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Survival impact of a KEAP1-NFE2L2 radiomics model in PDL1 ≥ 50% non-small cell lung cancer treated with pembrolizumab: the PEMBROMIC study

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Abstract

Background New factors predicting response in patients with a PD-L1 tumor proportion score (TPS) ≥ 50% for locally advanced or metastatic non-small cell lung cancer (NSCLC) are needed to better select first-line therapy. Based on the literature, we previously developed a radiomic model predicting the KEAP1/NFE2L2 mutational status.

Method This was a retrospective monocenter study including 94 consecutive patients with advanced or metastatic PD-L1 ≥ 50% NSCLC, treated with pembrolizumab, who underwent a pre-therapeutic FDG-PET/CT and were followed up for 1 year. Seventy-seven patients who did not progress within the first 60 days of treatment were analyzed. Each primary lesion was segmented by 2 physicians on PET and CT scans. Radiomic features were calculated using MIM software on both PET and CT imaging. A previously developed KEAP1/NFE2L2 radiomic prediction model (called MUT_{PET}) was applied to this cohort using the initial FDG-PET/CT. The primary endpoint was the validation of the MUT_{PET} model as a predictive factor of PFS via the non-invasive prediction of KEAP1/NEF2L2 mutation.

Results The main characteristics of this cohort were: median age of 67.0 years [range, 48.0–84.0], sex ratio M/F = 60/17, 74.0% of patients with a histopathology of adenocarcinoma and 85.0% with a stage IV disease. The median follow-up was 20.0 months [range, 15.3–23.9]. Fifty-six (72.2%) patients experienced a disease progression with a median PFS of 11.8 months (CI95% 8.6–15.8) among which 51 (66.2%) died. In univariable analysis, MUT_{PET} model was statistically significant as a predictive factor of improved PFS (HR = 0.51, CI95% 0.30–0.91, $p = 0.02$) whereas it was not statistically significant regarding OS (HR = 0.61, CI95% 0.34–1.11, $p = 0.10$). In multivariable analysis, the MUT_{PET} model was associated with a HR of 0.6 (CI95% 0.34–1.06, $p = 0.08$). Combining the MUT_{PET} prediction, the histology subtype and the existence of liver metastases, a multimodal nomogram was able to predict PFS (chi-test of 39.43, $p < 0.0001$).

Conclusion In PD-L1 TPS ≥ 50% NSCLC patients treated with pembrolizumab, our results suggest an improved PFS in patients predicted to be KEAP1/NFE2L2 mutated.

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Key messages

What is already known on this topic The KEAP1/NFE2L2 axis is of paramount importance for its role in cellular response to oxidative stress. Several studies report the prognostic role of KEAP1/NFE2L2 mutations in patients treated with systemic treatments such as immunotherapy. Genetic testing is rarely to never performed due to its cost and lack of availability. A radiomics model based on PET and CT-extracted features was previously developed for the prediction of the KEAP1/NFE2L2 mutational status.

What this study adds Using the previously developped KEAP/NFE2L2 prediction model, we demonstrated the impact of the KEAP1/NFE2L2 pathway on progression-free survival (PFS) in patients with PDL1 ≥ 50% advanced or metastatic non-small cell lung cancer (NSCLC) treated with first line pembrolizumab. Patients harboring a predicted mutation had an increased PFS when compared to non-mutated patients.

How this study might affect research, practice or policy Our work validates the role of the KEAP1/NFE2L2 pathway for the prediction of response to pembrolizumab. This tool could be used for the choice between pembrolizumab only vs. chemo-immunotherapy as first-line for PDL1 ≥ 50% advanced or metastatic NSCLC patients.

Keywords Non-small cell lung cancer, FDG-PET, Radiomic analysis, KEAP1/NFE2L2, Immune checkpoint inhibitors, Pembrolizumab

Introduction

Lung cancer is the second most common cancer in men and the third in women [1, 2], with non-small cell lung cancer (NSCLC) accounting for approximately 84% of all lung cancers. Management of NSCLC has made significant progress at all stages in recent years due to broader lung cancer screening, improved radiotherapy (RT) techniques, and improvement in treatment such as the advent of targeted therapies and immunotherapy with checkpoint inhibitors (ICI) [3–5].

Pembrolizumab was approved as first-line treatment for advanced NSCLC with programmed cell death ligand 1 (PD-L1) Tumor Proportion Score (TPS) ≥ 50%, based on the improved PFS and OS in KEYNOTE-024 study [6, 7]. However, even with a positive PD-L1 status, only a subset of patients responds to immunotherapy. In the KEYNOTE-024 study, the response rate in pembrolizumab arm alone was 45% despite focusing on PD-L1 TPS ≥ 50% tumors. This result was impressive, thus explaining pembrolizumab approval for advanced NSCLC first-line with PD-L1 TPS ≥ 50% that represents only 22% among patients with stage IIIB/IV NSCLC [8]. Later, chemo-immunotherapy in NSCLC, via KN-189 in non-squamous NSCLC [9] and KN409 in squamous NSCLC [10], further increased survival independent of PD-L1 expression, while overcoming the initial progression observed with immunotherapy alone.

