

## Développement et validation d'un modèle de prédiction de la réponse à l'immunothérapie en cancer du poumon non à petites cellules

Victor Comte <sup>1,2\*</sup>, Hornella Fokem-Fosso <sup>1\*</sup>,  
Narinée Hovhannisyan-Baghdasarian <sup>1</sup>, Nicolas Captier <sup>1</sup>,  
Marie Luporsi <sup>1,3</sup>, Erwin Woff <sup>1,4</sup>, Christophe Nioche <sup>1</sup>, Nicolas Girard <sup>5</sup>,  
Olivier Humbert <sup>2,6</sup>, Irène Buvat <sup>1</sup>, Fanny Orlhac <sup>1</sup>

1: Institut Curie, PSL University, Inserm LITO U1288, Orsay, France.

2: Université Côte d'Azur, Centre Antoine Lacassagne, Department of Nuclear Medicine, Nice, France.

3: Institut Curie, Department of Nuclear Medicine, Paris-St-Cloud, France.

4: Université libre de Bruxelles, Hôpital Universitaire de Bruxelles, Institut Jules Bordet, Department of Nuclear Medicine, Brussels, Belgium.

5: Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France.

6: IBV, Université Côte d'Azur, CNRS, Inserm, Nice, France.

# Contexte

---

Cancer bronchique non à petites cellules (CBNPC) avancé ou métastatique sans mutation activatrice

→ 1<sup>ère</sup> ligne : inhibiteurs de points de contrôle immunitaire



# Contexte

Cancer bronchique non à petites cellules (CBNPC) avancé ou métastatique sans mutation activatrice

→ 1<sup>ère</sup> ligne : inhibiteurs de points de contrôle immunitaire



↗ +10% de gain en survie chez les patients PD-L1 positifs

⚠ Expression de PD-L1 : pas un biomarqueur suffisant pour guider la prise en charge et sujet à une forte variabilité

➤ Ann Oncol. 2024 Oct;35(10):902-913. doi: 10.1016/j.annonc.2024.06.014. Epub 2024 Jun 29.

## Intrapatient variation in PD-L1 expression and tumor mutational burden and the impact on outcomes to immune checkpoint inhibitor therapy in patients with non-small-cell lung cancer

A Di Federico <sup>1</sup>, S L Alden <sup>2</sup>, J W Smithy <sup>3</sup>, B Ricciuti <sup>1</sup>, J V Alessi <sup>1</sup>, X Wang <sup>4</sup>, F Pecci <sup>1</sup>,  
G Lamberti <sup>1</sup>, M M Gandhi <sup>1</sup>, V R Vaz <sup>1</sup>, L F Spurr <sup>5</sup>, L M Sholl <sup>6</sup>, K L Pfaff <sup>7</sup>, S J Rodig <sup>6</sup>, Y Y Li <sup>8</sup>,  
A D Cherniack <sup>8</sup>, M Nishino <sup>9</sup>, B E Johnson <sup>1</sup>, M M Awad <sup>10</sup>

Affiliations + expand

PMID: 38950679 DOI: 10.1016/j.annonc.2024.06.014

# Contexte

Cancer bronchique non à petites cellules (CBNPC) avancé ou métastatique sans mutation activatrice

→ 1<sup>ère</sup> ligne : inhibiteurs de points de contrôle immunitaire



↗ +10% de gain en survie chez les patients PD-L1 positifs

⚠ Expression de PD-L1 : pas un biomarqueur suffisant pour guider la prise en charge et sujet à une forte variabilité

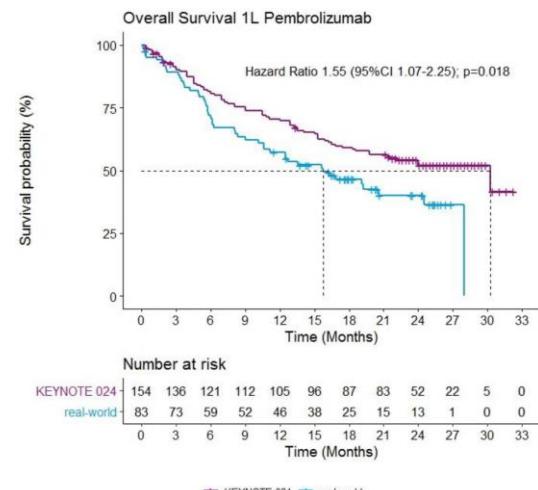
➤ Ann Oncol. 2024 Oct;35(10):902-913. doi: 10.1016/j.annonc.2024.06.014. Epub 2024 Jun 29.

## Intrapatient variation in PD-L1 expression and tumor mutational burden and the impact on outcomes to immune checkpoint inhibitor therapy in patients with non-small-cell lung cancer

A Di Federico <sup>1</sup>, S L Alden <sup>2</sup>, J W Smithy <sup>3</sup>, B Ricciuti <sup>1</sup>, J V Alessi <sup>1</sup>, X Wang <sup>4</sup>, F Pecci <sup>1</sup>,  
G Lamberti <sup>1</sup>, M M Gandhi <sup>1</sup>, V R Vaz <sup>1</sup>, L F Spurr <sup>5</sup>, L M Sholl <sup>6</sup>, K L Pfaff <sup>7</sup>, S J Rodig <sup>6</sup>, Y Y Li <sup>8</sup>,  
A D Cherniack <sup>8</sup>, M Nishino <sup>9</sup>, B E Johnson <sup>1</sup>, M M Awad <sup>10</sup>

Affiliations + expand

PMID: 38950679 DOI: 10.1016/j.annonc.2024.06.014



[Cramer-van der Welle et al, Sci Report 2021]

# Contexte

---

Plusieurs scores cliniques proposés dans la littérature :

- LIPI - Lung Immune Prognostic Index [Mezquita et al, JAMA Oncol 2018]
- EPSILoN [Prelaj et al, Cancers 2019]
- LIPS-3 - Lung Immuno-oncology Prognostic Score [Banna et al, ESMO Open 2021]
- ...

# Contexte

---

Plusieurs scores cliniques proposés dans la littérature :

- LIPI - Lung Immune Prognostic Index [Mezquita et al, JAMA Oncol 2018]
- EPSILoN [Prelaj et al, Cancers 2019]
- LIPS-3 - Lung Immuno-oncology Prognostic Score [Banna et al, ESMO Open 2021]
- ...



Aucun score utilisé en pratique clinique pour la prise en charge  
Pas ou peu contribution de l'imagerie

# Contexte

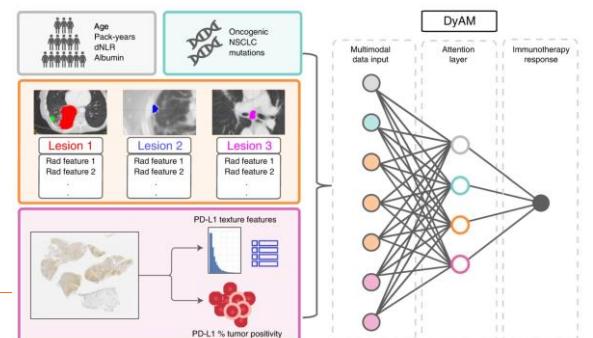
Plusieurs scores cliniques proposés dans la littérature :

- LIPI - Lung Immune Prognostic Index [Mezquita et al, JAMA Oncol 2018]
- EPSILoN [Prelaj et al, Cancers 2019]
- LIPS-3 - Lung Immuno-oncology Prognostic Score [Banna et al, ESMO Open 2021]
- ...



