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Jonathan Wong Chong

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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

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A mon jury de thèse

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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.

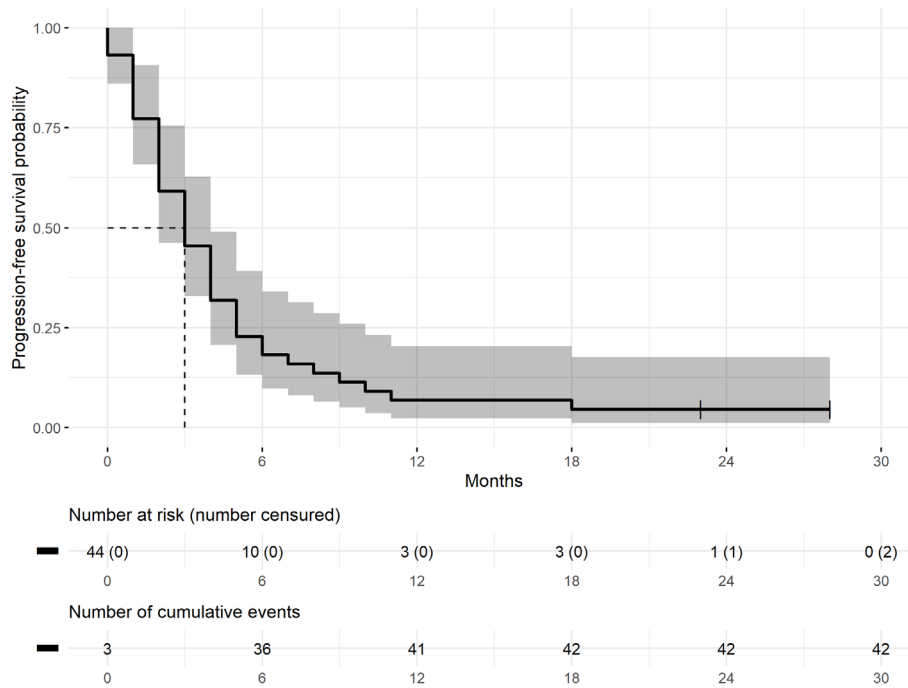


FIGURE 1: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS)

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).

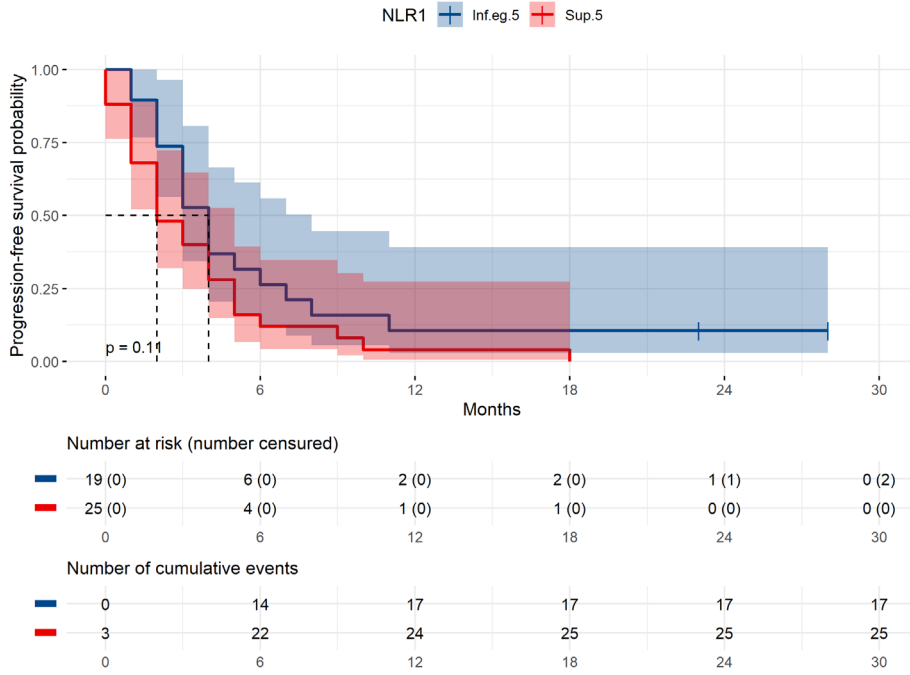


FIGURE 2: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS) (NLR=5)