The early identification of biomarkers for patients unlikely to respond to first-line pembrolizumab alone and more likely to benefit from chemo-immunotherapy intensification is therefore, a crucial step in selecting appropriate candidates, as no study has yet answered this question. Genomic alterations of NFE2L2, KEAP1, and CUL3 lead to constitutive activation of NRF2-dependent gene transcription that promotes cellular resistance to oxidative stress, xenobiotic efflux, proliferation, and metabolic reprogramming [11]. Somatic mutations in NFE2L2 and KEAP1 are found in respectively 3.5% to 15% and 12% to 17% of patients with NSCLC. NFE2L2 is a transcription factor that drives expression of free radical defense genes, which could interfere with radiation-induced DNA damage. KEAP1 is an adaptor protein that targets NFE2L2 for ubiquitination and proteasomal destruction under normal homeostasis. These new biomarkers are of clinical interest, as KEAP1/NFE2L2 mutations predict radiation resistance in patients with localized NSCLC treated with RT but not with surgery [11]. Some data also suggest a role for the KEAP1/NFE2L2 axis in the response to ICI [12, 13]. Mutational status of the KEAP1/NFE2L2 pathway is rarely performed. Thus, non-invasive and cost-effective assessment is needed.

Radiomics was developed to characterize tumor heterogeneity by extracting textural features (TFs) from different imaging modalities including positron-emission tomography with computed tomography (PET/CT) [14]. Pre-therapeutic ^{18}F-fluorodeoxyglucose (FDG) PET/CT is currently indicated for staging of locally and advanced NSCLC [15]. A radiomics model (MUT_{PET}) was previously developed to predict the KEAP1/NFE2L2 mutational status using the initial PET/CT. It was further tested in a cohort of patients treated with curative RT [16], confirming the shorter local progression free survival (PFS) in mutated tumours. Given the potential impact of the KEAP1-NFE2L2 pathway on response to ICI, testing the previously developed KEAP1-NFE2L2 prediction model on patients with advanced NSCLC treated with immunotherapy could be of interest.

The aim of this study was to establish new predictive factors of survival in PD-L1 TPS ≥ 50% NSCLC patients treated with pembrolizumab, via a radiomic model predicting the KEAP1/NFE2L2 mutational status.

Materials and methods

Patients

Consecutive patients with advanced or metastatic NSCLC treated with first-line pembrolizumab in four separate institutions, who underwent a pre-treatment FDG-PET/CT in a single center were retrospectively included from July 2017 to November 2021. The study was conducted in accordance with the Declaration of Helsinki and was approved by the French Advisory Committee on Information Processing in Health Research (CCTIRS). If patients were alive, they received a written information on the study to express their opposition (which no patient had done); for deceased patients, an exemption of information was obtained from CCTIRS.

Inclusion criteria were: (i) biopsy-proven NSCLC with PD-L1 TPS ≥ 50%, metastatic or locally advanced not accessible to surgery or radiotherapy; (ii) treatment with first-line monotherapy pembrolizumab (dose of 200 mg every 3 weeks as an intravenous infusion)— patients who received ≥ 1 dose of immunotherapy were evaluated; (iii) no other primary malignancies; (iv) availability of pre-treatment PET performed within 8 weeks preceding first pembrolizumab infusion, with normal glycemic values prior to the PET study and respect of EANM procedure guidelines [17].

Follow-up

Clinical data include age, sex, smoker status, performance status (PS), corticosteroids prescribed within 3 months prior to ICI, histology, AJCC stage, metastasis at diagnosis, pre- or concomitant radiotherapy and mutations. Patients were treated and followed-up in accordance with standard guidelines after a thoracic multidisciplinary board and were clinically followed up for at least 1 year to evaluate the PFS and overall survival (OS), as recommended by National Comprehensive Cancer Network and European and Society for Medical Oncology (ESMO). Follow-up relied majorly on a thoracic, abdominal, pelvic and cerebral CT performed every three months. Depending on the physician's choice, PET/CT was an option.

PFS, defined as the duration from start of ICI to disease progression or death of any cause, or to date of last follow-up, was chosen as primary endpoint. OS, defined as the duration from start of ICI to death or date of last follow-up, was chosen as secondary endpoint.

Given the singularity of hyperprogressors [18], patients who experienced hyperprogression were excluded. Several definitions of hyperprogression under immunotherapy were proposed [19, 20]. In the present study, it was defined as progression or death within 60 days of treatment [21].

Data acquisition

FDG-PET/CT images were acquired on two Biograph Vision™ mCT PET/CT 64 scanners system (Siemens Healthineers©, Erlangen, Germany) using the same technical settings. Patients fasted for 6 h before intravenous injection of approximately 3 MBq/kg of FDG. After injection, patients remained in a quiet room for approximately 60 min before imaging.

Initially, a cranio-caudal CT scan was obtained using a whole-body protocol immediately after intravenous iodinated contrast injection (1.5 mL/kg), unless contraindicated. The CT consisted of a 64-slice multidetector-row spiral scanner with the following standard parameters: transverse field of view of 700 mm, collimation of 16 × 1.2 mm, pitch = 1, tube voltage of 120 kV, and effective tube current of 80 mAs.

Then, PET images were acquired in the craniocaudal direction using a whole-body protocol (2 min per step) and were reconstructed using an ordered subset expectation maximization (OSEM) algorithm (True X = point spread function + time-of-flight compensation ordered subset expectation maximization-3D). Images were corrected for random coincidences, scatter and attenuation using the CT scan data and were smoothed with a Gaussian filter (full-width at half-maximum = 2 mm). The size of the reconstruction transaxial matrix was 200 × 200 voxels and the voxel size was 4.07 × 4.07 × 2 mm.

