-2.984), p=0.039] suggesting that an acceleration of increase in PLR as a biomarker of inflammation is related to worse prognosis.

Median overall survival time in our study was 17 months, which is longer than the reported 7 months in the nivolumab arm in the CHECKMATE-141 trial. However, in our cohort, 11 patients (25%) were treated beyond RECIST-defined progression (TBP) with a median treatment time beyond progression of 4.8 months (range, 0.8-25.4). Haddad et al. found that patients in the TBP arm in CHECKMATE-141 had median OS, starting at week 6 after RECIST-defined progression, of 8.4 months (95% CI, 6.6-10.8 months) in the TBP group and 3.8 months (95% CI, 2.1-5.3 months) in the NTBP (no treatment beyond first RECIST-defined progression group), suggesting that nivolumab can be continued in slow, asymptomatic disease progression (57). This may in part explain our results of increase in OS. Additionally, 24/44 patients (54.5%) had received at least another line of systemic therapy after nivolumab, further incrementally increasing OS. Aside from platinum, taxanes are known to be the most active single-agent chemotherapy regimen. Most patients (12/23 patients; 52.2%) in our study received paclitaxel after progression on nivolumab, while 15.4% (35/228) patients in the nivolumab arm of CHECKMATE-141 had received taxane as systemic therapy. Literature data seems to show benefits in terms of ORR and PFS with sequential administration of anti-PD1 therapy followed by paclitaxel-based chemotherapy in several cancer types such as NSCLC (58), urothelial cancer (59) and HNSCC (60–62). Indeed, Sato et al. recently published an observational prospective study of 97 patients treated for HNSCC showing that time to progression was significantly longer when paclitaxel-based therapy was administered after nivolumab than before nivolumab (7.4 months vs 4.9 months, p=0.020). However, with only 22

patients eligible for analysis, other confirmatory studies are required to validate nivolumab followed by paclitaxel as an optimal sequential treatment in HNSCC.

Objective response rates in our study cohort, consisting of a predominantly Caucasian population, was 15.9% (2 complete responses and 5 partial responses) as opposed to 13.3% (6 complete responses and 26 partial responses) in CHECKMATE-141. Ueda et al. (40) reported an ORR of 27.6% in a Japanese retrospective cohort, providing additional evidence that response to nivolumab may vary between populations. Indeed, Peng *et al.* have demonstrated that Asian cancer patients have a significantly improved survival benefit compared to non-Asian patients receiving PD-1/PD-L1 inhibitor-based therapy in a pooled metanalysis of 11,020 patients from 19 prospective randomized controlled clinical trials (63).

To our knowledge, few studies have evaluated variations of peripheral blood biomarkers such as NLR during treatment in HNSCC. One of them (64) concerned 47 patients with head and neck cancer in a cohort of 509 patients (9.2%) with several cancer types. Li *et al.* found a non-linear relationship between change in NLR and OS during ICI treatment. Only a moderate decrease in NLR was associated with an increase in OS. An excessive decrease in NLR showed worse OS. Park *et al.* (65) evaluated NLR at baseline and at week 6 of treatment by ICI and showed that decreasing NLR during treatment was associated with longer PFS.

The strength of our study thus resides in the dynamic analysis of variation of peripheral blood biomarkers of inflammation throughout treatment by nivolumab as it allowed patients to serve as their own reference concerning baseline and subsequent blood sample data. We believe that it is more clinically relevant than pretreatment values considering tumoral evolution on treatment. Potential confounders such as intake of medication (other than long course steroids)

and lifestyle-associated blood sample variations could thus be mitigated. We excluded patients with active cerebral metastases and history of auto-immune diseases which would potentially require high doses and/or long course use of steroids.

There are several shortcomings in our study. Our sample size was small and consisted of only 44 patients and was probably inadequately powered to show more prominent results between variation of peripheral blood biomarkers and response to nivolumab. Some shortcomings are inherent in the retrospective design of this study, performed in a single institution and on a predominantly Caucasian population. Concerning data collection, PDL1 and HPV status were unavailable for most patients; HPV status was available only for 5/12 patients with oropharyngeal tumors (4 HPV positive, 1 HPV negative), 6/13 patients with oral cavity (6 HPV negative), 4/13 patients with hypopharyngeal cancer (2 HPV positive, 2 HPV negative) and 1/6 patients with other tumor location (1 HPV negative). PDL1 status was only available for 3 patients [positive for 2 patients (66.7%), and negative for 1 patient (33.3%)]. We therefore could not make inferences between PD-L1 expression, HPV status and response. However, Foster *et al.* found NLR to be more strongly associated with outcome than PD-L1 positivity as the latter was neither associated with PFS nor OS. Other confounders such as intercurrent infection and the effects of chemotherapy administered prior to nivolumab may have altered values of inflammatory biomarkers during treatment by nivolumab. Our study population reported less grade 3 or 4 irAEs (4.5%) than the CHECKMATE-141 trial (16) with one case of grade 3 hypophysitis and a case of grade 3 dermatitis, leading to interruption of ICI treatment. Reported events such as irAEs may have been underestimated when not objectively graded according to the Common Terminology Criteria for Adverse Events (CTCAE) in electronic medical reports.

Reimbursement of nivolumab in R/M HNSCC was available regardless of PDL1 status during the study. However, literature data shows that PDL1 status alone is not a perfect biomarker of response. Recently, CPS-score has been developed to take into account PD-L1 expression on infiltrating T-cell lymphocytes as well as macrophages. Burtneß *et al.* have recently conducted a phase 3 multicentric randomised trial KEYNOTE-048 with pembrolizumab, an anti-PD1 antibody, associated with platinum based chemotherapy or alone against chemotherapy associated with cetuximab. This study has been approved by the EMA and have acquired reimbursement status in France as first-line treatment in metastatic or recurrent non-resectable HNSCC with a CPS score ≥ 1 (66). CPS score > 20 showed an increase in median OS to 14.7months against 13.6 months with CPS > 1 while median SOC (EXTREME) arm was 10.7 months. CPS-score could become a routine biomarker that should be systematically performed at diagnosis of metastatic HNSCC.