Aucun score utilisé en pratique clinique pour la prise en charge  
Pas ou peu contribution de l'imagerie

- [Vanguri et al, Nat Cancer 2022]

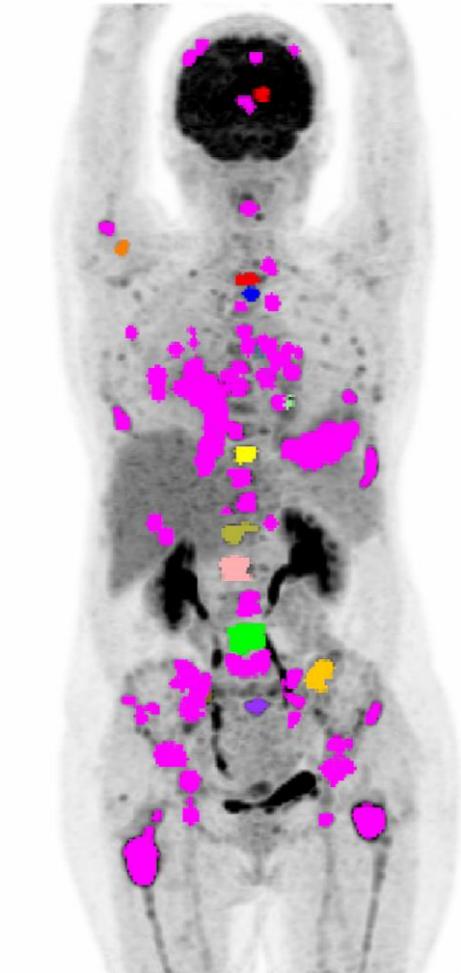


# Contexte



Place de la TEP-FDG dans la prise en charge pour le bilan d'extension

- TMTV – Total Metabolic Tumor Volume
- Dmax – distance entre les 2 lésions les plus éloignées
- SLR – Spleen-to-Liver Uptake Ratio
- ...



# Objectif

---



Développer et de valider sur une cohorte indépendante,

un modèle **multivarié** combinant des caractéristiques issues de la **TEP** réalisée avant traitement par **ICI** avec des **biomarqueurs cliniques et/ou biologiques** déjà identifiés dans la littérature,

afin de prédire la **survie globale** des patients atteints de CBNPC avancé traités en première ligne par **ICI** (+/- chimiothérapie)

# Matériel & Méthodes

---

## Critères d'inclusion des patients

- 1) CBNPC sans mutation activatrice EGFR/ALK
- 2) Patient ayant consenti à l'utilisation de ses données pour la recherche
- 3) Stage III ou IV, inéligible pour la chirurgie
- 4) TEP-FDG avant traitement par immunothérapie
- 5) Suivi de 12 mois minimum ou décès après initiation

# Matériel & Méthodes

## Critères d'inclusion des patients

- 1) CBNPC sans mutation activatrice EGFR/ALK
- 2) Patient ayant consenti à l'utilisation de ses données pour la recherche
- 3) Stage III ou IV, inéligible pour la chirurgie
- 4) TEP-FDG avant traitement par immunothérapie
- 5) Suivi de 12 mois minimum ou décès après initiation



**Cohorte 1** : 197 patients – Institut Curie  
→ développement du modèle



**Cohorte 2** : 86 patients – Centre Antoine Lacassagne  
→ évaluation des performances



# Matériel & Méthodes

## Analyse des images TEP

- Segmentation manuelle des lésions avec  $SUV > 4$  + labellisation : lung, bone, pleural, liver, other
- Ré-échantillonnage en  $2 \times 2 \times 2 \text{ mm}^3$

Scanner model	Manufacturer name	Slice thickness (mm)	Pixel spacing (mm)	Reconstruction method
Biograph 6	Siemens	5	[4.07, 4.07]	PSF 4i14s
Biograph 20	Siemens	2.03	[4.07, 4.07]	PSF+TOF 3i21s
Biograph 40	Siemens	2.03	[4.07, 4.07]	PSF+TOF 3i21s
Biograph Horizon	Siemens	2.03	[2.06, 2.06]	PSF+TOF 6i10s
Discovery 610	General Electric	3.27	[2.73, 2.73]	VPHDS
Discovery 690	General Electric	3.27	[2.73, 2.73]	VPFX
Discovery 710	General Electric	3.27	[2.73, 2.73]	VPFXS
Discovery IQ	General Electric	3.26	[2.73, 2.73]	QCHD
Discovery MI	General Electric	2.8	[2.73, 2.73]	QCFX
Gemini TF 16	Philips	4	[4.00, 4.00]	BLOB-OS-TF
Ingenuity TF	Philips	2	[2.00, 2.00]	BLOB-OS-TF
Vereos	Philips	2	[2.00, 2.00]	OSEM 3i5s:PSFI-Gau

# Matériel & Méthodes

## Analyse des images TEP

- Segmentation manuelle des lésions avec  $SUV > 4$  + labellisation : lung, bone, pleural, liver, other
- Ré-échantillonnage en  $2 \times 2 \times 2 \text{ mm}^3$
- 25 variables extraites

Acronym	Definition
<b>TMTV</b>	Total Metabolic Tumor Volume
<b>TMTV(lung)</b>	Total Metabolic Tumor Volume of lung lesions
<b>TMTV(bone)</b>	Total Metabolic Tumor Volume of bone lesions
<b>TMTV(pleura)</b>	Total Metabolic Tumor Volume of pleural metastatic lesions
<b>TMTV(liver)</b>	Total Metabolic Tumor Volume of liver lesions
<b>TMTV(others)</b>	Total Metabolic Tumor Volume of other metastatic lesions
<b>SDmax</b>	Distance between the two most distant lesions standardized by the body surface
<b>maxSUVmax or sdSUVmax</b>	Maximum or standard-deviation of SUVmax over all lesions
<b>maxSUVmean or sdSUVmean</b>	Maximum or standard-deviation of SUVmean over all lesions
<b>maxSUVpeak or sdSUVpeak</b>	Maximum or standard-deviation of SUVpeak over all lesions
<b>maxMTV or sdMTV</b>	Maximum or standard-deviation of Metabolic Tumor Volume (MTV) over all lesions
<b>maxTLG or sdTLG</b>	Maximum or standard-deviation of Total Lesion Glycolysis (TLG) over all lesions
<b>TTLG</b>	Total Lesion Glycosis of all lesions
<b>maxNHOcmax* or sdNHOcmax*</b>	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Centroid
<b>maxNHOPmax* or sdNHOPmax*</b>	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Perimeter
<b>minSphericity or sdSphericity</b>	Minimum or standard-deviation of Sphericity over all lesions
<b>SLR</b>	Spleen-to-Liver Ratio: Ratio between $SUV_{mean}(\text{spleen})$ measured in a sphere of 4 ml (diameter of 20 mm) located in healthy splenic tissue and $SUV_{mean}$ measured in healthy liver tissue (sphere of 14 ml, diameter of 20mm)

\* Definition in Hovhannisan-Baghdasarian et al. Promising candidate prognostic biomarkers in 18F-FDG PET images: evaluation in independent cohorts of NSCLC patients. *J Nucl Med*. 2024;65:635-642.

# Matériel & Méthodes

## Analyse des images TEP

- Segmentation manuelle des lésions avec  $SUV > 4$  + labellisation : lung, bone, pleural, liver, other
- Ré-échantillonnage en  $2 \times 2 \times 2 \text{ mm}^3$
- 25 variables extraites
  - 6 indices de charge tumorale**
  - 1 indice de dissémination**
  - 8 indices agrégés sur toutes les lésions soit par sd, soit par max ou min**
  - Total - TLG**
  - Spleen-to-Liver uptake Ratio**

Acronym	Definition
TMTV	Total Metabolic Tumor Volume
TMTV(lung)	Total Metabolic Tumor Volume of lung lesions
TMTV(bone)	Total Metabolic Tumor Volume of bone lesions
TMTV(pleura)	Total Metabolic Tumor Volume of pleural metastatic lesions
TMTV(liver)	Total Metabolic Tumor Volume of liver lesions
TMTV(others)	Total Metabolic Tumor Volume of other metastatic lesions
SDmax	Distance between the two most distant lesions standardized by the body surface
maxSUVmax or sdSUVmax	Maximum or standard-deviation of SUVmax over all lesions
maxSUVmean or sdSUVmean	Maximum or standard-deviation of SUVmean over all lesions
maxSUVpeak or sdSUVpeak	Maximum or standard-deviation of SUVpeak over all lesions
maxMTV or sdMTV	Maximum or standard-deviation of Metabolic Tumor Volume (MTV) over all lesions
maxTLG or sdTLG	Maximum or standard-deviation of Total Lesion Glycolysis (TLG) over all lesions
TTLG	Total Lesion Glycosis of all lesions
maxNHOcmax* or sdNHOcmax*	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Centroid
maxNHOPmax* or sdNHOPmax*	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Perimeter
minSphericity or sdSphericity	Minimum or standard-deviation of Sphericity over all lesions
SLR	Spleen-to-Liver Ratio: Ratio between SUVmean(spleen) measured in a sphere of 4 ml (diameter of 20 mm) located in healthy splenic tissue and SUVmean measured in healthy liver tissue (sphere of 14 ml, diameter of 20mm)

\* Definition in Hovhannisan-Baghdasarian et al. Promising candidate prognostic biomarkers in 18F-FDG PET images: evaluation in independent cohorts of NSCLC patients. *J Nucl Med*. 2024;65:635-642.