Images analysis and radiomics workflow

All primary tumors were analyzed using MIM software (MIM Maestro®, Cleveland, OH, USA). Before being processed, each PET and CT was rescaled, resulting in voxel sizes of 1 × 1 × 1 mm. Each primary lesion was segmented by two physicians using a gradient-based method (PET-EDGE) for the PET image. The PET segmentation was then transferred to the CT and subsequently manually refined, resulting in two separate volumes (PET and CT) for each reader and a manual modified version of PET-EDGE fixation on the CT. Reproducibility of the segmentations between the two readers was assessed using the DICE similarity coefficient. The PyRadiomics toolbox [22] was used to extract radiomics features of interest using a fixed bin width of 0.1 and 8 wavelet filters (all possible combinations of applying either a High or a Low pass filter in each of the three dimensions) for the PET and a fixed bin number of 64, 32 and 16 for the CT. As a result, (111 × 9) + (111 × 3) = 1332 features were extracted for each patient.

The previously developed model (MUT_{PET}) combined 5 radiomics features (4 extracted from the PET and one from the CT), following the IBSI guidelines [23]. Among the 4 PET-based features, 2 were extracted using the grey level size zone matric (the Large Area Low Gray Level Emphasis with the LLL wavelet filter and the Zone

Variance without wavelet filters) and 2 using grey-level co-occurrence matrix (the Maximal Correlation Coefficient with the HLL wavelet filter and the Maximum Probability with the HLH wavelet filter). The CT-based feature was the Maximum pixel value on the original image. Using several publicly available cohorts, this PET/CT-based radiomics model was developed and externally tested on a cohort of 151 patients treated with RT [16]. As proposed by Bourbonne et al., patients with a predicted risk >20% based on the MUT_{PET} model were classified as harboring a KEAP1 and/or NFE2L2 mutation and inversely [16]. The same model (same architecture based on a Multilayer Perceptron approach, same features, same coefficients and same probability threshold) was used for the present work. None of the patients used for the development or the testing of the KEAP1-NFE2L2 model were used in the present work.

In the initial work by Bourbonne et al. [16], the KEAP1-NFE2L2 PET/CT-based radiomics model was trained using data from the TCGA-LUSC [24], TCGA-LUAD [25], CPTAC-LSCC [26], CPTAC-LUAD [27] and NSCLC-Radiomics [28] datasets and further validated on the Radiogenomics cohort and a local retrospective cohort. To ensure transferability of the model, harmonization was performed separately for all radiomics features, using the a posteriori neuroCombat procedure [29, 30] and pooling the initial training set by Bourbonne et al.. with the present cohort. This was considered necessary given the differences in imaging and sequencing devices between the initial work and the present study.

These different steps are described in Fig. 1.

Statistics

Descriptive statistics were used to characterize the cohort. Quantitative variables were described as median and range. Qualitative variables were presented as number (n) and percentage (%).

The primary endpoint was the validation of the previously developed radiomics model (MUT_{PET}) as a predictive factor of PFS via the radiomic model of KEAP1/NEF2L2 mutation prediction using radiomic analysis of initial FDG PET/CT.

Secondary endpoints were evaluation of the radiomic model on OS and evaluation of clinical and histological parameters impacting PFS and OS.

An univariable analysis was first performed to test significance of the following factors: age > vs. ≤ 65 years, smoker status (actual/former vs. non-smoker), PS according to the Eastern Cooperative Oncology Group (ECOG-PS < 2 vs. ≥ 2), corticosteroids > 10 mg/day for 3 months or more before treatment (yes vs. no), histology (squamous cell carcinoma (SCC) vs. non SCC), metastasis at diagnosis (cerebral, hepatic, others), pre or concomitant radiotherapy (yes vs. no), and radiomics signature (MUT_{PET}). The Kaplan Meier method was used to estimate survival probabilities. A log-rank test was used to compare the PFS and OS distribution. The Harrell's C-index was also calculated for the MUT_{PET}.

A multivariable analysis using Cox proportional hazard model was then performed to assess the potential independent effect of predictive factors outlined in univariable analysis.

Three other exploratory axes were addressed, evaluation of complementarity of clinico-histological parameters and the radiomic model with the development of a PFS nomogram (one using the radiomic signature and