Although PD-L1 could not be systematically performed in our cohort, one case of complete response had CPS > 100 . One long responder had CPS ≥ 1 (estimated at 15) and in two cases of hyperprogression, CPS was respectively 0 and ≥ 1 (estimated at 15). Other predictive biomarkers such as MSI status seem to be more promising than PD-L1 immunohistochemistry expression (Ding and Chen 2019). Tumor mutational burden (TMB) is also being actively investigated. However, recent findings on correlation between TMB and neoantigen formation show that TMB is unlikely to be a good candidate predictive biomarker, especially when TMB is not correlated to CD8+ neoantigens as shown in an internal cohort (67) of HNSCC.

We expected to have less mitigated results concerning the rate of variation of peripheral blood biomarkers, but with a median TTF of 3 months with nivolumab, we believe that more blood sample data on a larger population are required to identify variations with greater statistical significance. Machine learning approaches are increasingly likely to decipher trends and

variations with the application of techniques such as symbolic regression (68) which could allow to find underlying formulae of variation peripheral blood samples, and thus provide a more accurate model that could be used for prediction.

Section 5: Conclusion (EN)

This retrospective study highlights that rates of change of LWR, PLR and monitoring of inflammatory biomarkers such as NLR, during treatment by ICI may be considered as prognosis factors of response to nivolumab in R/M HNSCC. We found that high LWR at 2 cycles of nivolumab was a good prognosis factor, and that an increase in the rate of change of LWR was associated with an increase in OS and TTF. An increase in the rate of change of PLR and an increase in NLR are factors of poor prognosis. Thus, an increase in lymphocyte count on nivolumab seems to be a good biomarker of efficacy on immunotherapy. Further studies consisting of larger population sample sizes are required to validate such findings for routine use in the clinical setting.

Section 5bis : Conclusion (FR)

Cette étude rétrospective a permis de mettre en évidence et de confirmer les données de la littérature concernant des facteurs prédictifs biologiques de réponse au nivolumab dans les carcinomes épidermoïdes de la tête et du cou récidivants et/ou métastatiques, sur des prises de sang réalisées en routine. Une augmentation du taux de variation du LWR et une faible valeur de NLR en cours de traitement par nivolumab sont associées à un meilleur pronostic (augmentation de la SG et du TTF) alors qu'une augmentation du PLR et du NLR sont des facteurs de mauvais pronostics dans les carcinomes épidermoïdes de la tête et du cou. L'augmentation du nombre de lymphocytes sous immunothérapie semble donc être un bon marqueur d'efficacité du traitement. Cependant, des études se portant sur un plus grand nombre de patients devront être réalisées afin de valider ces résultats avant une éventuelle application en pratique clinique.

Pierre CLAVELOU
Doyen-Directeur



Professeur ~~Xavier~~ DURANDO
MEDECIN
Centre Jean Perrin
N° RPPS : 10003170858
N° FINESS : 630000479

Section 6: References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424.
2. Données globales d'épidémiologie des cancers - Epidémiologie des cancers [Internet]. Données globales d'épidémiologie des cancers. [cited 2020 Nov 29]. Available from: https://www.e-cancer.fr/content/download/266450/3759432/file/Synthese_Estimations%20nationales%20incidence%20et%20mortalite%20par%20cancer_juillet_2019.pdf
3. Palle C. Les évolutions de la consommation d'alcool en France et ses conséquences 2000-2018. :18.
4. Consommation d'alcool en France : où en sont les Français ? [Internet]. [cited 2020 Dec 16]. Available from: </les-actualites/2020/consommation-d-alcool-en-france-ou-en-sont-les-francais>
5. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Five-Year Survival and Correlates Among Patients With Advanced Melanoma, Renal Cell Carcinoma, or Non–Small Cell Lung Cancer Treated With Nivolumab. *JAMA Oncol*. 2019 Oct;5(10):1411–20.
6. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015 May 21;372(21):2018–28.
7. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee J-L, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. *N Engl J Med*. 2017 16;376(11):1015–26.
8. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2015 Nov 5;373(19):1803–13.
9. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2017;18(3):312–22.
10. Fuchs CS, Doi T, Jang RW, Muro K, Satoh T, Machado M, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. *JAMA Oncol*. 2018 10;4(5):e180013.
11. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet Lond Engl*. 2017 Jun 24;389(10088):2492–502.
12. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015 Jan 22;372(4):311–9.
13. Overman MJ, McDermott R, Leach JL, Lonardi S, Lenz H-J, Morse MA, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017;18(9):1182–91.
14. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med*. 2016 Nov 10;375(19):1856–67.
15. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn M-J, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet Lond Engl*. 2019 12;393(10167):156–67.
16. Ferris RL, Blumenschein G, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncol*. 2018;81:45–51.
17. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer*. 2016 May;16(5):275–87.
18. Jiménez-Sánchez A, Memon D, Pourpe S, Veeraraghavan H, Li Y, Vargas HA, et al. Heterogeneous Tumor-Immune Microenvironments among Differentially Growing Metastases in an Ovarian Cancer Patient. *Cell*. 2017 Aug 24;170(5):927-938.e20.
19. Karpathiou G, Casteillo F, Giroult J-B, Forest F, Fournel P, Monaya A, et al. Prognostic impact of immune microenvironment in laryngeal and pharyngeal squamous cell carcinoma: Immune cell subtypes, immunosuppressive pathways and clinicopathologic characteristics. *Oncotarget*. 2017 Mar 21;8(12):19310–22.