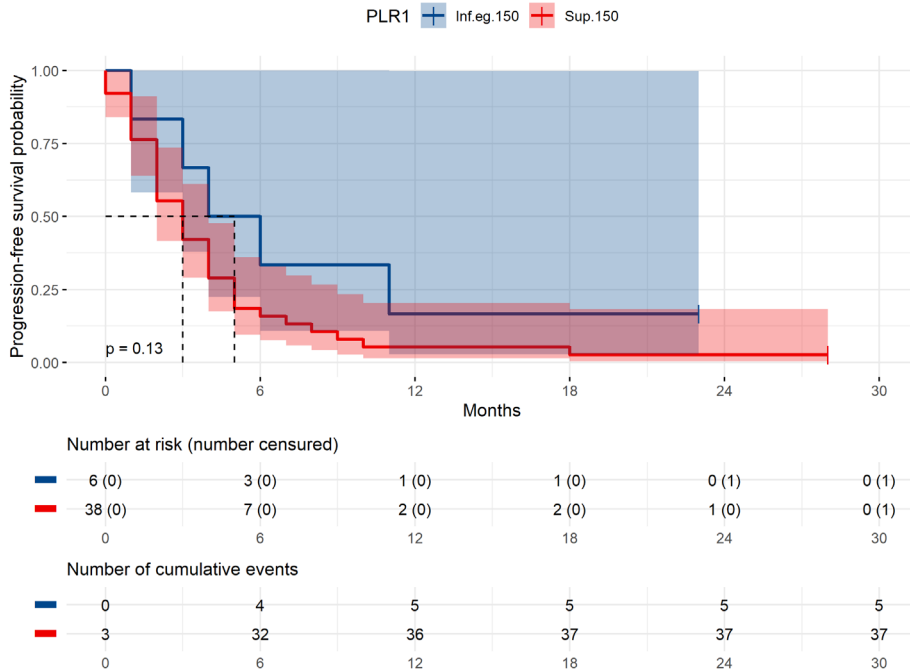


FIGURE 3: KAPLAN-MEIER CURVE OF PROGRESSION-FREE-SURVIVAL (PFS) (PLR=150)

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.

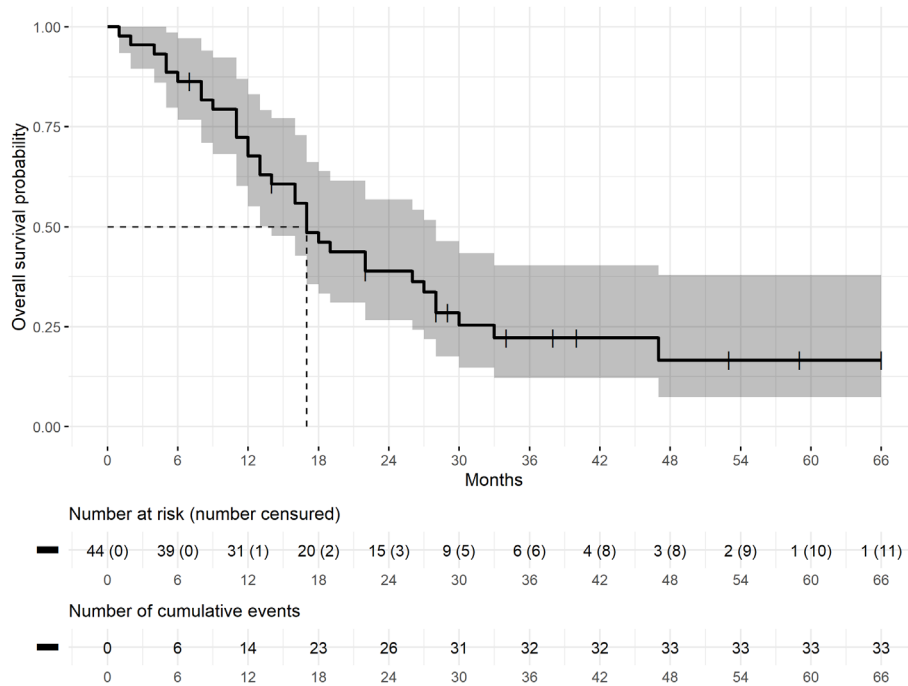


FIGURE 4: KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS)

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.