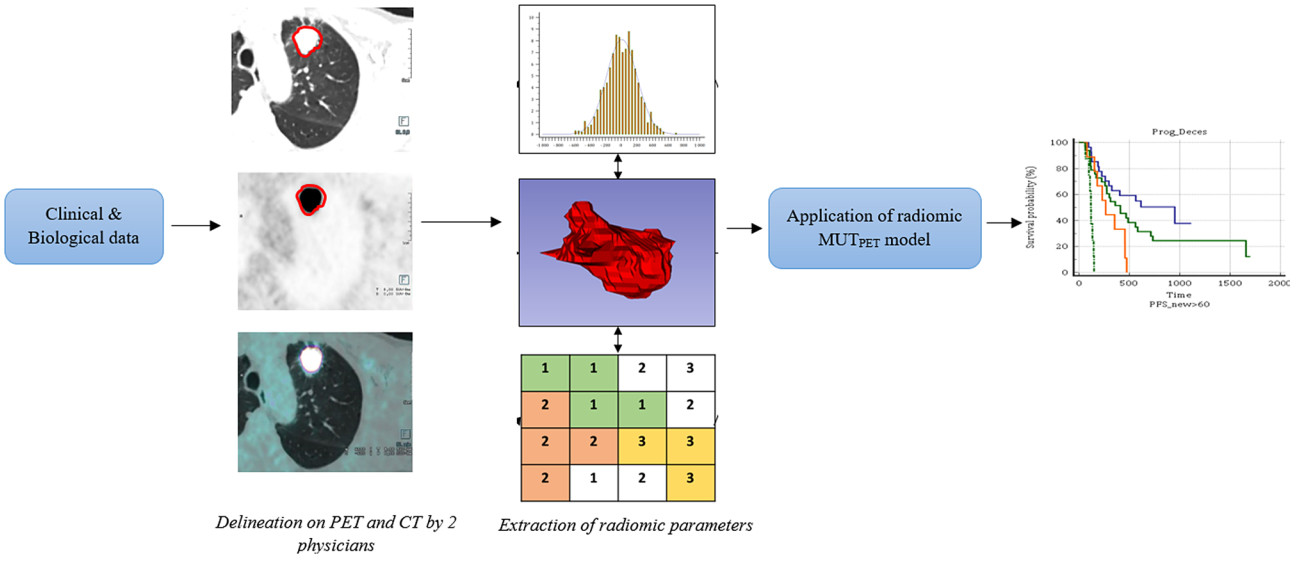

Fig. 1 Workflow for the radiomics analysis

one using clinical and histological features only), evaluation of the robustness of prediction of the radiomic model and evaluation of the models on the non-selected population (without exclusion of hyper-progressive patients). Calculation of the nomogram coefficients relied on the multivariable Cox regression hazard ratios. Robustness of the prediction was assessed using the 2 blindly performed delineations using the DICE score for the assessment of delineation variability and the predicted risks for comparison. The significance level of p-value was 0.05. All statistics were realized with SPSS Statisitics and MedCalc Statistical Software.

Results

Population

Between July 2017 to November 2021, 94 patients with advanced NSCLC who received first-line pembrolizumab and who underwent a pre-treatment FDG-PET/CT were identified and followed-up until October 2022. Seventeen patients were classified as hyperprogressors and thus excluded. Data were calculated in the remaining 77 patients with a median age of 67.3 years (range, 65.7 to 70.3). The main characteristics of the cohort are described in Table 1. Fifty-seven patients (74.0%) presented an adenocarcinoma histology, 17 (22.1%) presented a SCC and 3 patients (3.9%) presented not otherwise specified (NOS) subtype. According to the 8th Edition of TNM in Lung Cancer [31], 66 patients (85.7%) were stage IV, 11 patients (14.3%) were locally advanced. ECOG PS was 0–1 in 57/77 patients (74.0%).

Outcomes

Median follow-up was 20.0 months (range, 15.3 to 23.9). Fifty-six (72.2%) patients harbored a disease progression with a median PFS of 11.8 months (Confidence interval (CI)95% 8.6–15.8) and 51 patients (66.2%) died during

Table 1 Characteristics of patients at baseline

Characteristics	No of patients (*n* = 77)	No of MP (*n* = 35)	No of NMP (*n* = 42)
Age years, median (range)	67 (48–84)	67 (52–83)	66 (48–84)
Sex (male / female)	60/17	29/6	31/11
Smoker status, n (%)			
Actual or former smoker	68 (88)	30 (86)	38 (91)
Non smoker	09 (12)	5 (14)	4 (9)
ECOG Performance Status, n (%)			
0–1	57 (74)	27 (77)	30 (71)
2–3	20 (26)	8 (23)	12 (29)
Corticoids > 10 mg/day within 3 months prior to ICI, n (%)			
Yes	10 (13)	2 (6)	8 (19)
No	67 (87)	33 (94)	34 (81)
Histology, n (%)			
Squamous cell carcinoma	17 (22)	6 (17)	11 (26)
Adenocarcinoma	57 (74)	28 (80)	29 (69)
Other	03 (4)	1 (3)	2 (5)
TNM stage, n (%)			
II (T3 N0 M0)	01 (1)	0 (0)	1 (2)
III (T1 N2 M0) /(T2 N1 M0)/(T2 N2 M0)(T3 N1/N2 M0) (T4a N0, N1 M0)	10 (13)	5 (14)	5 (12)
IV (T4a N2 M0) (T4b Nx M0) (Tx N3 M0) (Tx, Nx, M1)	66 (86)	30 (86)	36 (86)
Metastasis at diagnosis, n of patients			
Cerebral	14	3	11
Hepatic	10	3	7
Bone	26	12	14
Other metastatis	43	21	22
Pre or concomitant radiotherapy on metastasis			
Yes	31 (40)	17 (49)	14 (33)
No	46 (60)	18 (51)	28 (67)
Mutations (for adenocarcinoma), n (%)	18		
KRAS	15 (83)	5 (28)	10 (55)
BRAF	2 (11)	0 (0)	2 (11)
MET	1 (6)	1 (6)	0 (0)

(Abbreviations: No of MP/NMP = number of patients predicted as mutated / non mutated; ECOG = Eastern Cooperative Oncology Group, TNM = 8th Edition of primary tumor (T), regional lymph node(s) involvement (N), and distant metastases (M) in Lung Cancer), ICI: Immune Checkpoint Inhibitor

Table 2 Univariable and multivariable analyses regarding progression-free survival

	Univariable analysis		Multivariable analysis	
Parameters	HR (CI95%)	*P*-value	HR (CI95%)	*P*-value
MUT_{PET}model	0.51 (0.30–0.91)	0.02*	0.60 (0.34–1.06)	0.08
Age	1.02 (0.98–1.05)	0.30		
>vs. ≤ 65 years				
Smoker status		0.41		
No vs. yes (former or actual)				
Performance status		0.72		
Corticoids > 10 mg/day within 3 months prior to ICI	0.90 (0.39–2.12)	0.82		
Histology				
SCC vs. non SCC	1.98 (1.08–3.62)	0.03*	1.75 (0.94–3.24)	0.08
Concomitant RT of metastatic sites	1.00 (0.59–1.72)	0.98		
Cerebral metastasis	1.51 (0.71–3.20)	0.29		
Liver metastasis	8.80 (3.55–22.03)	< 0.0001*	7.67 (3.02–19.46)	< 0.0001*
Other metastasis	1.12 (0.62–2.03)	0.71		