20. Kulangara K, Hanks DA, Waldroup S, Peltz L, Shah S, Roach C, et al. Development of the combined positive score (CPS) for the evaluation of PD-L1 in solid tumors with the immunohistochemistry assay PD-L1 IHC 22C3 pharmDx. *J Clin Oncol*. 2017 May 20;35(15_suppl):e14589–e14589.
21. Ma Y, Wang Q, Dong Q, Zhan L, Zhang J. How to differentiate pseudoprogression from true progression in cancer patients treated with immunotherapy. *Am J Cancer Res*. 2019 Aug 1;9(8):1546–53.
22. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017 Mar 1;18(3):e143–52.
23. Saâda-Bouزيد E, Defaucheux C, Karabajakian A, Coloma VP, Servois V, Paoletti X, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol Off J Eur Soc Med Oncol*. 2017 Jul 1;28(7):1605–11.
24. Adashek JJ, Subbiah IM, Matos I, Garralda E, Menta AK, Ganeshan DM, et al. Hyperprogression and Immunotherapy: Fact, Fiction, or Alternative Fact? *Trends Cancer*. 2020 Mar 1;6(3):181–91.
25. Carroll K, Tringale KR, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2017 May 20;35(15_suppl):6026–6026.
26. Zargar M, McFarlane T, Chan KKW, Wong WWL. Cost-Effectiveness of Nivolumab in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma. *The Oncologist*. 2018 Feb;23(2):225–33.
27. Schernberg A, Sagaon-Teyssier L, Schwarzingler M. Clinical and economic burden of head and neck cancer: a nationwide retrospective cohort study from France. *Clin Outcomes Res CEOR*. 2019 Jul 22;11:441–51.
28. Tringale KR, Carroll KT, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness Analysis of Nivolumab for Treatment of Platinum-Resistant Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck. *J Natl Cancer Inst*. 2018 01;110(5):479–85.
29. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol*. 2020 Nov;20(11):651–68.
30. Burugu S, Dancsok AR, Nielsen TO. Emerging targets in cancer immunotherapy. *Semin Cancer Biol*. 2018;52(Pt 2):39–52.
31. de Ruiter EJ, Ooft ML, Devriese LA, Willems SM. The prognostic role of tumor infiltrating T-lymphocytes in squamous cell carcinoma of the head and neck: A systematic review and meta-analysis. *Oncoimmunology [Internet]*. 2017 Aug 9 [cited 2020 Dec 14];6(11). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674970/>
32. Ho WJ, Yarchoan M, Hopkins A, Mehra R, Grossman S, Kang H. Association between pretreatment lymphocyte count and response to PD1 inhibitors in head and neck squamous cell carcinomas. *J Immunother Cancer*. 2018 31;6(1):84.
33. Campian JL, Sarai G, Ye X, Marur S, Grossman SA. Association between severe treatment-related lymphopenia and progression-free survival in patients with newly diagnosed squamous cell head and neck cancer. *Head Neck*. 2014 Dec;36(12):1747–53.
34. Granot Z. Neutrophils as a Therapeutic Target in Cancer. *Front Immunol [Internet]*. 2019 [cited 2020 Nov 15];10. Available from: <https://www.frontiersin.org/articles/10.3389/fimmu.2019.01710/full>
35. Capone M, Giannarelli D, Mallardo D, Madonna G, Festino L, Grimaldi AM, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. *J Immunother Cancer*. 2018 16;6(1):74.
36. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. *Lung Cancer Amst Neth*. 2017;111:176–81.
37. Foster CC, Kochanny S, Khattri A, Acharya R, Dekker A, Tan Y-HC, et al. Association of a baseline neutrophil-to-lymphocyte ratio (NLR) with progression-free and overall survival in head and neck cancer patients receiving anti-PD-1 therapy. *J Clin Oncol*. 2018 May 20;36(15_suppl):6038–6038.
38. Lalani A-KA, Xie W, Martini DJ, Steinharter JA, Norton CK, Krajewski KM, et al. Change in Neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. *J Immunother Cancer*. 2018 22;6(1):5.
39. Russo A, Franchina T, Ricciardi GRR, Battaglia A, Scimone A, Berenato R, et al. Baseline neutrophilia, derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), and outcome in non small cell lung cancer (NSCLC) treated with Nivolumab or Docetaxel. *J Cell Physiol*. 2018;233(10):6337–43.

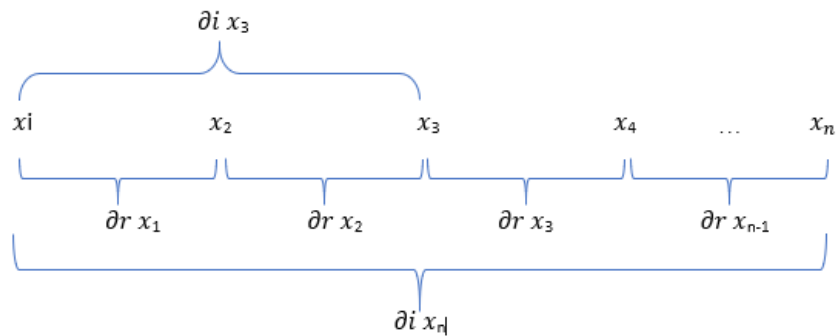
40. Ueda T, Chikui N, Takumida M, Furuie H, Kono T, Taruya T, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) is associated with clinical outcome in recurrent or metastatic head and neck cancer patients treated with nivolumab. *Acta Otolaryngol (Stockh)*. 2020 Feb;140(2):181–7.
41. Grisaru-Tal S, Itan M, Klion AD, Munitz A. A new dawn for eosinophils in the tumour microenvironment. *Nat Rev Cancer*. 2020 Oct;20(10):594–607.
42. Martinelli-Kläy CP, Mendis BRRN, Lombardi T. Eosinophils and Oral Squamous Cell Carcinoma: A Short Review [Internet]. Vol. 2009, *Journal of Oncology*. Hindawi; 2009 [cited 2020 Nov 18]. p. e310132. Available from: <https://www.hindawi.com/journals/jo/2009/310132/>
43. Qian B, Pollard JW. Macrophage Diversity Enhances Tumor Progression and Metastasis. *Cell*. 2010 Apr 2;141(1):39–51.
44. Marone G, Gambardella AR, Mattei F, Mancini J, Schiavoni G, Varricchi G. Basophils in Tumor Microenvironment and Surroundings. *Adv Exp Med Biol*. 2020;1224:21–34.
45. Marone G, Schroeder JT, Mattei F, Loffredo S, Gambardella AR, Poto R, et al. Is There a Role for Basophils in Cancer? *Front Immunol*. 2020;11:2103.
46. Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P, et al. Platelet “first responders” in wound response, cancer, and metastasis. *Cancer Metastasis Rev*. 2017 Jun 1;36(2):199–213.
47. Palacios-Acedo AL, Mège D, Crescence L, Dignat-George F, Dubois C, Panicot-Dubois L. Platelets, Thrombo-Inflammation, and Cancer: Collaborating With the Enemy. *Front Immunol* [Internet]. 2019 [cited 2020 Nov 21];10. Available from: <https://www.frontiersin.org/articles/10.3389/fimmu.2019.01805/full#B26>
48. Masucci MT, Minopoli M, Del Vecchio S, Carriero MV. The Emerging Role of Neutrophil Extracellular Traps (NETs) in Tumor Progression and Metastasis. *Front Immunol* [Internet]. 2020 [cited 2020 Dec 15];11. Available from: <https://www.frontiersin.org/articles/10.3389/fimmu.2020.01749/full>
49. Grimm M, Rieth J, Hoefert S, Krimmel M, Rieth S, Teriete P, et al. Standardized pretreatment inflammatory laboratory markers and calculated ratios in patients with oral squamous cell carcinoma. *Eur Arch Oto-Rhino-Laryngol Off J Eur Fed Oto-Rhino-Laryngol Soc EUFOS Affil Ger Soc Oto-Rhino-Laryngol - Head Neck Surg*. 2016 Oct;273(10):3371–84.
50. Ogata T, Satake H, Ogata M, Hatachi Y, Inoue K, Hamada M, et al. Neutrophil-to-lymphocyte ratio as a predictive or prognostic factor for gastric cancer treated with nivolumab: a multicenter retrospective study. *Oncotarget*. 2018 Oct 2;9(77):34520–7.
51. Bilen MA, Martini DJ, Liu Y, Lewis C, Collins HH, Shabto JM, et al. The prognostic and predictive impact of inflammatory biomarkers in patients who have advanced-stage cancer treated with immunotherapy. *Cancer*. 2019 01;125(1):127–34.
52. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. *Sci Rep*. 2019 Dec 23;9(1):19673.
53. Shi M, Zhao W, Zhou F, Chen H, Tang L, Su B, et al. Neutrophil or platelet-to-lymphocyte ratios in blood are associated with poor prognosis of pulmonary large cell neuroendocrine carcinoma. *Transl Lung Cancer Res*. 2020 Feb;9(1):45–54.
54. Petrova MP, Eneva MI, Arabadjiev JI, Conev NV, Dimitrova EG, Koynov KD, et al. Neutrophil to lymphocyte ratio as a potential predictive marker for treatment with pembrolizumab as a second line treatment in patients with non-small cell lung cancer. *Biosci Trends*. 2020;14(1):48–55.
55. Haddad CR, Guo L, Clarke S, Guminski A, Back M, Eade T. Neutrophil-to-lymphocyte ratio in head and neck cancer. *J Med Imaging Radiat Oncol*. 2015;59(4):514–9.
56. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell*. 2012 Mar 20;21(3):309–22.
57. Haddad R, Concha-Benavente F, Blumenschein G, Fayette J, Guigay J, Colevas AD, et al. Nivolumab treatment beyond RECIST-defined progression in recurrent or metastatic squamous cell carcinoma of the head and neck in CheckMate 141: A subgroup analysis of a randomized phase 3 clinical trial. *Cancer*. 2019 Sep 15;125(18):3208–18.
58. Schvartsman G, Peng SA, Bis G, Lee JJ, Benveniste MFK, Zhang J, et al. Response rates to single-agent chemotherapy after exposure to immune checkpoint inhibitors in advanced non-small cell lung cancer. *Lung Cancer Amst Neth*. 2017 Oct;112:90–5.
59. Szabados B, van Dijk N, Tang YZ, van der Heijden MS, Wimalasingham A, Gomez de Liano A, et al. Response Rate to Chemotherapy After Immune Checkpoint Inhibition in Metastatic Urothelial Cancer. *Eur Urol*. 2018 Feb 1;73(2):149–52.