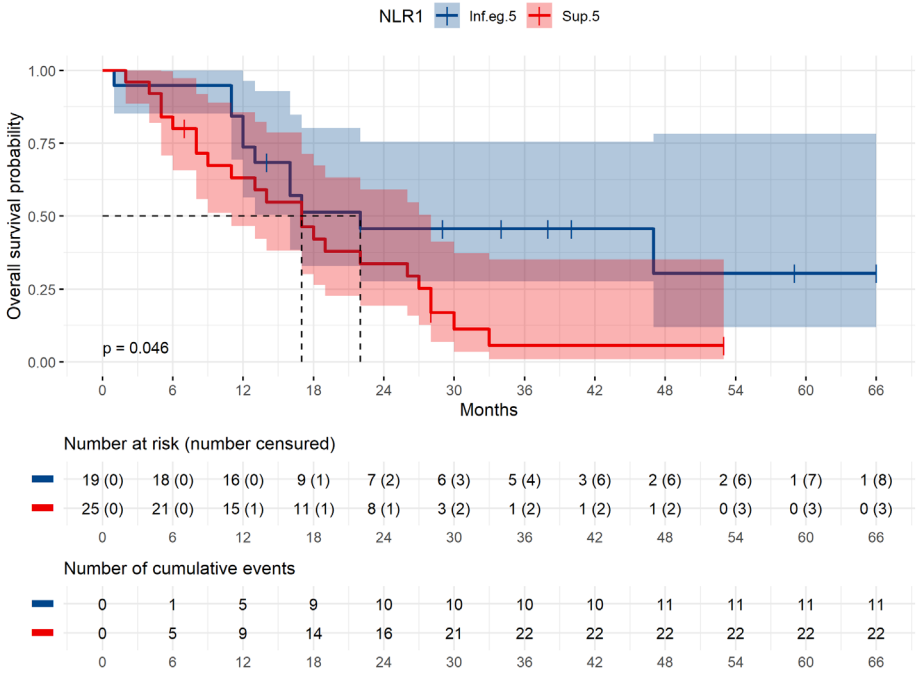


FIGURE 5: KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS) (NLR=5)

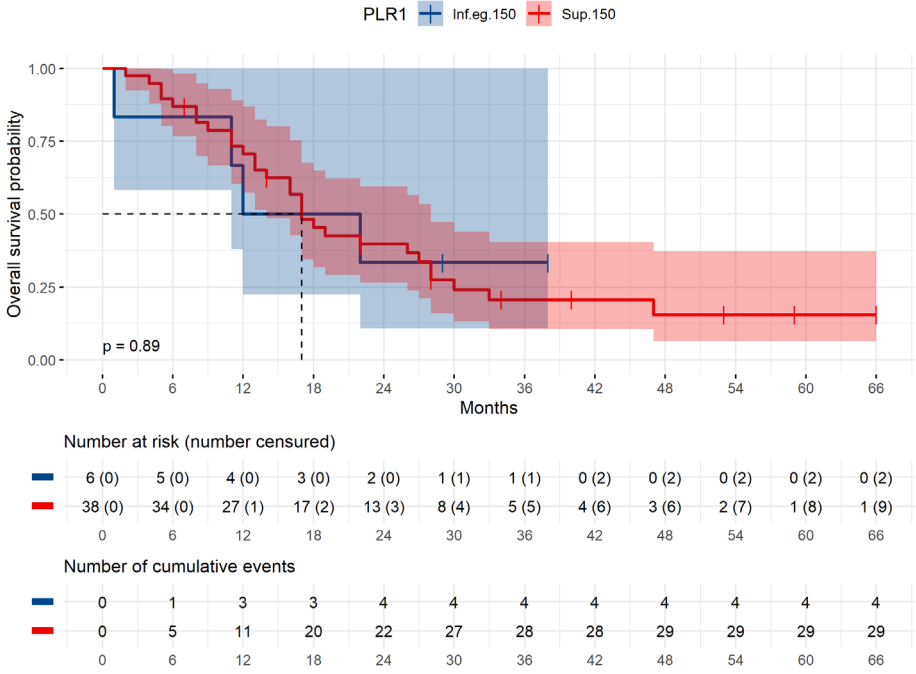


FIGURE 6 : KAPLAN-MEIER CURVE OF OVERALL SURVIVAL (OS) (PLR=150)

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.

