

A. Puszkiel (1,2), P. Boudou-Rouquette (3), J. Arrondeau (3), M. Wislez (3), E. Fabre (4), G. Bianconi (1), X. Declèves (1,2), A. Juinot (3,5), S. De Percin (3), J. Alexandre (3), F. Goldwasser (3,5), B. Blanchet (1)

(1) Université Paris Cité, Inserm UMR-S1144, Paris, France (2) Cochin University Hospital, Paris, France (3) Medical Oncology Department, Cochin University Hospital, CARPEM, Paris, France (4) Thoracic Oncology Department, Hôpital Européen Georges Pompidou, CARPEM, Université Paris Cité, Paris, France (5) CERTIM, Cochin University Hospital, Paris, France

Background

Objectives

- **Nivolumab** – immune checkpoint inhibitor (anti PD-1) used in the treatment of non-small-cell lung cancer (NSCLC) [1]
 - **Basal hypermetabolism** – increased resting energy expenditure (REE) by more than 10% at treatment initiation [2]
 - Hypermetabolism is associated with **malnutrition and cachexia** which can increase elimination CL of nivolumab (increased protein catabolism) [3,4]
- To evaluate the association between basal REE and nivolumab CL using population PK model
 - To identify the impact of basal REE and nivolumab CL on progression-free survival in NSCLC patients

Methods

- Population PK model

 - 98 patients and 324 nivolumab plasma concentrations
 - MonolixSuite 2023R software (Lixoft)
 - REE was measured (mREE) using ambulatory indirect calorimetry and compared with the theoretical (tREE) value prior to treatment initiation
 - If mREE/tREE > 110% → hypermetabolism
- Survival analysis

 - Individual nivolumab CL was obtained from the final PK model (SAEM method)
 - Primary endpoint: progression-free survival (PFS) – time since treatment start until disease progression or death from any cause
 - Median PFS was 3.43 months (CI95=2.62-5.18)
 - Cox proportional hazard models in R software (version 4.1.2)

Results

Final population PK model

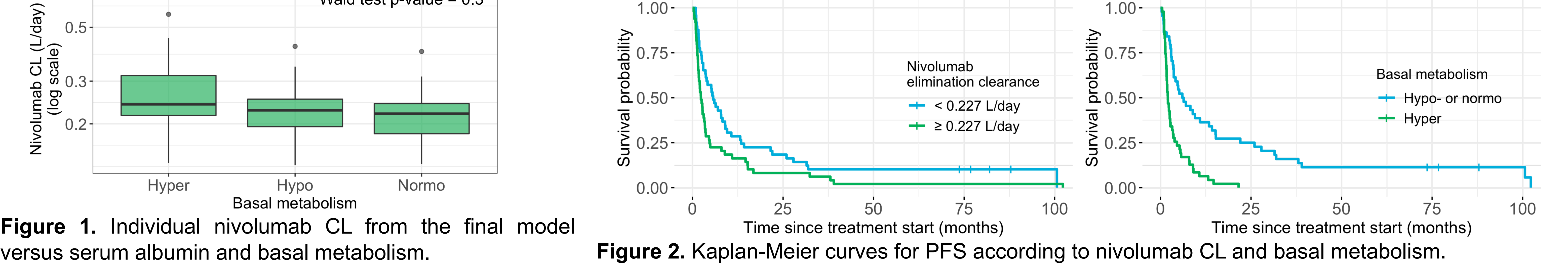
Survival analysis

Table 1. Estimates of the final PopPK model.

Parameters	Mean estimate	RSE%
CL (L/day)	0.228	4.7
β_{albumin}	-0.914	27.1
V1 (L)	4.23	7.8
β_{BW}	0.867	35.0
Q (L/day)	0.77 (fixed)	-
V2 (L)	2.83	19.0
IIV on CL	0.340	14.5
IIV on V1	0.233	40.6
IIV on V2	0.508	39.9
Residual error		
Additive (mg/L)	1.75	26.8
Proportional	0.133	16.2

Table 2. Cox proportional hazard models for progression-free survival.

Variable	Univariate analysis		Multivariate analysis	
	HR (CI95%)	p-value	HR (CI95%)	p-value
Age	1.01 (0.98 – 1.03)	0.65		
Nivolumab CL				
< median (reference)				
≥ median	1.66 (1.10 – 2.50)	0.016	1.77 (1.11 – 2.82)	0.017
Basal metabolism				
Hypo- or normo- (reference)				
Hyper-	2.90 (1.81 – 4.65)	<0.00001	4.19 (2.40 – 7.32)	<0.00001
Glasgow Prognostic Score				
0 (reference)				
1	1.83 (1.11 – 3.01)	0.02		
2	1.69 (0.97 – 2.96)	0.07		
Serum albumine	0.98 (0.94 – 1.01)	0.159		
CRP				
≤ 10 mg/L (reference)				
10 – 50 mg/L	1.82 (1.15 – 2.88)	0.01	1.59 (0.92 – 2.74)	0.09
> 50 mg/L	1.68 (0.94 – 2.99)	0.08	1.15 (0.62 – 2.13)	0.65
TBW weight loss in the last three months				
< 5 % (reference)				
> 5 %	1.50 (0.95 – 2.38)	0.08	2.58 (1.49 – 4.47)	0.0007
ECOG Performance Status				
1 (reference)				
≥ 2	1.15 (0.76 – 1.75)	0.512		



Conclusions

References

These results suggest that basal hypermetabolism not only reflects cachexia (correlated to nivolumab CL) but also a reduced ability of the patient to develop an active immune response to nivolumab.

Perspectives:

- Survival analysis will be carried out in MonolixSuite 2023R software (Lixoft)

[1] Desnoyer *et al.* Eur J Cancer 2020. 128: 119-128.

[2] Boudou-Rouquette *et al.*, EBioMedicine 2021. 73: 103630.

[3] Bajaj *et al.* CPT Pharmacometrics Syst. Pharmacol. 2017. 6, 58–66.

[4] Chatelut *et al.* Pharmacol Res Perspect. 2021; 9:e00757.