60. Sukari A, Nagasaka M, Abdallah N. Responses in patients receiving sequential paclitaxel post progression on PD1 inhibitors. *Oral Oncol*. 2018 May;80:100–2.
61. Fushimi C, Okamoto I, Matsuki T, Masubuchi T, Okada T, Sato H, et al. Salvage Chemotherapy After Nivolumab for Recurrent or Metastatic Head and Neck Carcinoma. *Anticancer Res*. 2020 Sep;40(9):5277–83.
62. Sato Y, Fukuda N, Fujiwara YU, Wang X, Urasaki T, Ohmoto A, et al. Efficacy of Paclitaxel-based Chemotherapy After Progression on Nivolumab for Head and Neck Cancer. *Vivo Athens Greece*. 2021 Apr;35(2):1211–5.
63. Peng L, Qin B-D, Xiao K, Xu S, Yang J-S, Zang Y-S, et al. A meta-analysis comparing responses of Asian versus non-Asian cancer patients to PD-1 and PD-L1 inhibitor-based therapy. *Oncol Immunology*. 2020 Jan 1;9(1):1781333.
64. Li M, Spakowicz D, Burkart J, Patel S, Husain M, He K, et al. Change in neutrophil to lymphocyte ratio during immunotherapy treatment is a non-linear predictor of patient outcomes in advanced cancers. *J Cancer Res Clin Oncol*. 2019 Oct;145(10):2541–6.
65. Park JC, Durbeck J, Clark JR. Predictive value of peripheral lymphocyte counts for immune checkpoint inhibitor efficacy in advanced head and neck squamous cell carcinoma. *Mol Clin Oncol [Internet]*. 2020 Dec [cited 2021 Mar 13];13(6). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7657085/>
66. Burtneess B, Harrington KJ, Greil R, Soulières D, Tahara M, Castro G de, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet*. 2019 Nov 23;394(10212):1915–28.
67. McGrail DJ, Pilié PG, Rashid NU, Voorwerk L, Slagter M, Kok M, et al. High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types. *Ann Oncol [Internet]*. 2021 Mar 15 [cited 2021 Mar 20];0(0). Available from: [https://www.annalsofncology.org/article/S0923-7534\(21\)00123-X/abstract](https://www.annalsofncology.org/article/S0923-7534(21)00123-X/abstract)
68. Udrescu S-M, Tegmark M. AI Feynman: A physics-inspired method for symbolic regression. *Sci Adv*. 2020 Apr 1;6(16):eaay2631.

Section 7: Appendix and Supplementary material

Appendix I: How variations of peripheral blood parameters were calculated ?

The exact methodology for calculation of variations is as follows :



By definition, x is the variable investigated and its value (e.g LWR, PLR, NLR etc ...).
 i is the initial blood parameter before administration of nivolumab. Subsequently, x_2, x_3, \dots, x_n are the respective blood sample analysis performed, every 2 cycles (or every month) of nivolumab.

For example: Let x = Lymphocyte to total white blood cell ratio (LWR),

Then, the rate of change from initial values ($\partial i (x)$) to the x_n^{th} blood sample performed would be as follows:

$$\partial i LWR = \frac{LWR_n - LWR_i}{LWR_i}$$

And the rate of change between two consecutive blood samples, would be as follows:

$$\partial r LWR = \frac{LWR_n - LWR_{n-1}}{LWR_n}$$

This would give respectively the rate of change of initial values of LWR and the relative rate of change of values of LWR between two given blood samples.