(Abbreviations: CI = Confidence interval ; ICI = Immune Checkpoint Inhibitor ; SCC = squamous cell carcinoma ; RT = radiotherapy)

*Significant *P*-value (< 0.05)

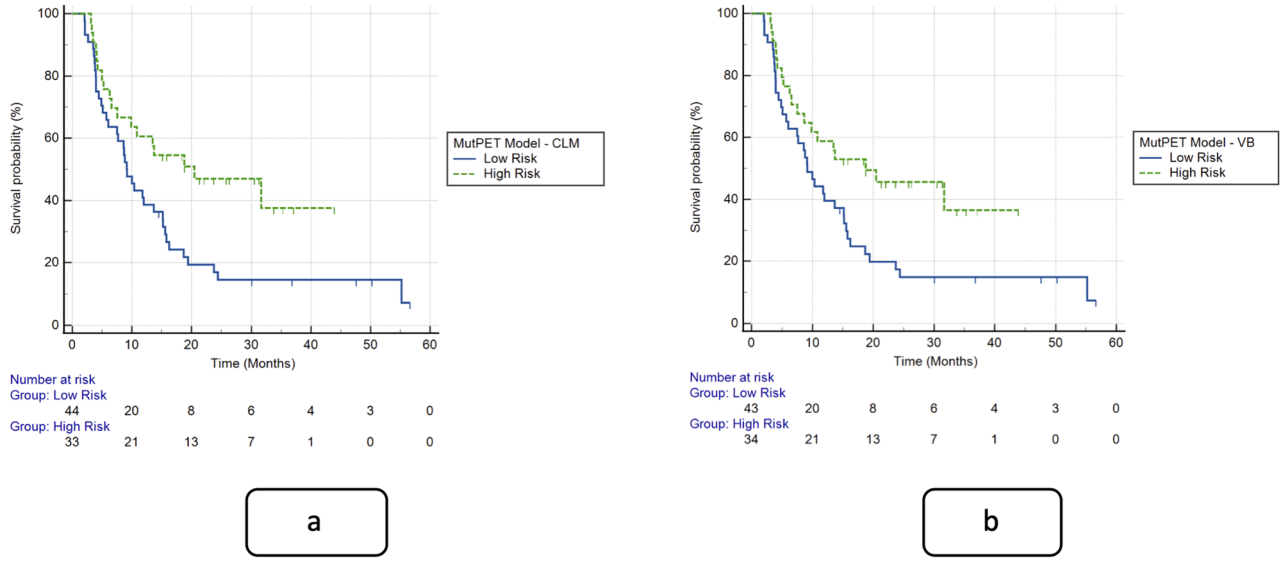

Fig. 2 Progression-free survival as stratified by the MUT_{PET} model, using CLM delineations (2**a**) and VB (2**b**) delineations

the follow-up period secondary to their NSCLC with a median OS of 22.9 months (CI95% 15.6–25.9).

Primary outcome

In univariable analysis, the MUT_{PET} model was statistically significant as a predictive factor of improved PFS (Hazard Ratio (HR) = 0.51, CI95% 0.30–0.91, $p = 0.02$) when mutated (Table 2; Fig. 2a and b): median PFS 18.8 months (CI95% 7.5–31.7) versus 9.2 months (5.7–15.2). This was not validated in multivariable analysis (HR = 0.60, CI95% 0.34–1.06, $p = 0.08$) (Table 2).

Secondary outcomes

Evaluation of the radiomic model on OS

In univariable analysis, the MUT_{PET} model was not statistically significant as a predictive factor of improved OS (HR = 0.61, CI95% 0.34–1.11, $p = 0.10$) (Table 2). The median OS in case of mutation was 27.9 months (CI95% 20.0-42.4) versus 18.0 months (10.6–26.4) when the mutation was predicted to be absent.

Evaluation of clinical and histological parameters impacting PFS

In univariable analysis, SCC histology (HR = 1.98, CI95% 1.08–3.62, $p = 0.03$) and the presence of liver metastases (HR = 8.8, CI95% 3.55–22.03, $p < 0.0001$) were predictive factors for a decreased PFS (Table 2).

In multivariable analysis, only liver metastases were associated with a shorter PFS (HR = 7.67, CI95% 3.02–19.46, $p < 0.0001$) (Table 2).

Table 3 Univariable and multivariable analyses regarding overall survival

	Univariable analysis		Multivariable analysis	
Parameters	HR (CI95%)	*P*-value	HR (CI95%)	*P*-value
MUT_{PET}model	0.61 (0.34–1.11)	0.108	0.70 (0.39–1.28)	0.251
Age	1.02 (0.9–1.05)	0.272		
>vs. ≤ 65 years				
Smoker status		0.333		
No vs. yes (former or actual)				
Performance status		0.781		
Corticoids > 10 mg/day within 3 months prior to ICI	0.97 (0.41–2.31)	0.951		
Histology				
SCC vs. non SCC	1.13 (0.76–2.72)	0.261		
Concomitant RT of metastatic sites	1.20 (0.68–2.12)	0.522		
Liver metastasis	9.80 (4.06–23.68)	< 0.0001*	8.96 (3.68–21.81)	< 0.0001*

(Abbreviations: CI = Confidence interval ; ICI = Immune Checkpoint Inhibitor ; SCC = squamous cell carcinoma ; RT = radiotherapy)

*Significant P-value (< 0.05)