# Matériel & Méthodes

## Analyse des images TEP

- Segmentation manuelle des lésions avec  $SUV > 4$  + labellisation : lung, bone, pleural, liver, other
- Ré-échantillonnage en  $2 \times 2 \times 2 \text{ mm}^3$
- 25 variables extraites
  - 6 indices de charge tumorale**
  - 1 indice de dissémination**
  - 8 indices agrégés sur toutes les lésions soit par sd, soit par max ou min**
  - Total - TLG**
  - Spleen-to-Liver uptake Ratio**

🚫 Pas d'index de texture

Acronym	Definition
TMTV	Total Metabolic Tumor Volume
TMTV(lung)	Total Metabolic Tumor Volume of lung lesions
TMTV(bone)	Total Metabolic Tumor Volume of bone lesions
TMTV(pleura)	Total Metabolic Tumor Volume of pleural metastatic lesions
TMTV(liver)	Total Metabolic Tumor Volume of liver lesions
TMTV(others)	Total Metabolic Tumor Volume of other metastatic lesions
SDmax	Distance between the two most distant lesions standardized by the body surface
maxSUVmax or sdSUVmax	Maximum or standard-deviation of SUVmax over all lesions
maxSUVmean or sdSUVmean	Maximum or standard-deviation of SUVmean over all lesions
maxSUVpeak or sdSUVpeak	Maximum or standard-deviation of SUVpeak over all lesions
maxMTV or sdMTV	Maximum or standard-deviation of Metabolic Tumor Volume (MTV) over all lesions
maxTLG or sdTLG	Maximum or standard-deviation of Total Lesion Glycolysis (TLG) over all lesions
TTLG	Total Lesion Glycosis of all lesions
maxNHOcmax* or sdNHOcmax*	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Centroid
maxNHOPmax* or sdNHOPmax*	Maximun or standard-deviation over all lesions of the Normalized distance from the Hotspot of the radiotracer uptake (SUVmax) to the tumor Perimeter
minSphericity or sdSphericity	Minimum or standard-deviation of Sphericity over all lesions
SLR	Spleen-to-Liver Ratio: Ratio between $SUV_{mean}(\text{spleen})$ measured in a sphere of 4 ml (diameter of 20 mm) located in healthy splenic tissue and $SUV_{mean}$ measured in healthy liver tissue (sphere of 14 ml, diameter of 20mm)

\* Definition in Hovhannisan-Baghdasarian et al. Promising candidate prognostic biomarkers in 18F-FDG PET images: evaluation in independent cohorts of NSCLC patients. *J Nucl Med*. 2024;65:635-642.

## Analyse statistique

### Cohorte 1

👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation

## Analyse statistique

### Cohorte 1

👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation

👉 Dichotomisation des caractéristiques par le seuil qui maximise la statistique du log-rank

## Analyse statistique

### Cohorte 1

- 👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation
- 👉 Dichotomisation des caractéristiques par le seuil qui maximise la statistique du log-rank
- 👉 Modèle multivarié en utilisant « *stepwise backward selection* » basé sur l'AIC → **NSCLC-Pro**

## Analyse statistique

### Cohorte 1

- 👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation
- 👉 Dichotomisation des caractéristiques par le seuil qui maximise la statistique du log-rank
- 👉 Modèle multivarié en utilisant « *stepwise backward selection* » basé sur l'AIC → **NSCLC-Pro**
- 👉 Seuil pour distinguer des patients « **Low-risk** » vs « **High-risk** » suivant l'OS (test du log-rank)

## Analyse statistique

### Cohorte 1

- 👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation
- 👉 Dichotomisation des caractéristiques par le seuil qui maximise la statistique du log-rank
- 👉 Modèle multivarié en utilisant « *stepwise backward selection* » basé sur l'AIC → **NSCLC-Pro**
- 👉 Seuil pour distinguer des patients « **Low-risk** » vs « **High-risk** » suivant l'OS (test du log-rank)
- 👉 Validation croisée 5-folds x 100 fois et comparaison avec TMTV, âge et PDL1

## Analyse statistique

### Cohorte 1

- 👉 Sélection des caractéristiques TEP : 1 indice par groupe de corrélation
- 👉 Dichotomisation des caractéristiques par le seuil qui maximise la statistique du log-rank
- 👉 Modèle multivarié en utilisant « *stepwise backward selection* » basé sur l'AIC → **NSCLC-Pro**
- 👉 Seuil pour distinguer des patients « **Low-risk** » vs « **High-risk** » suivant l'OS (test du log-rank)
- 👉 Validation croisée 5-folds x 100 fois et comparaison avec TMTV, âge et PDL1

### Cohorte 2

- Evaluation de **NSCLC-Pro** model, courbe de Kaplan-Meier, test du log-rank

# Résultats – caractéristiques des patients

Patient characteristics	Cohort 1			p-value (ICI vs ICI-C)	Cohort 2			p-value (ICI vs ICI-C)
	All patients	Treated by ICI	Treated by ICI-C		All patients	Treated by ICI	Treated by ICI-C	
<b>Number of patients</b>	197	71	126	0.201	86	54	32	1.000
<b>Sex</b>								
Male	123 (62%)	49 (69%)	74 (59%)		50 (58%)	31 (57%)	19 (59%)	
Female	74 (38%)	22 (31%)	52 (41%)		36 (42%)	23 (43%)	13 (41%)	
<b>Age</b>				0.160				0.987
< 70 y	133 (68%)	43 (61%)	90 (71%)		55 (64%)	34 (63%)	21 (66%)	
≥ 70 y	64 (32%)	28 (39%)	36 (29%)		31 (36%)	20 (37%)	11 (34%)	
<b>Performance Status (PS)</b>				0.743				0.914
< 2	178 (90%)	63 (89%)	115 (91%)		68 (79%)	42 (78%)	26 (81%)	
≥ 2	19 (10%)	8 (11%)	11 (9%)		18 (21%)	12 (22%)	6 (19%)	
<b>PD-L1 expression analysis</b>								
< 1%	33 (17%)	0 (0%)	31 (25%)	< 0.001	10 (12%)	0 (0%)	10 (32%)	< 0.001
1-49%	97 (49%)	2 (3%)	60 (47%)		11 (13%)	0 (0%)	11 (34%)	
<b>≥ 50%</b>	<b>67 (34%)</b>	<b>69 (97%)</b>	<b>35 (28%)</b>		<b>65 (75%)</b>	<b>54 (100%)</b>	<b>11 (34%)</b>	

ICI: immunotherapy alone. ICI-C: immunotherapy in combination with chemotherapy.

In parentheses: percentage relative to the total number of patients in each column.

In bold: pvalue lower than 5%

# Résultats – caractéristiques des patients

Patient characteristics	Cohort 1			p-value (ICI vs ICI-C)	Cohort 2			Cohort 1 vs Cohort 2
	All patients	Treated by ICI	Treated by ICI-C		All patients	Treated by ICI	Treated by ICI-C	
<b>Number of patients</b>	197	71	126	0.201	86	54	32	
<b>Sex</b>								1.000
Male	123 (62%)	49 (69%)	74 (59%)		50 (58%)	31 (57%)	19 (59%)	
Female	74 (38%)	22 (31%)	52 (41%)		36 (42%)	23 (43%)	13 (41%)	
<b>Age</b>				0.160				0.987
< 70 y	133 (68%)	43 (61%)	90 (71%)		55 (64%)	34 (63%)	21 (66%)	
≥ 70 y	64 (32%)	28 (39%)	36 (29%)		31 (36%)	20 (37%)	11 (34%)	
<b>Performance Status (PS)</b>				0.743				0.914
< 2	178 (90%)	63 (89%)	115 (91%)		68 (79%)	42 (78%)	26 (81%)	
≥ 2	19 (10%)	8 (11%)	11 (9%)		18 (21%)	12 (22%)	6 (19%)	
<b>PD-L1 expression analysis</b>								< 0.001
< 1%	33 (17%)	0 (0%)	31 (25%)	< 0.001	10 (12%)	0 (0%)	10 (32%)	< 0.001
1-49%	97 (49%)	2 (3%)	60 (47%)		11 (13%)	0 (0%)	11 (34%)	
≥ 50%	67 (34%)	69 (97%)	35 (28%)		65 (75%)	54 (100%)	11 (34%)	

ICI: immunotherapy alone. ICI-C: immunotherapy in combination with chemotherapy.