Appendix II: TNM Staging according to primary tumor location

TABLE III: TNM¹ STAGING ACCORDING TO PRIMARY TUMOR LOCATION

Primary tumor location	Total n (%)	Staging ¹	n
Hypopharyngeal	13 (30)	I	1
		II	3
		III	2
		IVA	5
		IVB	2
Oral cavity	13 (30)	I	0
		II	1
		III	2
		IVA	10
		IVB	0
Oropharyngeal	11 (25)	I	1
		II	3
		III	6
		IVA	0
		IVB	0
		IVC	2
Other	6 (14)	III	4
		IVB	2

1: TNM CLASSIFICATION FOR HEAD AND NECK CANCER, 8TH EDITION

N : ABSOLUTE NUMBER OF PATIENTS

Appendix III: Immune-related adverse effects (irAEs)

TABLE IV : IMMUNE-RELATED ADVERSE EFFECTS

irAE	Number (%)
Digestive	
Grade 0	36 (81.8)
Grade 1	6 (13.6)
Grade 2	2 (4.5)
Grade ≥ 3	0
Respiratory	
Grade 0	37 (84.1)
Grade 1	6 (13.6)
Grade 2	1 (2.3)
Grade ≥ 3	0
Cutaneous	
Grade 0	37 (84.1)
Grade 1	4 (9.1)
Grade 2	2 (4.5)
Grade ≥ 3	1 (2.3)
Other	
Grade 0	43 (97.7)
Grade 1	0
Grade 2	0
Grade ≥ 3	1 (2.3)

Abbreviations : irAE : immune-related adverse events ; Grades according to the CTCAE v4.0

Appendix IV: Response to nivolumab data

Multivariate analysis

No	Variable	Niveau	Est	OR (IC 95%)	p	p modèle
1	Meta.Ganglions.Nivo	Oui	1.483	4.404 (1.085 -- 20.266)	.044	.013
2	NLR.2		-0.109	0.897 (0.770 -- 0.992)	.09	

Univariate – Qualitative data

No	Variable	OR	95% CI	p	p adjust	RR
19	Meta.Ganglions.Nivo	4.35	(0.99 -- 21.18)	.029	.42	2.32
20	Meta.Autre.Nivo	0.17	(0.01 -- 1)	.042	.42	0.27
8	Tabagisme			.094	.483	
11	Respiratory			.097	.483	
3	Loc.primitif			.126	.503	
12	Cutaneous			.178	.592	
18	Meta.Poumon.Nivo	0.45	(0.09 -- 1.86)	.341	.913	0.65
1	Sexe	3.48	(0.33 -- 179.81)	.38	.913	1.16
17	Stade.Nivo			.411	.913	
4	cT			.51	.954	
2	PS			.525	.954	
13	Chirurgie.R1	0.36	(0 -- 4.11)	.632	.977	0.39
10	Digestive			.686	.977	
5	cN			.73	.977	
16	Prior.Cetu	1.57	(0.33 -- 8.68)	.733	.977	1.15
6	cM	0.89	(0.01 -- 18.63)	.99	.99	0.89
7	Stade.diag			.99	.99	
9	Alcohol			.99	.99	
14	Reirradiation	1.12	(0.08 -- 11.23)	.99	.99	1.11
15	RT.meta	1.21	(0.2 -- 6.46)	.99	.99	1.16

Univariate – Quantitative data

No	Variable	Est (Oui - Non)	95% CI	p	p adjust
1	Age.trt.loc	-3.00	(-8.99 -- 4)	.333	.752
2	BMI	-1.15	(-3.52 -- 1.16)	.24	.719
3	Delai.trtloc.Nivo	-5.00	(-16 -- 7)	.37	.752
22	LWR.1	-0.02	(-0.08 -- 0.03)	.298	.752
23	LWR.2	-0.05	(-0.09 -- 0.01)	.069	.593
24	LWR.3	-0.04	(-0.1 -- 0)	.062	.593
25	LWR.4	0.01	(-0.07 -- 0.08)	.936	.976
26	LWRdi.2	-0.18	(-0.45 -- 0.07)	.135	.593
27	LWRdi.3	-0.09	(-0.41 -- 0.21)	.478	.763
28	LWRdi.4	-0.02	(-0.36 -- 0.23)	.767	.959
29	LWRdr.3	0.09	(-0.12 -- 0.35)	.383	.752
30	LWRdr.4	-0.02	(-0.3 -- 0.37)	.927	.976
4	NLR.1	1.42	(-1.09 -- 3.99)	.335	.752
5	NLR.2	2.88	(-0.21 -- 7.8)	.084	.593
6	NLR.3	2.22	(-0.27 -- 5.93)	.062	.593
7	NLR.4	-0.03	(-3.4 -- 2.54)	.979	.979
8	NLRdi.2	0.32	(-0.12 -- 0.76)	.196	.655
9	NLRdi.3	0.18	(-0.19 -- 0.86)	.413	.752
10	NLRdi.4	0.17	(-0.46 -- 0.78)	.572	.817
11	NLRdr.3	-0.15	(-0.48 -- 0.24)	.426	.752
12	NLRdr.4	0.04	(-0.56 -- 0.42)	.879	.976
13	PLR.1	-15.98	(-212.92 -- 99.07)	.71	.959
14	PLR.2	-4.22	(-165.31 -- 144.51)	.944	.976
15	PLR.3	85.40	(-30.4 -- 217.75)	.158	.593
16	PLR.4	7.99	(-279.79 -- 141.57)	.851	.976
17	PLRdi.2	0.06	(-0.17 -- 0.42)	.563	.817
18	PLRdi.3	0.21	(-0.09 -- 0.63)	.147	.593
19	PLRdi.4	0.30	(-0.04 -- 0.75)	.12	.593
20	PLRdr.3	0.05	(-0.23 -- 0.36)	.762	.959
21	PLRdr.4	0.14	(-0.2 -- 0.49)	.483	.763

Appendix V: Time-to-Treatment failure data

Multivariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p modèle
1	LWRdr.4		-3.000	0.050 (0.009 -- 0.285)	.001	
2	PS	2-3	2.463	11.737 (2.753 -- 50.040)	.001	< .001
3	Reponse.site.Prim	Oui	-2.787	0.062 (0.015 -- 0.262)	< .001	

Univariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p adjust
12	Age.trt.loc		-0.033	0.967 (0.937 -- 0.999)	.051	.134
8	Alcohol	Active	-0.031	0.969 (0.481 -- 1.951)	.93	.948
13	BMI		-0.093	0.911 (0.827 -- 1.004)	.053	.134
14	Chirurgie.R1	Oui	0.889	2.434 (1.001 -- 5.919)	.075	.166
5	cM	1	1.183	3.263 (0.952 -- 11.189)	.101	.191
4	cN	2-3	0.101	1.106 (0.560 -- 2.182)	.77	.836
3	cT	3-4	0.359	1.431 (0.654 -- 3.131)	.353	.5
11	Cutaneous	1-3	-0.089	0.915 (0.399 -- 2.099)	.833	.867
18	Delai.trtloc.Nivo		-0.005	0.995 (0.987 -- 1.003)	.177	.273
9	Digestive	1-2	0.094	1.099 (0.495 -- 2.443)	.818	.867
2	Loc.primitif	Hypopharyngea	0.540	1.715 (0.678 -- 4.337)	.488	.638
43	LWR.1		-6.007	0.002 (0.000 -- 0.102)	.001	.006
44	LWR.2		-8.894	0.000 (0.000 -- 0.019)	< .001	.001
45	LWR.3		-6.714	0.001 (0.000 -- 0.297)	.01	.048
46	LWR.4		-8.656	0.000 (0.000 -- 0.072)	.002	.017
47	LWRdi.2		-0.509	0.601 (0.265 -- 1.366)	.204	.305
48	LWRdi.3		0.243	1.275 (0.590 -- 2.755)	.551	.668
49	LWRdi.4		-0.287	0.750 (0.284 -- 1.980)	.539	.668
50	LWRdr.3		0.842	2.320 (1.209 -- 4.452)	.026	.089
51	LWRdr.4		-1.952	0.142 (0.033 -- 0.604)	.009	.044
22	Meta.Autre.Nivo	Oui	0.463	1.589 (0.852 -- 2.964)	.155	.254
21	Meta.Ganglions.Nivc	Oui	-0.391	0.676 (0.364 -- 1.256)	.212	.309
20	Meta.Poumon.Nivo	Oui	0.158	1.171 (0.642 -- 2.136)	.607	.703
25	NLR.1		0.081	1.085 (1.037 -- 1.135)	.001	.012
26	NLR.2		0.097	1.102 (1.061 -- 1.146)	< .001	.001
27	NLR.3		0.079	1.082 (1.040 -- 1.125)	.001	.007
28	NLR.4		0.067	1.069 (1.026 -- 1.114)	.007	.039
29	NLRdi.2		0.545	1.725 (1.143 -- 2.602)	.018	.069
30	NLRdi.3		0.229	1.257 (0.757 -- 2.088)	.388	.535
31	NLRdi.4		0.239	1.270 (0.993 -- 1.626)	.096	.191
32	NLRdr.3		-0.805	0.447 (0.189 -- 1.059)	.062	.143
33	NLRdr.4		0.392	1.479 (1.079 -- 2.029)	.034	.097
34	PLR.1		0.001	1.001 (1.000 -- 1.002)	.028	.089
35	PLR.2		0.001	1.001 (1.000 -- 1.002)	.015	.063
36	PLR.3		0.001	1.001 (1.000 -- 1.002)	.153	.254
37	PLR.4		0.001	1.001 (1.000 -- 1.002)	.111	.196
38	PLRdi.2		0.609	1.839 (1.030 -- 3.280)	.055	.134
39	PLRdi.3		0.556	1.743 (0.974 -- 3.121)	.083	.176
40	PLRdi.4		0.295	1.343 (0.933 -- 1.934)	.162	.259
41	PLRdr.3		-0.337	0.714 (0.227 -- 2.244)	.564	.668
42	PLRdr.4		0.314	1.369 (0.990 -- 1.894)	.105	.191
17	Prior.Cetu	Yes	-0.804	0.448 (0.226 -- 0.887)	.027	.089
1	PS	2-3	0.796	2.216 (1.106 -- 4.436)	.03	.089
15	Reirradiation	Yes	-0.173	0.842 (0.329 -- 2.153)	.713	.791
24	Rep.Meta	Oui	-1.231	0.292 (0.121 -- 0.702)	.006	.035
23	Reponse.site.Prim	Oui	-1.675	0.187 (0.085 -- 0.412)	< .001	.001
10	Respiratory	1-2	0.753	2.124 (0.919 -- 4.913)	.102	.191
16	RT.meta	Yes	0.220	1.246 (0.636 -- 2.440)	.528	.668
6	Stade.diag	Reg-Meta	0.129	1.138 (0.610 -- 2.121)	.683	.774
19	Stade.Nivo	Regional	0.377	1.387 (0.375 -- 5.122)	.454	.61
7	Tabagisme	Active	0.013	1.013 (0.544 -- 1.887)	.967	.967
		Oropharyngeal	-0.083	0.920 (0.349 -- 2.427)		
		Oral cavity	0.201	1.222 (0.487 -- 3.070)		
		Metastatic	0.618	1.855 (0.562 -- 6.122)		

Appendix VI: Progression-free survival data

Multivariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p modèle
1	PLRdi.3		0.561	1.752 (1.028 -- 2.984)	.039	< .001
2	Reponse.site.Prim	Oui	-2.088	0.124 (0.048 -- 0.323)	< .001	

Univariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p adjust
12	Age.trt.loc		-0.03	0.964 (0.930 -- 0.998)	.052	.243
8	Alcohol	Active	0.331	1.393 (0.683 -- 2.840)	.373	.595
13	BMI		-0.07	0.927 (0.843 -- 1.019)	.108	.324
14	Chirurgie.R1	Oui	0.399	1.491 (0.616 -- 3.604)	.397	.595
5	cM	1	1.185	3.272 (0.934 -- 11.46)	.103	.324
4	cN	2-3	-0.147	0.863 (0.434 -- 1.718)	.678	.786
3	cT	3-4	0.401	1.494 (0.685 -- 3.258)	.295	.579
11	Cutaneous	1-3	-0.20	0.811 (0.354 -- 1.857)	.613	.727
18	Delai.trtloc.Nivo		-0.00	0.997 (0.989 -- 1.004)	.372	.595
9	Digestive	1-2	-0.05	0.948 (0.431 -- 2.084)	.894	.93
2	Loc.primitif	Hypopharyngea	0.468	1.597 (0.605 -- 4.216)	.42	.595
43	LwR.1		-5.05	0.006 (0.000 -- 0.26)	.004	.028
44	LwR.2		-6.07	0.002 (0.000 -- 0.195)	.003	.026
45	LwR.3		-5.26	0.005 (0.000 -- 0.98)	.04	.202
46	LwR.4		-3.39	0.033 (0.000 -- 3.33)	.14	.357
47	LwRdi.2		-0.31	0.727 (0.329 -- 1.606)	.417	.595
48	LwRdi.3		0.126	1.134 (0.525 -- 2.450)	.753	.817
49	LwRdi.4		0.023	1.023 (0.484 -- 2.166)	.952	.952
50	LwRdr.3		0.450	1.568 (0.793 -- 3.100)	.226	.502
51	LwRdr.4		-0.68	0.506 (0.155 -- 1.646)	.265	.547
22	Meta.Autre.Nivo	Oui	0.553	1.739 (0.920 -- 3.286)	.096	.324
21	Meta.Ganglions.Nivo	Oui	-0.73	0.481 (0.248 -- 0.932)	.027	.171
20	Meta.Poumon.Nivo	Oui	0.261	1.298 (0.639 -- 2.409)	.409	.595
25	NLR.1		0.077	1.080 (1.031 -- 1.131)	.003	.026
26	NLR.2		0.072	1.075 (1.038 -- 1.112)	.001	.015
27	NLR.3		0.067	1.069 (1.029 -- 1.111)	.003	.026
28	NLR.4		0.013	1.013 (0.979 -- 1.048)	.492	.632
29	NLRdi.2		0.421	1.524 (1.012 -- 2.295)	.065	.277
30	NLRdi.3		0.232	1.261 (0.781 -- 2.036)	.358	.595
31	NLRdi.4		0.096	1.100 (0.846 -- 1.430)	.498	.632
32	NLRdr.3		-0.39	0.675 (0.304 -- 1.501)	.332	.595
33	NLRdr.4		0.104	1.109 (0.829 -- 1.485)	.508	.632
34	PLR.1		0.000	1.000 (1.000 -- 1.001)	.381	.595
35	PLR.2		0.001	1.001 (1.000 -- 1.002)	.176	.414
36	PLR.3		0.000	1.000 (1.000 -- 1.001)	.417	.595
37	PLR.4		0.000	1.000 (0.999 -- 1.001)	.461	.632
38	PLRdi.2		0.564	1.758 (0.983 -- 3.145)	.074	.292
39	PLRdi.3		0.482	1.620 (0.950 -- 2.762)	.096	.324
40	PLRdi.4		0.271	1.311 (0.924 -- 1.861)	.179	.414
41	PLRdr.3		0.214	1.238 (0.426 -- 3.597)	.695	.788
42	PLRdr.4		0.215	1.240 (0.880 -- 1.747)	.268	.547
17	Prior.Cetu	Yes	-0.76	0.463 (0.234 -- 0.919)	.033	.189
1	PS	2-3	0.515	1.674 (0.864 -- 3.245)	.137	.357
15	Reirradiation	Yes	-0.05	0.951 (0.371 -- 2.439)	.917	.935
24	Rep.Meta	Oui	-1.387	0.250 (0.098 -- 0.64)	.003	.026
23	Reponse.site.Prim	Oui	-1.90	0.148 (0.063 -- 0.348)	< .001	< .001
10	Respiratory	1-2	0.677	1.968 (0.848 -- 4.565)	.14	.357
16	RT.meta	Yes	0.244	1.277 (0.648 -- 2.515)	.487	.632
6	Stade.diag	Reg-Meta	-0.19	0.825 (0.435 -- 1.565)	.558	.678
19	Stade.Nivo	Regional	0.046	1.047 (0.278 -- 3.946)	.718	.796
7	Tabagisme	Active	0.045	1.046 (0.553 -- 1.977)	.891	.93
		Oropharyngeal	-0.03	0.967 (0.351 -- 2.669)		
		Metastatic	0.308	1.361 (0.413 -- 4.486)		
		Oral cavity	0.542	1.720 (0.649 -- 4.557)		

Appendix VII: Overall survival data

Multivariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p modèle
1	LWRdr.4		-2.397	0.091 (0.017 -- 0.479)	.005	.001
2	Meta.Poumon	Oui	1.973	7.195 (1.821 -- 28.421)	.005	