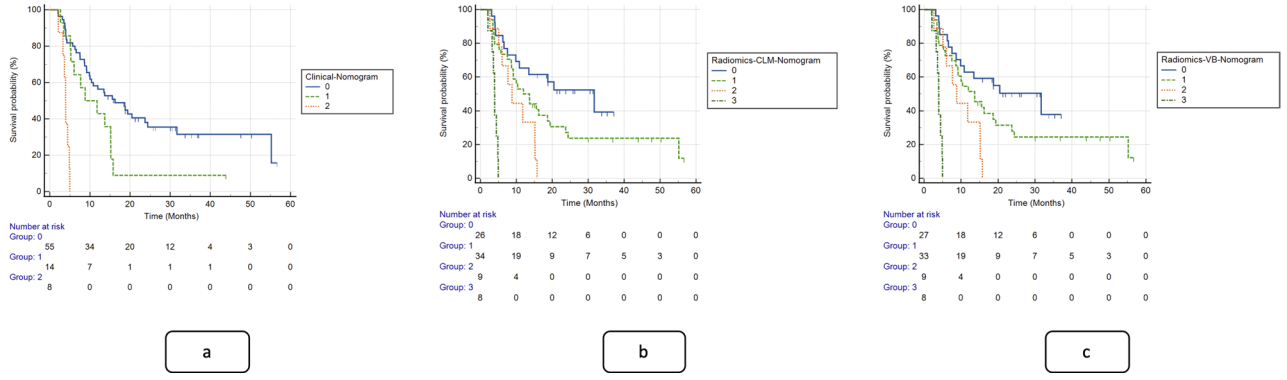

Fig. 3 Progression-free survival as stratified by the Clinical-Nomogram (3**a**), the Radiomics-CLM-Nomogram (3**b**) and the Radiomics-VB-Nomogram (3**c**)

Evaluation of clinical and histological parameters impacting OS

In univariable analysis, only liver metastases were statistically correlated with a poor response (HR = 9.805, CI95% 4.06–23.68, $p < 0.0001$) (Table 3). This was also significant in multivariable analysis (HR = 8.96, CI95% 3.68–21.81, $p < 0.0001$) (Table 3).

Development of the PFS nomograms

Regarding the first nomogram we developed, and considering the results of the previous multivariable analyses, a score of 1 (risk factor) was assigned to patients with SCC histology. A score of 8 was assigned to the presence of liver metastases. The radiomic score was not used. Thus, we obtained 3 groups (from 0 for no point to 3 for ≥ 8 points). A statistical difference in PFS between the groups was found (Clinical Nomogram, chi-test of 35.17, $p < 0.0001$) (Fig. 3a).

Regarding the second nomogram, a score of 1 (risk factor) was assigned to patients predicted as non-mutated and to patients with SCC histology. A score of 7 was assigned to the presence of liver metastases. Thus, 4 groups emerged (from 0 for no point to 3 for ≥ 7 points) with a statistical difference between each group regarding PFS (CLM Nomogram, chi-test of 39.43, $p < 0.0001$) (Fig. 3b). The nomogram obtained with the second physician found the same results (VB Nomogram, chi-test of 38.86, $p < 0.0001$) (Fig. 3c).

These nomogram results suggest that the radiomic mutation prediction score may have an impact in predicting the response to ICI.

We also tested the clinical and radiomics nomograms on OS and the results where concordant, although not statistically significant (respectively, supplementary Figs. 1, 2 and 3).

Robustness of the radiomic model

Concerning robustness of the radiomic model, only 1/77 (1.3%) patient differed in the prediction of the presence of KEAP1/NFE2L2 mutation, comparing the 2 physicians' outlines, thus showing good reproducibility. The mean DICE coefficients between the 2 readers were respectively 0.89 (CI95% 0.86–0.91) and 0.85 (CI95% 0.83–0.87) for the PET and CT delineations.

Evaluation of the radiomics model and nomogram in the non-selected cohort

Out of the initial 94 eligible patients, 17 patients (18.1%) were excluded because of the hyperprogressive status. In the overall cohort, the MUT_{PET} model based on VB delineations was not statistically significant as a predictive factor of improved PFS (HR = 0.70, CI95% 0.44–1.12, $p = 0.14$) nor OS (HR = 0.80, CI95% 0.49–1.31, $p = 0.38$), as seen in Supplementary Figs. 4a-b and 5a-b, respectively. The CLM-based radiomics nomogram outperformed the clinical nomogram for both PFS and OS prediction. Performance of the nomograms are summarized as Supplementary Table 1 while Kaplan Meier curves are provided as Supplementary Fig. 6a-b for the clinical nomogram, 7a-b for the CLM-delineations based nomogram and 8a-b for the VB-delineations based nomogram.

Discussion

The aim of this study was to establish new predictive features of survival in patients with advanced or metastatic NSCLC first-line with PD-L1 TPS ≥ 50% treated with pembrolizumab. A previously developed MUT_{PET} model predicting the KEAP1/NFE2L2 mutational status was validated in our cohort of PD-L1 TPS ≥ 50% as a predictive factor of response to ICI (HR = 0.51, CI95% 0.30–0.91, $p = 0.02$) when mutated. Robustness of the prediction was also validated on the cohort of 77 patients as only one classification differed between the two readers. Moreover, combining the MUT_{PET} prediction with other clinical features (histology and liver metastases status) could increase the PFS stratification.