In parentheses: percentage relative to the total number of patients in each column.

In bold: pvalue lower than 5%

## ECOG PERFORMANCE SCALE

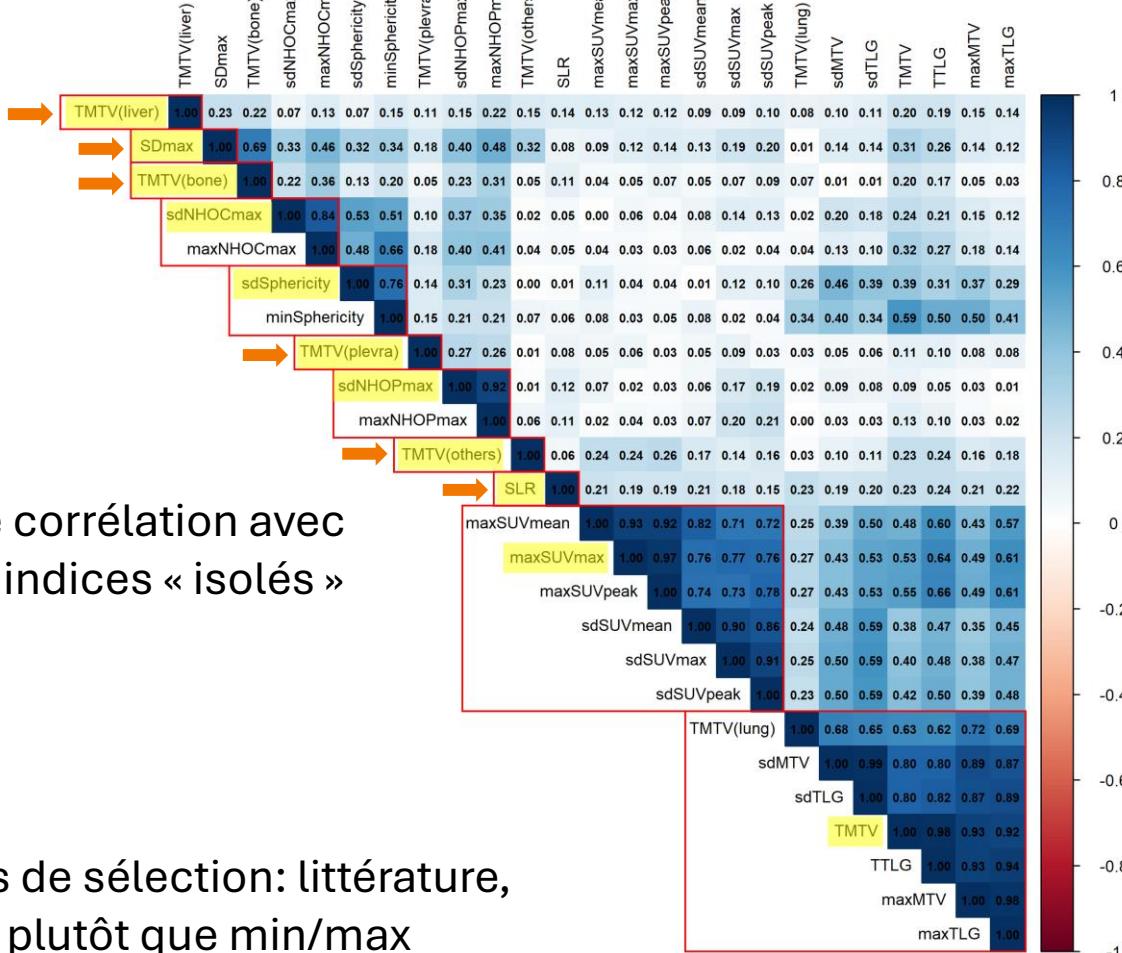
Rating a patient's well-being



# Résultats – sélection des caractéristiques TEP

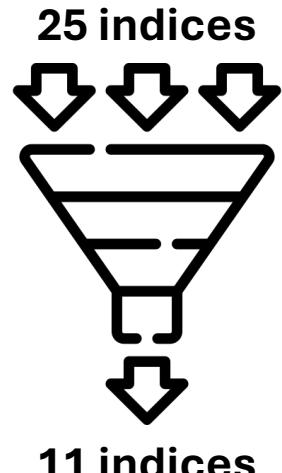


## Cohorte 1



11 groupes de corrélation avec  
 $R \geq 0,7$  dont 6 indices « isolés »

Critères de sélection: littérature,  
sd plutôt que min/max



# Résultats – analyse uni-multivariée



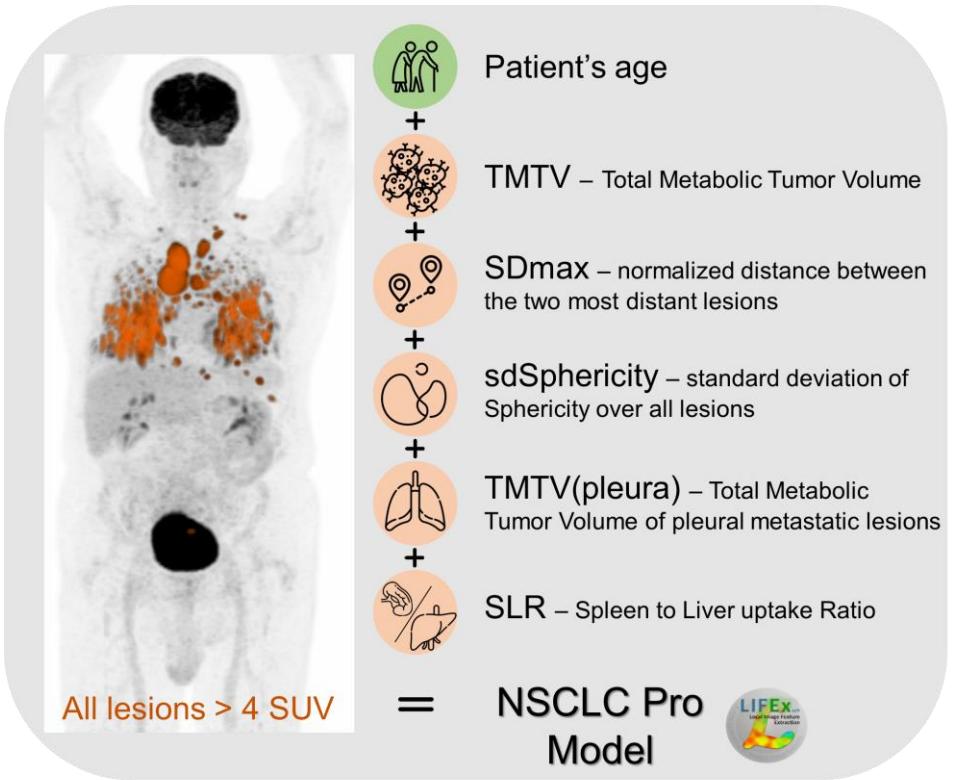
## Cohorte 1

Feature (cut-off)	Univariable analysis		
	HR	95% CI	pvalue
<b>Age</b>			
< 70 y	-		
≥ 70 y	1.8	[1.23-2.64]	0.003
<b>Sex</b>			
Female			
Male	1.31	[0.88-1.96]	0.179
<b>PD-L1 expression analysis</b>			
< 1%	1.43	[0.83-2.47]	0.197
1-49%	-		
≥ 50%	0.88	[0.58-1.36]	0.575
<b>Treatment</b>			
ICI	-		
ICI-C	1.02	[0.69-1.50]	0.922
<b>Performance Status (PS)</b>			
< 2	-		
≥ 2	1.72	[0.95-3.14]	0.075
<b>TMTV</b>			
High (> 82.6 cm <sup>3</sup> )	-		
Low	0.48	[0.33-0.70]	< 0.001
<b>SD max</b>			
High (> 16.07)	-		
Low	0.49	[0.33-0.71]	< 0.001
<b>SLR</b>			
High (> 0.72)	-		
Low	0.39	[0.17-0.88]	0.024
<b>maxSUVmax</b>			
High (> 15.7)	-		
Low	0.79	[0.54-1.15]	0.219
<b>sdSphericity</b>			
High (> 0.09)	-		
Low	0.51	[0.35-0.74]	< 0.001
<b>sdNHOCmax</b>			
High (> 0.23)	-		
Low	0.54	[0.35-0.83]	0.006
<b>sdNHOPmax</b>			
High (> 0.20)	-		
Low	0.64	[0.43-0.93]	0.019
<b>TMTV(pleura)</b>			
High (> 2.16 cm <sup>3</sup> )	-		
Low	0.49	[0.29-0.83]	0.008
<b>TMTV(bone)</b>			
High (> 0.58 cm <sup>3</sup> )	-		
Low	0.57	[0.39-0.84]	0.004
<b>TMTV(others)</b>			
High (> 7.85 cm <sup>3</sup> )	-		
Low	0.77	[0.43-1.37]	0.37