Univariate analysis

No	Variable	Niveau	Est	HR (IC 95%)	p	p adjust
48	LWR.3		-5.210	0.005 (0.000 -- 3.656)	.085	.305
47	LWR.2		-4.675	0.009 (0.000 -- 1.552)	.053	.216
49	LWR.4		-4.711	0.009 (0.000 -- 7.507)	.146	.364
46	LWR.1		-4.614	0.010 (0.000 -- 0.654)	.019	.129
54	LWRdr.4		-2.000	0.135 (0.023 -- 0.791)	.022	.13
26	Reponse.site.Prim	Oui	-1.085	0.336 (0.151 -- 0.750)	.007	.081
23	Prior.Cetu	Yes	-1.054	0.349 (0.165 -- 0.734)	.007	.081
1	Sexe	Male	-1.026	0.359 (0.144 -- 0.895)	.047	.216
24	Rep.Nivo	Oui	-0.960	0.380 (0.174 -- 0.832)	.011	.086
27	Rep.Meta	Oui	-0.680	0.506 (0.187 -- 1.373)	.179	.387
14	Alcohol	Active	-0.600	0.548 (0.225 -- 1.336)	.161	.364
15	Digestive	1-2	-0.560	0.570 (0.216 -- 1.507)	.231	.454
10	Meta.Ganglions	Oui	-0.370	0.685 (0.317 -- 1.481)	.324	.511
13	Tabagisme	Active	-0.320	0.721 (0.349 -- 1.493)	.372	.511
17	Cutaneous	1-3	-0.280	0.755 (0.285 -- 1.997)	.560	.676
22	RT.meta	Yes	-0.170	0.843 (0.389 -- 1.827)	.662	.771
5	cN	2-3	-0.118	0.889 (0.412 -- 1.919)	.766	.844
35	NLRdr.3		-0.105	0.897 (0.329 -- 2.440)	.830	.895
52	LWRdi.4		-0.070	0.924 (0.372 -- 2.292)	.862	.895
19	BMI		-0.070	0.928 (0.838 -- 1.028)	.142	.364
7	Stade.diag	Reg-Meta	-0.070	0.932 (0.451 -- 1.925)	.850	.895
18	Age.trt.loc		-0.060	0.935 (0.898 -- 0.970)	.002	.051
50	LWRdi.2		-0.030	0.964 (0.415 -- 2.241)	.933	.95
37	PLR.1		0.000	1.000 (0.999 -- 1.001)	.671	.771
38	PLR.2		0.001	1.001 (0.999 -- 1.002)	.347	.511
40	PLR.4		0.001	1.001 (1.000 -- 1.002)	.261	.473
39	PLR.3		0.001	1.001 (1.000 -- 1.002)	.263	.473
11	Meta.Foie	Oui	0.025	1.025 (0.309 -- 3.398)	.967	.967
31	NLR.4		0.035	1.036 (0.995 -- 1.079)	.131	.364
28	NLR.1		0.049	1.050 (1.003 -- 1.099)	.051	.216
29	NLR.2		0.061	1.063 (1.018 -- 1.110)	.011	.086
30	NLR.3		0.081	1.084 (1.035 -- 1.136)	.002	.051
4	cT	3-4	0.134	1.143 (0.469 -- 2.786)	.766	.844
25	Durée.trt.loc		0.188	1.206 (0.966 -- 1.507)	.152	.364
34	NLRdi.4		0.226	1.254 (0.943 -- 1.667)	.159	.364
51	LWRdi.3		0.252	1.286 (0.565 -- 2.928)	.564	.676
33	NLRdi.3		0.252	1.286 (0.732 -- 2.260)	.394	.519
41	PLRdi.2		0.271	1.312 (0.698 -- 2.466)	.415	.534
43	PLRdi.4		0.285	1.330 (0.874 -- 2.023)	.235	.454
2	PS	2-3	0.288	1.334 (0.633 -- 2.812)	.455	.571
32	NLRdi.2		0.322	1.380 (0.835 -- 2.279)	.226	.454
12	Meta.Autre	Oui	0.339	1.403 (0.688 -- 2.861)	.355	.511
45	PLRdr.4		0.352	1.422 (0.956 -- 2.115)	.131	.364
53	LWRdr.3		0.373	1.452 (0.695 -- 3.032)	.350	.511
36	NLRdr.4		0.387	1.472 (1.030 -- 2.104)	.056	.216
9	Meta.Os	Oropharyngeal Oui	0.387	1.473 (0.426 -- 5.089)		
39	Meta.Os	Oui	0.399	1.490 (0.632 -- 3.513)	.375	.511
42	PLRdi.3		0.509	1.663 (0.870 -- 3.179)	.148	.364
21	Reirradiation	Yes	0.535	1.708 (0.653 -- 4.466)	.304	.511
44	PLRdr.3		0.617	1.854 (0.500 -- 6.874)	.356	.511
6	cM	1	0.642	1.900 (0.562 -- 6.418)	.335	.511
20	Chirurgie.R1	Oui	0.686	1.985 (0.812 -- 4.853)	.162	.364
8	Meta.Poumon	Oui	0.707	2.028 (0.995 -- 4.137)	.052	.216
3	Loc.primitif	Oral cavity Hypopharyngea	0.826	2.284 (0.726 -- 7.189)		
3	Loc.primitif	Hypopharyngea	0.865	2.375 (0.746 -- 7.566)	.346	.511
16	Respiratory	1-2	1.576	4.834 (1.905 -- 12.260)	.003	.051

Conseil national de l'ordre des médecins)

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.

WONG CHONG Jonathan

Signature

SERMENT D'HIPPOCRATE

En présence des Maîtres de cette FACULTE et de mes chers CONDISCIPLES, je promets et je jure d'être fidèle aux lois de l'Honneur et de la Probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et je n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes MAÎTRES, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les HOMMES m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'OPPROBRE et méprisé de mes confrères si j'y manque.

WONG CHONG Jonathan

Signature

Facteurs biologiques prédictifs de réponse au nivolumab dans les carcinomes épidermoïdes de la tête et du cou

Contexte: Plus de 80% des patients recevant du nivolumab en 2^{ème} ligne de traitement dans les carcinomes épidermoïdes de la tête et du cou (CETEC) récidivants et/ou métastatiques n'obtiendront aucun bénéfice au traitement, sans qu'il soit possible de les identifier.

Objectif principal: Déterminer la corrélation entre les variations des paramètres sanguins tels que le rapport neutrophiles sur lymphocytes (NLR), plaquettes sur lymphocytes (PLR), lymphocytes sur globules blancs totaux (LWR) et la réponse au nivolumab dans les CETEC.

Matériels et Méthodes: Nous avons analysé rétrospectivement les données biologiques de 44 patients atteints de CETEC ayant reçu du nivolumab et au moins une ligne antérieure de traitement systémique au Centre Jean Perrin, France de mars 2018 à décembre 2020.

Résultats: Le taux de réponses objectives était de 15.9%. Un NLR bas à 2 cycles de nivolumab était associé à une meilleure réponse [OR=0.897, p=0.013]. La médiane de survie globale (SG) était de 17 mois (CI95% 14-28). Une augmentation du LWR du 6^{ème} au 8^{ème} cycle de nivolumab était associée à une meilleure survie globale [HR=0.091, p=0.005]. La médiane de survie sans progression (SSP) était de 3 mois. L'augmentation du PLR entre la valeur initiale et le 6^{ème} cycle de nivolumab était associée à une diminution de la SSP [HR= 1.752, p=0.039]. Les patients ayant un NLR ≤ 5 et PLR ≤ 150 avaient une médiane de délai avant arrêt du traitement (TTF) augmentée de 1 à 3 mois (p=0.012) et de 3 à 5 mois (p=0.027) par rapport aux patients ayant un NLR > 5 et PLR > 150 respectivement. L'augmentation du LWR du 6^{ème} au 8^{ème} cycle était significativement associée à une augmentation du TTF [HR= 0.050, p=0.001].

Conclusion: Une augmentation du taux de variation du LWR et une faible valeur de NLR en cours de traitement par nivolumab sont associées à une augmentation de la SG et du TTF. Une augmentation du PLR et du NLR sont des facteurs de mauvais pronostics. L'augmentation du nombre de lymphocytes sous immunothérapie semble être un bon marqueur d'efficacité du traitement dans les CETEC.

Mots-clés :

- Nivolumab
- HNSCC
- NLR
- LWR
- Facteurs prédictifs
- Pronostics
- PD-1/PD-L1
- Carcinomes épidermoïdes