To the exception of oncogene-addicted NSCLC, PDL-1 expression is the main standard biomarker used in NSCLC to orientate treatment choices. However, as shown in the KEYNOTE-024 study, the response rate in pembrolizumab arm alone was 45% despite focusing on PD-L1 TPS ≥ 50% tumors. From this perspective and in the era of personalized medicine, there is an unmet need for laboratory and imaging biomarkers suitable for identifying patients who are more likely to benefit from ICI. In this context, a multimodal approach combining clinicopathological and quantitative imaging features seems interesting [32]. Radiomics have not yet been employed in daily clinical practice as there are many pitfalls in terms of reproducibility, calibration of PET/CT and lack of physiopathological explanation. On the other hand, the radiomics approach has the advantage of being non-invasive and cost-effective. In a review summarizing the current radiomic evidence on ICI in oncology, 18 studies were found to evaluate the impact of radiomics in NSCLC patients treated with ICI [33]. One of the first studies in the setting of NSCLC and ICI was from Mu et al. [34], who developed a multiparametric radiomic signature from baseline CT, PET, and PET/CT for predicting patients with clinical benefit and survival from ICI. They found that features of heterogeneity, such as short run low gray emphasis or short zone emphasis, were able to predict durable benefit with good results (area under the curve (AUC) was 0.86 for training, 0.83 for retrospective, and 0.81 for prospective test cohorts). Nevertheless, an important limitation of the study was the lack of patients' data on PD-L1 expression, not enabling the comparison of their model with the PD-L1 status. In 2020, Valentinuzzi et al. [35]. created a FDG-PET/CT radiomics signature (iRADIOMICS) consisting of the most promising radiomics features extracted by the FDG-PET images and able to predict the response of metastatic NSCLC (stage IV) to pembrolizumab compared to the clinical standards (PD-L1 immunohistochemistry and iRECIST). Thirty patients receiving pembrolizumab were scanned with FDG PET/CT at baseline and months 1 and 4. At baseline PET, none of the standard volume or intensity-based features (volume and SUVmax) were able to discriminate responders from non-responders. On the contrary, the predictive power of the baseline iRADIOMICS signature was higher than the PD-L1 signature (AUC of 0.81 vs. 0.60) and comparable to month 1 and month 4 iRECIST signatures (AUC of 0.79 and 0.81, respectively), allowing earlier identification of the response by at least one month. Multivariable baseline iRADIOMICS was found to be superior to the current standards (PD-L1 and iRECIST signatures). Similar to other published data [36], this approach harbors substantial differences in comparison to ours: the iRADIOMICS signature directly predicts the response to ICI and thus is only useable in this setting. Our approach consists in the evaluation of a radiomics model on a different population and the different population than the original intent.

In the literature, presence of a KEAP1/NFE2L2 mutation appears to be associated with greater radioresistance, leading to increased local recurrence rates after radiotherapy (RT) than after surgery [37]. Authors reported that KEAP1 and NFE2L2 mutations were significantly associated with local recurrence (LR) after RT with a 2-year LR of 42.4% versus 12.5% for wildtype ($p = 0.005$). The same team found that loss of KEAP1 leads to radioprotection by decreasing DNA damage via enhanced free radical scavenging (lower ROS levels and higher levels of glutathione (GSH), a key intracellular antioxidant that has previously been implicated in contributing to radioresistance) [11]. By using a low dose of glutaminase inhibitor (CB-839), the GSH level decreased, allowing a radiosensitivation of KEAP1 mutant cells to similar levels as KEAP1 wild-type cells; this approach could improve local control of mutant tumors.

There are conflicting results regarding the survival impact of the KEAP1/NFE2L2 mutation in NSCLC patients treated with ICI. In a 2020 study from Xu et al.

[12] the correlation between KEAP1/NFE2L2 mutations and tumor mutational burden (TMB) and PD-L1 was investigated. The mutations appeared in various cancers but the highest mutation incidences occurred in SCC [38]. Higher TMB value and PD-L1 expression were associated with KEAP1/NFE2L2 mutations compared with wild-type, both of which are biomarkers for ICI [12, 21]. Their study showed an improved survival of patients with KEAP1/NFE2L2 mutant with ICI compared with other treatments (median overall survival 22.52 months vs. 12.89, $p = 0.0034$). On the other hand, the 2020 study from Zhu et al. [13]. used two independent cohorts (the OAK and POPLAR study cohort) of 853 patients with advanced NSCLC to analyze the prognostic effect of KEAP1/NFE2L2 on ICI. KEAP1/NFE2L2 mutation was associated with poorer OS and PFS (OS: HR = 1.7, $p < 0.001$; PFS: HR = 1.4, $p < 0.001$). In mutated lung adenocarcinoma, OS and PFS with ICI were lower than in wild-type (OS: HR = 1.8, $p < 0.001$; PFS: HR = 1.4, $p = 0.0014$); whereas in SCC, OS was lower in mutated lesions (HR = 1.4, $p = 0.0473$) but there was no difference in PFS (HR = 1.2, $p = 0.1588$). In accordance with the report by Xu et al. [12] our study suggests that our NFE2L2/KEAP1 mutation prediction model may help to better select patients responding to ICI; since the presence of the mutation is indeed associated with an increased response to ICI. Of note, none of these studies focused on the PDL1 >50% population, with further research being needed.

In our analysis, we showed that liver metastases was an independent prognostic factor for PFS ($p < 0.0001$) and OS ($p < 0.0001$). To date, data on patients with liver metastases have been reported in 9 studies (2024 patients for OS and 1371 patients for PFS). A direct comparison showed that patients without liver metastases seemed to benefit more from immunotherapy treatment when compared to patients with liver metastases (HR = 0.76, CI95% 0.71–0.81 vs. HR = 0.86, CI95% 0.74-1.00, respectively) [39]. In the Danish national registry of patients treated with ICI for NSCLC, the presence of liver metastases was associated with a decreased OS (HR = 1.47), which is consistent with our results [40].