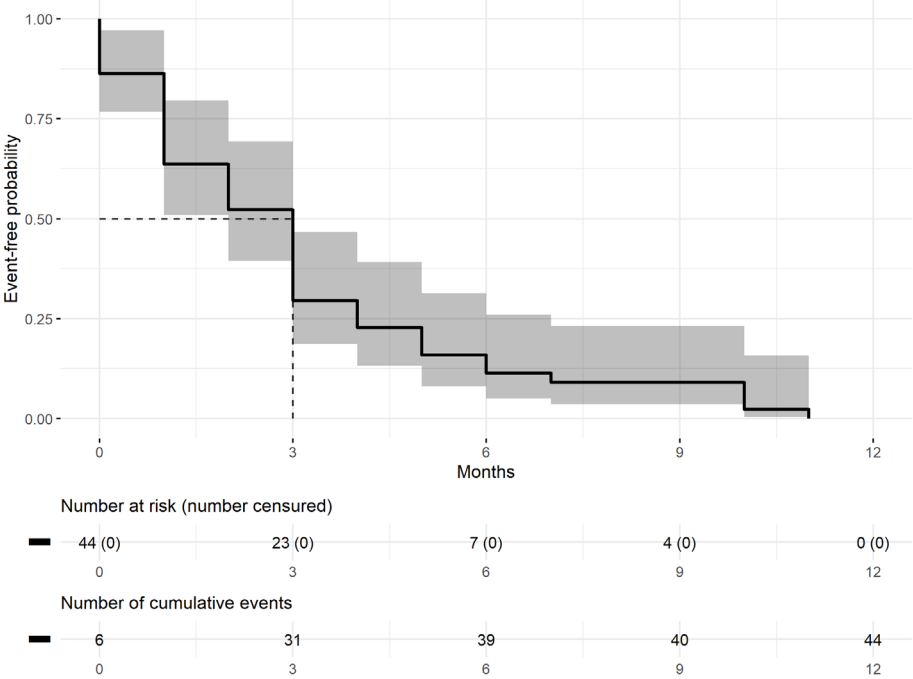


FIGURE 7: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF)

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.

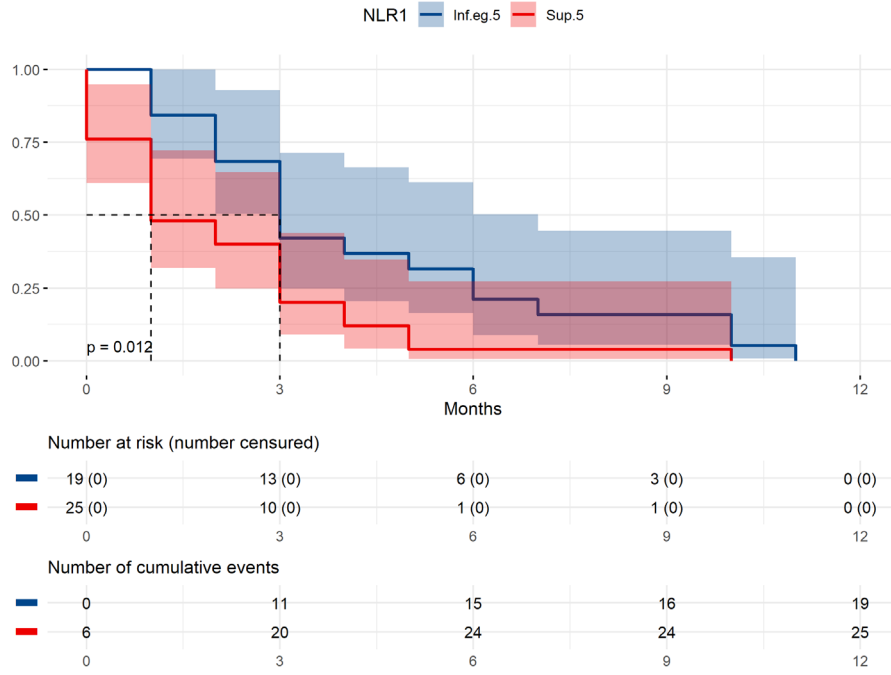


FIGURE 8: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (NLR=5)