# Résultats – analyse uni-multivariée



## Cohorte 1



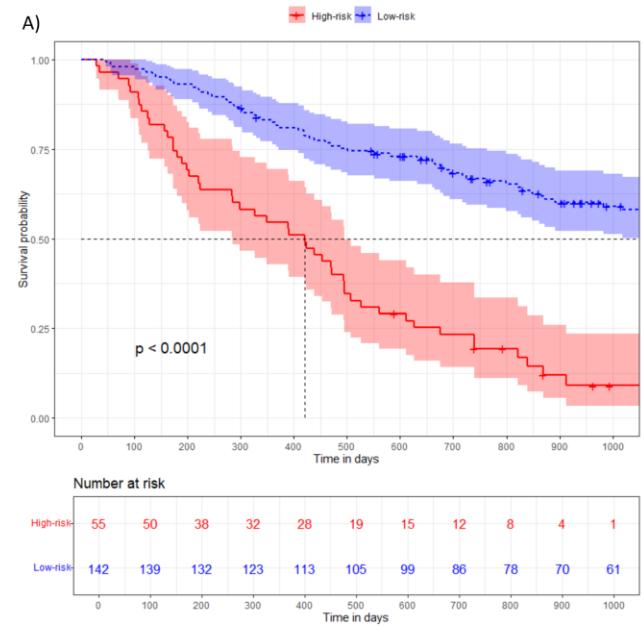
Feature (cut-off)	Univariable analysis			Multivariable analysis		
	HR	95% CI	pvalue	HR	95% CI	pvalue
<b>Age</b>						
< 70 y	-			-		
$\geq 70$ y	1.8	[1.23-2.64]	0.003	2.27	[1.52-3.39]	< 0.001
<b>Sex</b>						
Female						
Male	1.31	[0.88-1.96]	0.179			
<b>PD-L1 expression analysis</b>						
< 1%	1.43	[0.83-2.47]	0.197			
1-49%	-					
$\geq 50$ %	0.88	[0.58-1.36]	0.575			
<b>Treatment</b>						
ICI	-					
ICI-C	1.02	[0.69-1.50]	0.922			
<b>Performance Status (PS)</b>						
< 2	-					
$\geq 2$	1.72	[0.95-3.14]	0.075			
<b>TMTV</b>						
High ( $> 82.6 \text{ cm}^3$ )	-			-		
Low	0.48	[0.33-0.70]	< 0.001	0.6	[0.40-0.91]	0.016
<b>SD max</b>						
High ( $> 16.07$ )	-			-		
Low	0.49	[0.33-0.71]	< 0.001	0.51	[0.34-0.75]	< 0.001
<b>SLR</b>						
High ( $> 0.72$ )	-			-		
Low	0.39	[0.17-0.88]	0.024	0.48	[0.21-1.11]	0.087
<b>maxSUVmax</b>						
High ( $> 15.7$ )	-					
Low	0.79	[0.54-1.15]	0.219			
<b>sdSphericity</b>						
High ( $> 0.09$ )	-			-		
Low	0.51	[0.35-0.74]	< 0.001	0.64	[0.42-0.98]	0.04
<b>sdNHOCmax</b>						
High ( $> 0.23$ )	-					
Low	0.54	[0.35-0.83]	0.006			
<b>sdNHOPmax</b>						
High ( $> 0.20$ )	-					
Low	0.64	[0.43-0.93]	0.019			
<b>TMTV(pleura)</b>						
High ( $> 2.16 \text{ cm}^3$ )	-			-		
Low	0.49	[0.29-0.83]	0.008	0.49	[0.29-0.84]	0.009
<b>TMTV(bone)</b>						
High ( $> 0.58 \text{ cm}^3$ )	-					
Low	0.57	[0.39-0.84]	0.004			
<b>TMTV(others)</b>						
High ( $> 7.85 \text{ cm}^3$ )	-					
Low	0.77	[0.43-1.37]	0.37			

# Résultats – analyse uni-multivariée



## Cohorte 1

A)