We found that a SCC histology tended to be significant for an unfavorable PFS ($p = 0.08$); this differs from the literature. Indeed, in the KN24 study, PFS was significantly better for squamous histology [6]. This trend was confirmed in the EMPOWER-Lung1 trial evaluating cemiplimab in first-line treatment of advanced NSCLC with PD-L1 TPS ≥ 50%, with a larger squamous histology population than in KN24 [41]. Nevertheless, other data in the literature suggest that squamous cell histology has a poorer response to ICI compared to non-squamous cell histology as illustrated by the KEYNOTE-010 study, evaluating pembrolizumab as a second-line therapy compared to docetaxel [42].

In our series, the presence of brain metastases was not significantly correlated to survival, which is consistent with the literature. In fact, a review of 12 studies involving a total of 566 patients with brain metastases showed that ICI was active and effective as a single agent [43]. Efficacy of ICI in patients with brain metastases was further confirmed by a larger review including 46 trials (3160 participants) [44].

At present, we do not know when intensification of chemotherapy in addition to ICI appears to be indicated, except in nonsmoking patients. In a large retrospective cohort study using a real-world depersonalized database, patients with metastatic non SCC-NSCLC with high PD-L1 expression started first-line ICI-mono ($n = 351$) or ICI-chemo ($n = 169$). Both median OS and PFS did not differ between the 2 groups [median OS: ICI-chemo, 21.0 months vs. ICI-mono, 22.1 months, a HR = 1.03, CI95% 0.77–1.39, $p = 0.83$; median PFS: ICI-chemo, 10.8 months vs. ICI-mono, 11.5 months, HR = 1.04, CI95% 0.78–1.37, $p = 0.81$] [45]. Although trials are ongoing to prospectively evaluate these strategies (NCT04547504), identification of KEAP1/NFE2L2 mutational status may be relevant in choosing this intensification in case of wild-type status.

Exclusion of hyperprogressors i.e., patients who progressed within 60 days of starting treatment, from the analysis is debatable. This choice was justified by their singularities and the correlation with worse chances of survival [17]. This phenomenon is not rare: 18% of our initial cohort was excluded which is consistent with literature as it was representing 4% to 29% of the population in retrospective studies with different definitions [17]. Indeed, several definitions of hyperprogression under immunotherapy were proposed [19, 20]. In the present study, we defined it as progression or death within 60 days of treatment, taking the cut-off that stood out the most [21]. This removal limits the external validity of this study. Of note, while the MUT_{PET} model was not significantly prognostic of PFS and OS, its association with clinical features within the radiomics nomogram resulted in a higher performance than the clinical nomogram alone when evaluated in the non-selected population. These results hint at the possibility of using the model as a baseline prognostic tool, even though, it was built on a cohort excluding patients with hyperprogressive NSCLC. Regarding additional limitations, we based all of our analysis on a KEAP1/NFE2L2 mutation that was currently not proven in our patients, thus limiting the strength of our study. However, this PET/CT-based radiomics model was developed and previously externally validated on a cohort of 151 patients treated with RT [16]. Apart from these limitations, we acknowledge the retrospective nature of our study as well as the small sample size due to the selection of patients who

received ICI alone in first-line metastatic disease. This reduced our population because when the general state of the patient is preserved, chemo-ICI is privileged, even if monotherapy remains a therapeutic standard in addition to chemo-ICI if the PD-L1 is higher than 50% [46]. In addition, the small sample size makes the presence of major prognostic factors such as liver metastases overwhelmingly important in the statistical analysis, making the emergence of other prognostic factors difficult to assess.

Finally, this study underlines the definite interest of radiomics to determine not only the prognosis but also the genomics, which would allow to better personalize the treatment of patients in strategies of therapeutic intensification or de-escalation [47]. To strengthen our analysis, we included two operators who independently perform the segmentation. Using our radiomic model for mutation prediction, only 1 of 77 patients differed in prediction highlighting the robustness of our model.

Conclusion

In this retrospective study of advanced or metastatic PD-L1 TPS ≥ 50% NSCLC treated with first-line pembrolizumab, we validated a previously developed MUT_{PET} model predicting the KEAP1/NFE2L2 mutational status as a predictive factor of increased survival when mutated. Moreover, our results suggest combining the MUT_{PET} prediction with other clinical features (histology and liver metastases status) could increase the PFS stratification.

Abbreviations

CI	Confidence interval
CT	Computed tomography
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
NSCLC	Non-small cell lung cancer
TPS	Tumor proportion score
OS	Overall survival
PD-L1	Programmed cell death ligand 1
PET	Positron-emission tomography
PFS	Progression free survival
PS	Performance status
RT	Radiotherapy
SCC	Squamous cell carcinoma
TMB	Tumor mutational burden

Supplementary Information

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Supplementary Material 1

Author contributions

Conceptualization, C.L.M, V.B and K.A; Methodology, V.B, K.A and C.L.M; Software, V.B and D.B; Validation, R.A, R.D; Formal analysis, V.B and K.A; Investigation, C.L.M and K.A; Resources, R.A, R.D, M.C, K.A; Data curation, V.B; Writing-original draft preparation, C.L.M; Writing-review and editing, K.A and V.B; Visualization, O.P and M.C; Supervision, V.B and K.A; Project administration, K.A, V.B, .R.A; Guarantor, K.A.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

This study was approved by approved by the Ethics Committee of University Hospital, Brest, France (Ethic committee ID: 29BRC23.0142, NCT ID: NCT05996263).

Patient consent for publication

All participants gave informed consent to participate in the study before taking part.

Competing interests

The authors declare no competing interests.

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