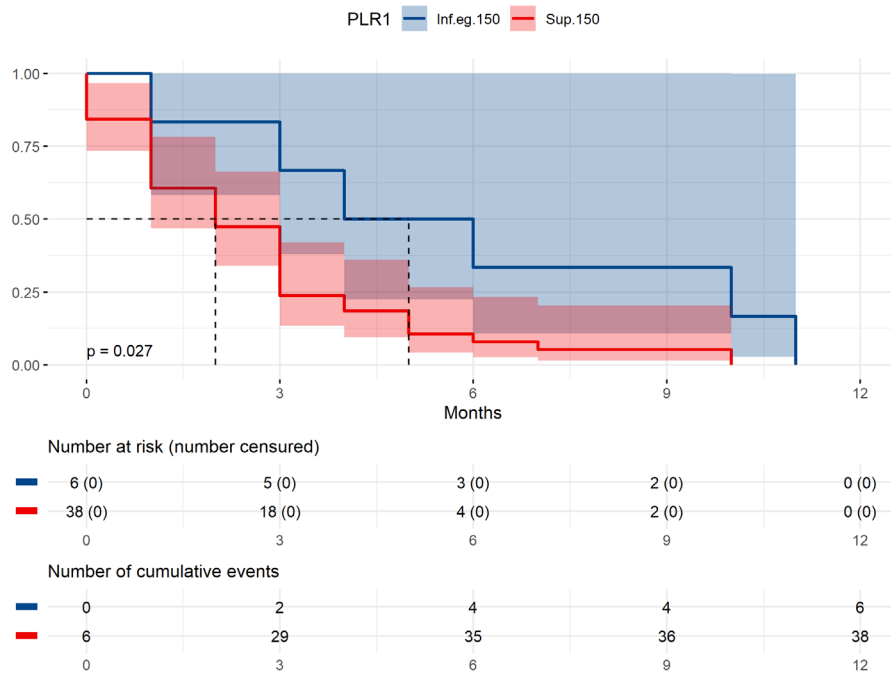


FIGURE 9: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (PLR=150)

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.

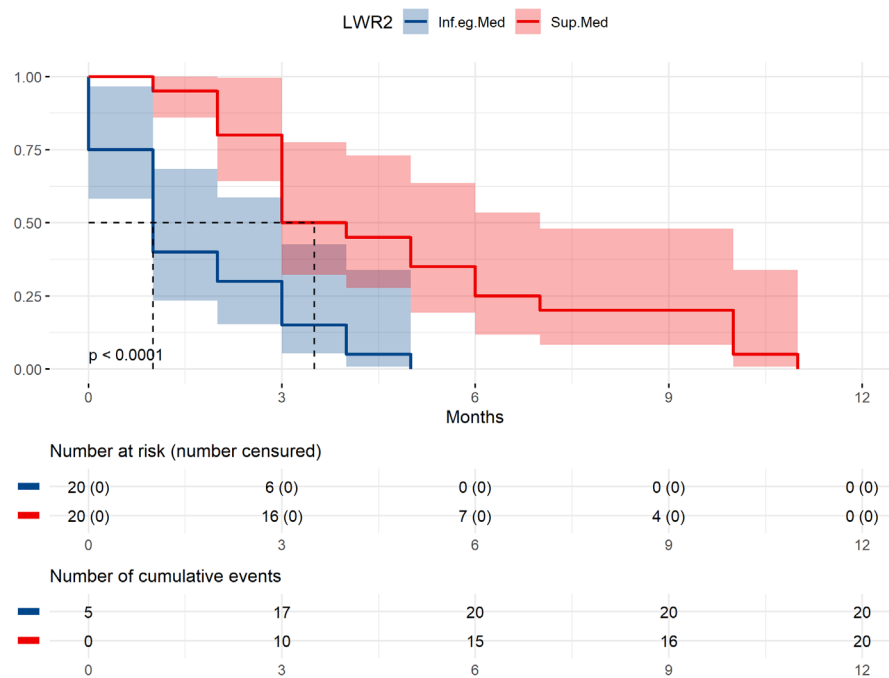


FIGURE 10: KAPLAN-MEIER CURVE OF TIME-TO-TREATMENT FAILURE (TTF) (LWR2=0.12)

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. Burtneiss *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.

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N° FINESS : 630000479

Section 6: References

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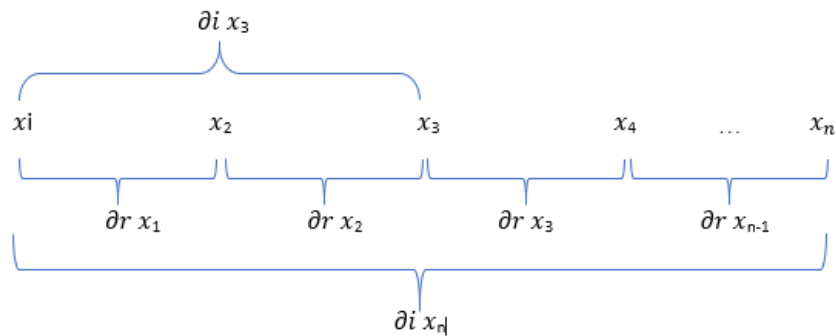
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Section 7: Appendix and Supplementary material

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 , up to 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)	.56	.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)	.83	.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)	.85	.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)	.35	.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