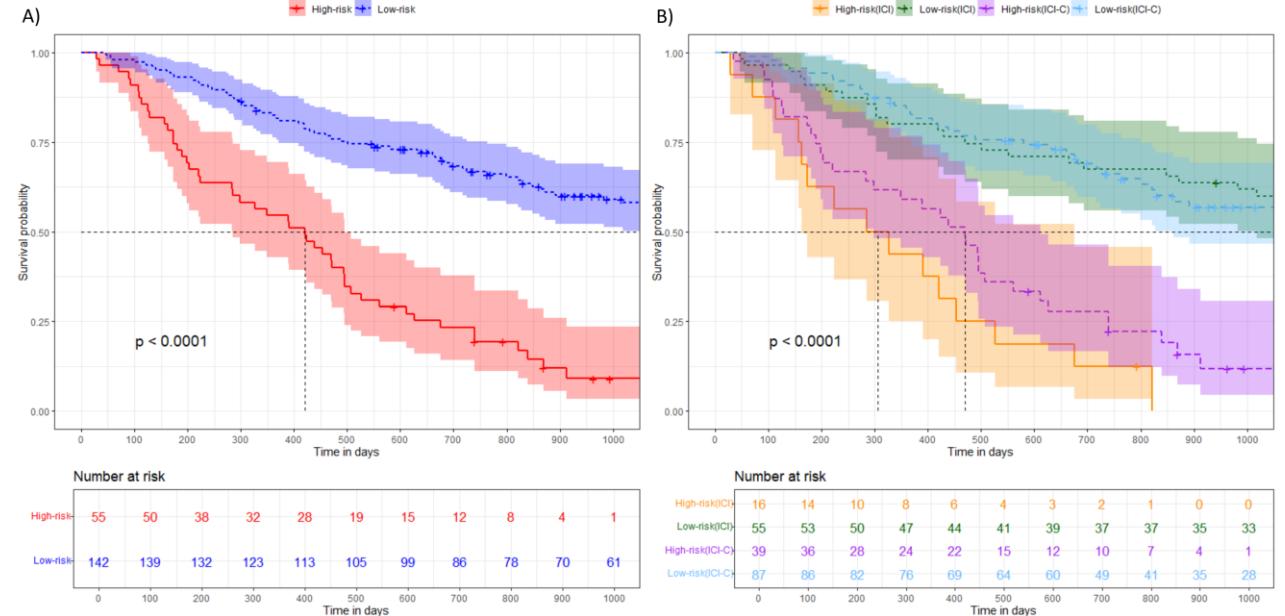


Feature (cut-off)	Univariable analysis			Multivariable analysis		
	HR	95% CI	pvalue	HR	95% CI	pvalue
<b>Age</b>						
< 70 y	-			-		
≥ 70 y	1.8	[1.23-2.64]	0.003	2.27	[1.52-3.39]	< 0.001
<b>Sex</b>						
Female						
Male	1.31	[0.88-1.96]	0.179			
<b>PD-L1 expression analysis</b>						
< 1%	1.43	[0.83-2.47]	0.197			
1-49%	-					
≥ 50%	0.88	[0.58-1.36]	0.575			
<b>Treatment</b>						
ICI	-					
ICI-C	1.02	[0.69-1.50]	0.922			
<b>Performance Status (PS)</b>						
< 2	-					
≥ 2	1.72	[0.95-3.14]	0.075			
<b>TMTV</b>						
High ( $> 82.6 \text{ cm}^3$ )	-					
Low	0.48	[0.33-0.70]	< 0.001	0.6	[0.40-0.91]	0.016
<b>SD max</b>						
High ( $> 16.07$ )	-					
Low	0.49	[0.33-0.71]	< 0.001	0.51	[0.34-0.75]	< 0.001
<b>SLR</b>						
High ( $> 0.72$ )	-					
Low	0.39	[0.17-0.88]	0.024	0.48	[0.21-1.11]	0.087
<b>maxSUVmax</b>						
High ( $> 15.7$ )	-					
Low	0.79	[0.54-1.15]	0.219			
<b>sdSphericity</b>						
High ( $> 0.09$ )	-					
Low	0.51	[0.35-0.74]	< 0.001	0.64	[0.42-0.98]	0.04
<b>sdNHOCmax</b>						
High ( $> 0.23$ )	-					
Low	0.54	[0.35-0.83]	0.006			
<b>sdNHOPmax</b>						
High ( $> 0.20$ )	-					
Low	0.64	[0.43-0.93]	0.019			
<b>TMTV(pleura)</b>						
High ( $> 2.16 \text{ cm}^3$ )	-					
Low	0.49	[0.29-0.83]	0.008	0.49	[0.29-0.84]	0.009
<b>TMTV(bone)</b>						
High ( $> 0.58 \text{ cm}^3$ )	-					
Low	0.57	[0.39-0.84]	0.004			
<b>TMTV(others)</b>						
High ( $> 7.85 \text{ cm}^3$ )	-					
Low	0.77	[0.43-1.37]	0.37			

# Résultats – analyse uni-multivariée



## Cohorte 1

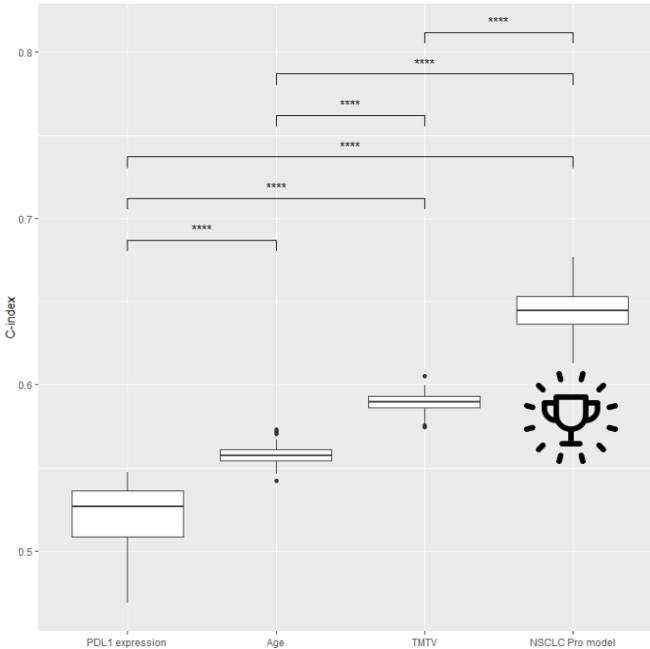


Feature (cut-off)	Univariable analysis			Multivariable analysis		
	HR	95% CI	pvalue	HR	95% CI	pvalue
<b>Age</b>						
< 70 y	-			-		
≥ 70 y	1.8	[1.23-2.64]	0.003	2.27	[1.52-3.39]	< 0.001
<b>Sex</b>						
Female						
Male	1.31	[0.88-1.96]	0.179			
<b>PD-L1 expression analysis</b>						
< 1%	1.43	[0.83-2.47]	0.197			
1-49%	-					
≥ 50%	0.88	[0.58-1.36]	0.575			
<b>Treatment</b>						
ICI	-					
ICI-C	1.02	[0.69-1.50]	0.922			
<b>Performance Status (PS)</b>						
< 2	-					
≥ 2	1.72	[0.95-3.14]	0.075			
<b>TMTV</b>						
High (> 82.6 cm <sup>3</sup> )	-					
Low	0.48	[0.33-0.70]	< 0.001	0.6	[0.40-0.91]	0.016
<b>SD max</b>						
High (> 16.07)	-					
Low	0.49	[0.33-0.71]	< 0.001	0.51	[0.34-0.75]	< 0.001
<b>SLR</b>						
High (> 0.72)	-					
Low	0.39	[0.17-0.88]	0.024	0.48	[0.21-1.11]	0.087
<b>maxSUVmax</b>						
High (> 15.7)	-					
Low	0.79	[0.54-1.15]	0.219			
<b>sdSphericity</b>						
High (> 0.09)	-					
Low	0.51	[0.35-0.74]	< 0.001	0.64	[0.42-0.98]	0.04
<b>sdNHOCmax</b>						
High (> 0.23)	-					
Low	0.54	[0.35-0.83]	0.006			
<b>sdNHOPmax</b>						
High (> 0.20)	-					
Low	0.64	[0.43-0.93]	0.019			
<b>TMTV(pleura)</b>						
High (> 2.16 cm <sup>3</sup> )	-					
Low	0.49	[0.29-0.83]	0.008	0.49	[0.29-0.84]	0.009
<b>TMTV(bone)</b>						
High (> 0.58 cm <sup>3</sup> )	-					
Low	0.57	[0.39-0.84]	0.004			
<b>TMTV(others)</b>						
High (> 7.85 cm <sup>3</sup> )	-					
Low	0.77	[0.43-1.37]	0.37			

# Résultats – validation croisée 5 folds x 100 fois



## Cohorte 1

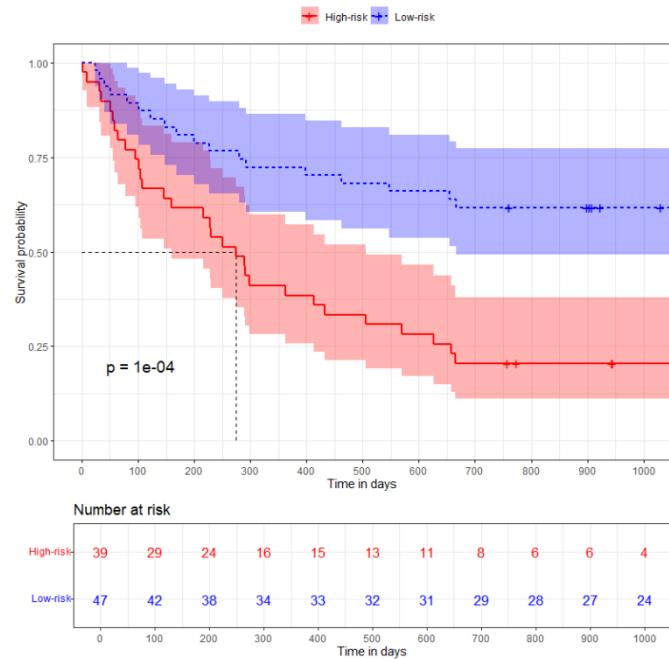


OS rate	Age cut-off = 70 y	PD-L1 expression cut-off = 1%	TMTV cut-off = 82.6 cm <sup>3</sup>	NSCLC-Pro model
<b>1y-OS</b>				
Low-risk	78%	77%	80%	82%
High-risk	67%	65%	67%	55%
<b>2y-OS</b>				
Low-risk	61%	56%	65%	67%
High-risk	42%	45%	40%	23%

# Résultats – validation externe



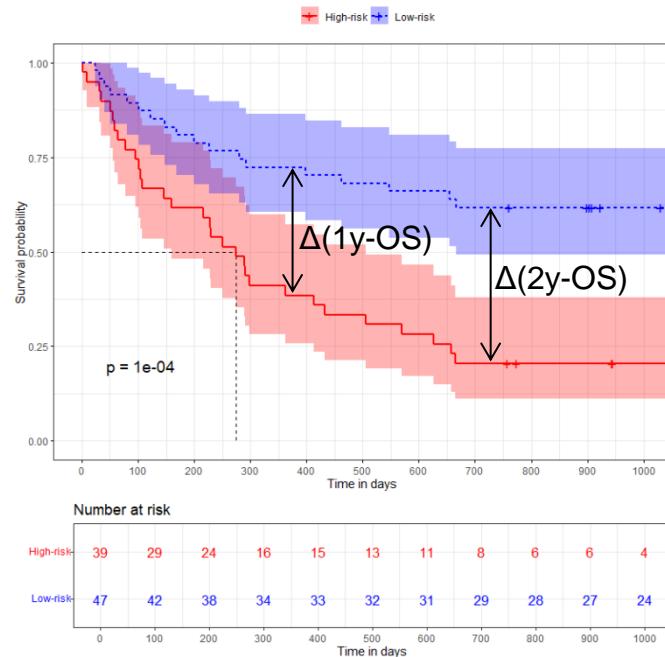
## Cohorte 2



# Résultats – validation externe



## Cohorte 2

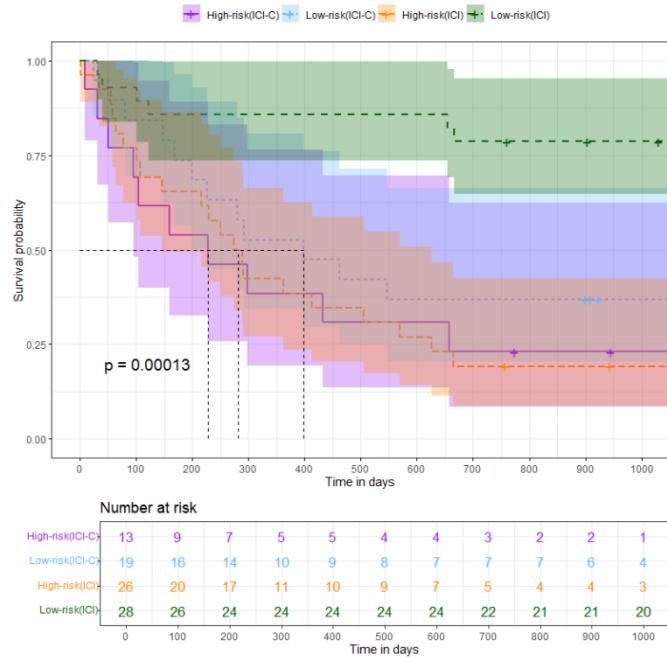


---

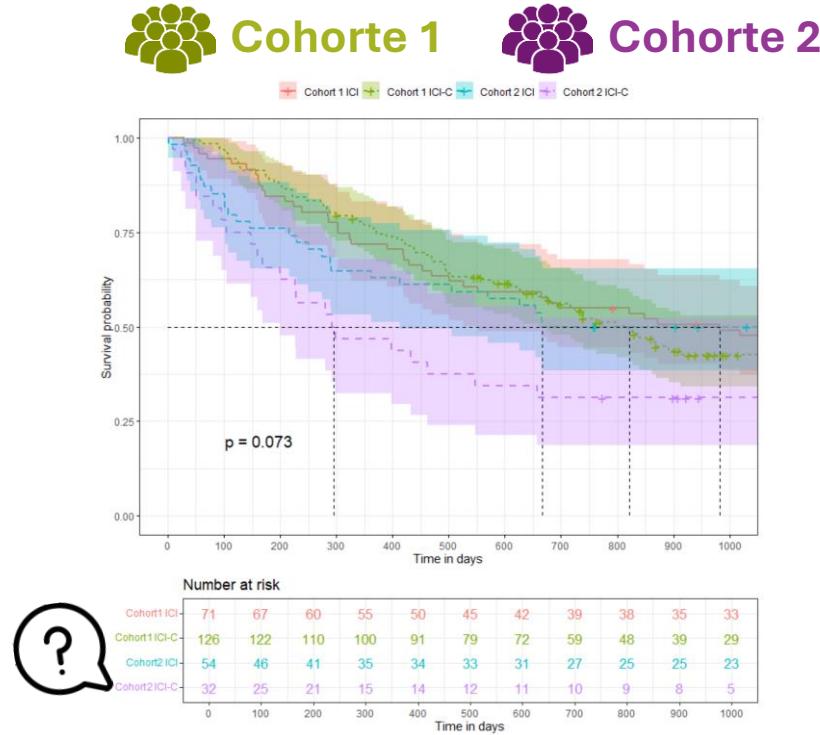
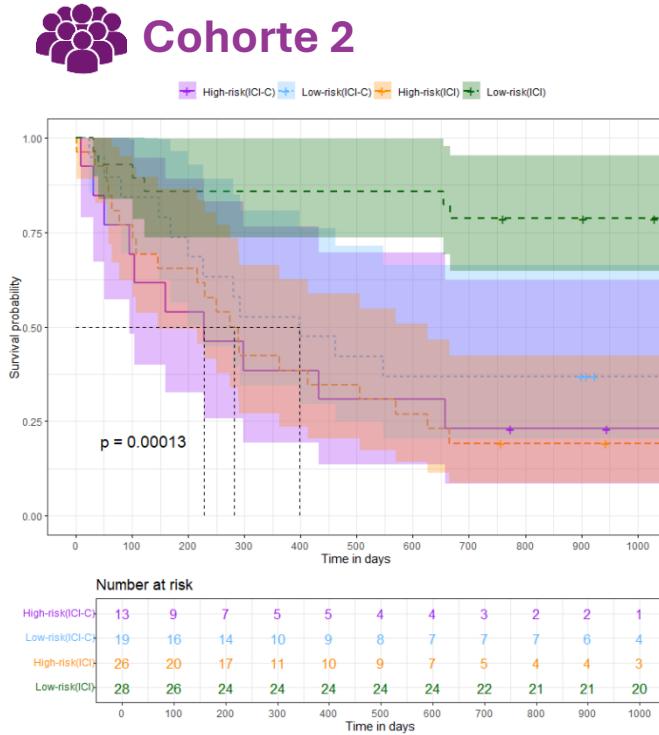
	1y-OS	2y-OS
	Low-risk	82%
	High-risk	55%
	$\Delta$	<b>27%</b>
	Low-risk	72%
	High-risk	39%
	$\Delta$	<b>33%</b>

# Résultats – validation externe

## Cohorte 2



# Résultats – validation externe



# Résultats – score METRICS

## METRICS Tool v1.0

Please fill out all conditions first for relevant sections and then all active items to calculate METRICS score.

Please note that default option is "No".

? Stands for explanation of items and conditions.

C Stands for conditional items or sections.

### Items/Conditions

### Definitions

### Weights

### Options

### Study Design

Item#1	Adherence to radiomics and/or machine learning-specific checklists or guidelines	0.0368	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#2	Eligibility criteria that describe a representative study population	0.0735	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#3	High-quality reference standard with a clear definition	0.0919	<input checked="" type="radio"/> Yes <input type="radio"/> No

### Imaging Data

Item#4	Multi-center	0.0438	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#5	Clinical translatability of the imaging data source for radiomics analysis	0.0292	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#6	Imaging protocol with acquisition parameters	0.0438	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#7	The interval between imaging used and reference standard	0.0292	<input checked="" type="radio"/> Yes <input type="radio"/> No

### Segmentation

Condition#1	Does the study include segmentation?	<input checked="" type="radio"/> Yes <input type="radio"/> No
Condition#2	Does the study include fully automated segmentation?	<input type="radio"/> Yes <input checked="" type="radio"/> No
Item#8	Transparent description of segmentation methodology	0.0337
Item#9	Formal evaluation of fully automated segmentation	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#10	Test set segmentation masks produced by a single reader or automated tool	0.0112

### Image Processing and Feature Extraction

Condition#3	Does the study include hand-crafted feature extraction?	<input checked="" type="radio"/> Yes <input type="radio"/> No
	Appropriate use of image preprocessing techniques with transparent description	0.0622
Item#11	Use of standardized feature extraction software	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#12	Transparent reporting of feature extraction parameters, otherwise providing a default configuration statement	0.0311

### Feature Processing

Condition#4	Does the study include tabular data?	<input checked="" type="radio"/> Yes <input type="radio"/> No
Condition#5	Does the study include end-to-end deep learning?	<input type="radio"/> Yes <input checked="" type="radio"/> No
Item#14	Removal of non-robust features	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#15	Removal of redundant features	0.0200
Item#16	Appropriateness of dimensionality compared to data size	<input checked="" type="radio"/> Yes <input type="radio"/> No

### Preparation for Modeling

Item#18	Proper data partitioning process	0.0599	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#19	Handling of confounding factors	0.0300	<input checked="" type="radio"/> Yes <input type="radio"/> No

### Metrics and Comparison

Item#20	Use of appropriate performance evaluation metrics for task	0.0352	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#21	Consideration of uncertainty	0.0234	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#22	Calibration assessment	0.0176	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#23	Use of uni-parametric imaging or proof of its inferiority	0.0117	<input checked="" type="radio"/> Yes <input type="radio"/> No

Item#24	Comparison with a non-radiomic approach or proof of added clinical value	0.0293	<input checked="" type="radio"/> Yes <input type="radio"/> No
Item#25	Comparison with simple or classical statistical models	0.0176	<input checked="" type="radio"/> Yes <input type="radio"/> No
<b>Testing</b>			
Item#26	Internal testing	0.0375	<input type="radio"/> Yes <input checked="" type="radio"/> No
Item#27	External testing	0.0749	<input checked="" type="radio"/> Yes <input type="radio"/> No
<b>Open Science</b>			
Item#28	Data availability	0.0075	<input type="radio"/> Yes <input checked="" type="radio"/> No
Item#29	Code availability	0.0075	<input type="radio"/> Yes <input checked="" type="radio"/> No
Item#30	Model availability	0.0075	<input checked="" type="radio"/> Yes <input type="radio"/> No
Total METRICS score: 89.4%			
Quality category: Excellent			
Publication ID:			

If you publish any work which uses this tool, please cite the following publication:

Kocak B, Akinci D'Antonioli T, Mercaldo N, et al. METhodological Radiomic Score (METRICS): a quality scoring tool for radiomics research endorsed by EuSoML. Insights Imaging. 2024;15(1):8. Published 2024 Jan 17. doi:10.1186/s13244-023-01572-w

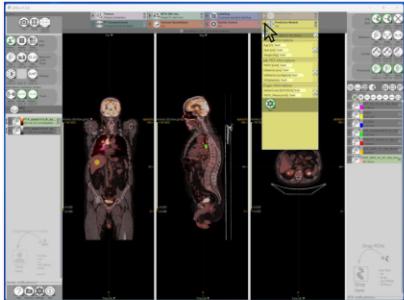
<https://metricsscore.github.io/metrics/METRICS.html>

# Module NSCLC-Pro Score dans LIFEx



## Step 3: Calculate the *NSCLC-Pro Score*\*

Open Predictive Models toolbox.



Update model parameters by clicking on



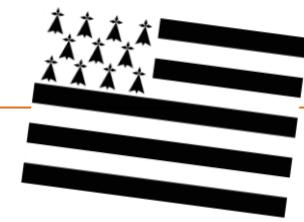
Run the model ,  
the prediction result is displayed.



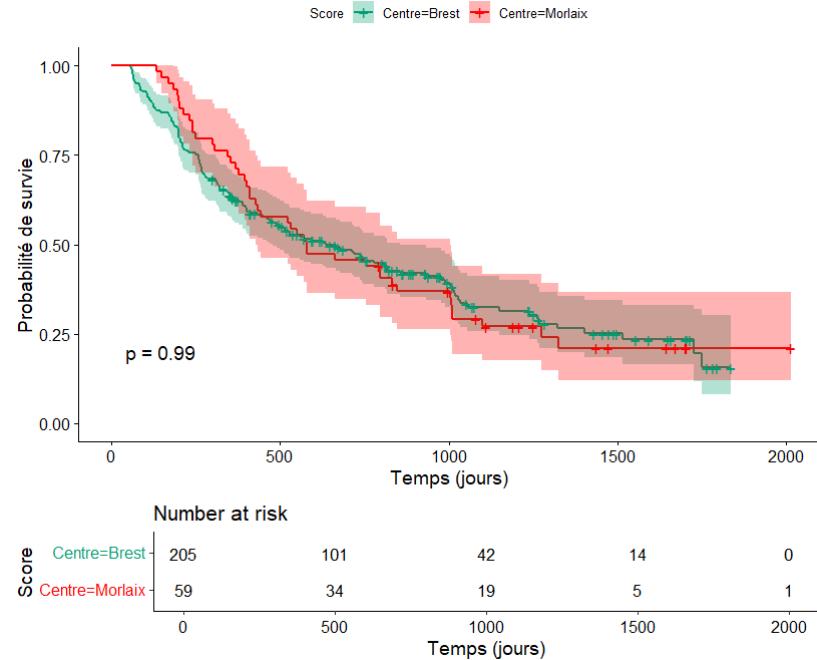
Age, size and weight are filled in automatically from the Dicoms header fields. If these data are missing, you can complete them manually, as they are required for the score calculation.

\*: *NSCLC-Pro Score* is the subject of a declaration of invention. Please contact [contact@lifexsoft.org](mailto:contact@lifexsoft.org) for further information.

# Résultats – 2<sup>ème</sup> validation externe et indépendante !



## Cohorte 3



R. Abgral<sup>1,2</sup>, D. Bourhis<sup>1,2</sup>, V. Bourbonne<sup>3</sup>, K. Amrane<sup>4</sup>, C. Le Meur<sup>3</sup>,  
M. Geier<sup>5,2</sup>, R. Floch<sup>1</sup>, K. Kerleguer<sup>1</sup>, P. Salaün<sup>1,2</sup>

1: Molecular Imaging and Radiotheranostic Department, University Hospital of Brest, Brest, France

2: UMR 1304 Inserm GETBO, Brest, France

3: Radiotherapy Department, University Hospital of Brest, Brest, France

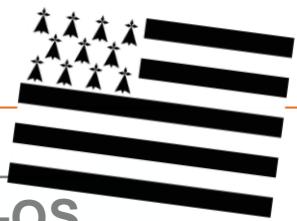
4: Oncology Department, Regional Hospital of Morlaix, Morlaix, France

5: Thoracic Oncology Department, University Hospital of Brest, Brest, France

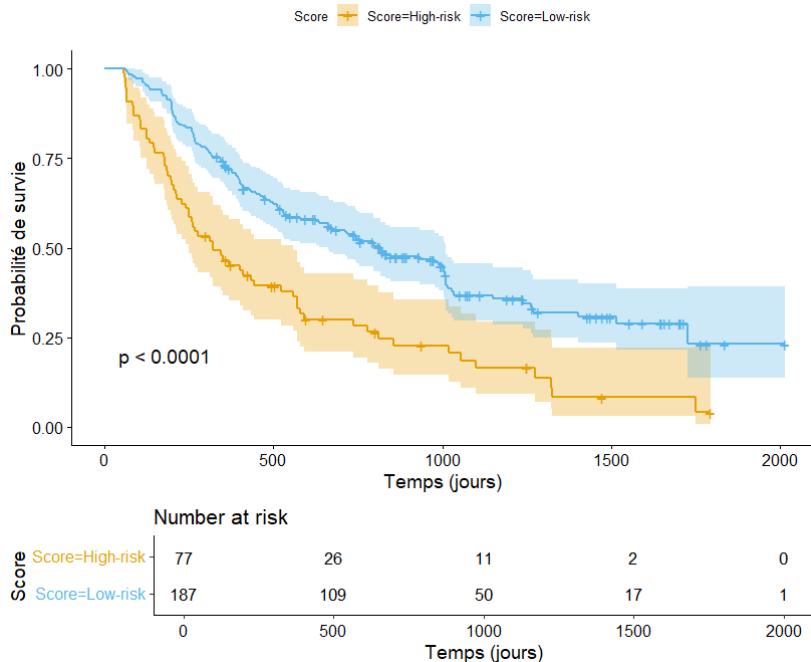
264 patients avec CBNPC traités par  
ICI+chimio en 1<sup>ère</sup> et 2<sup>ème</sup> ligne



# Résultats – 2<sup>ème</sup> validation externe et indépendante !



## Cohorte 3



	1y-OS	2y-OS
	Low-risk    82%	67%
	High-risk    55%	23%
	Δ    27%	44%
	Low-risk    72%	62%
	High-risk    39%	21%
	Δ    33%	41%
	Low-risk    72%	54%
	High-risk    47%	30%
	Δ    25%	24%

# Conclusion

- Développement sur une cohorte rétrospective de 197 patients
- Signature simple et interprétable = âge + 5 indices TEP avant traitement
- Performances pronostiques confirmées sur 2 cohortes indépendantes
  - ✓ Total = 350 patients de 3 centres
  - ✓ ICI ou ICI+C – 1<sup>ère</sup> ou 2<sup>ème</sup> ligne
- Module **NSCLC-Pro model** disponible dans LIFEx pour validation externe

