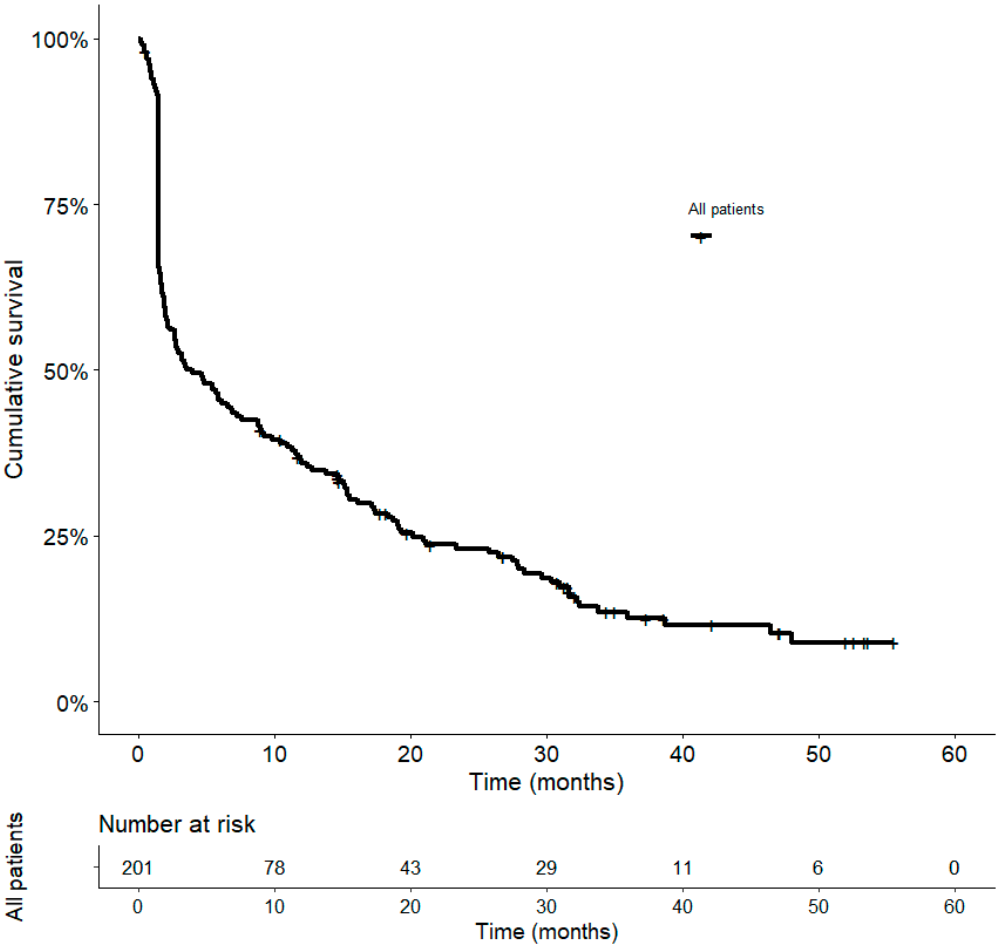
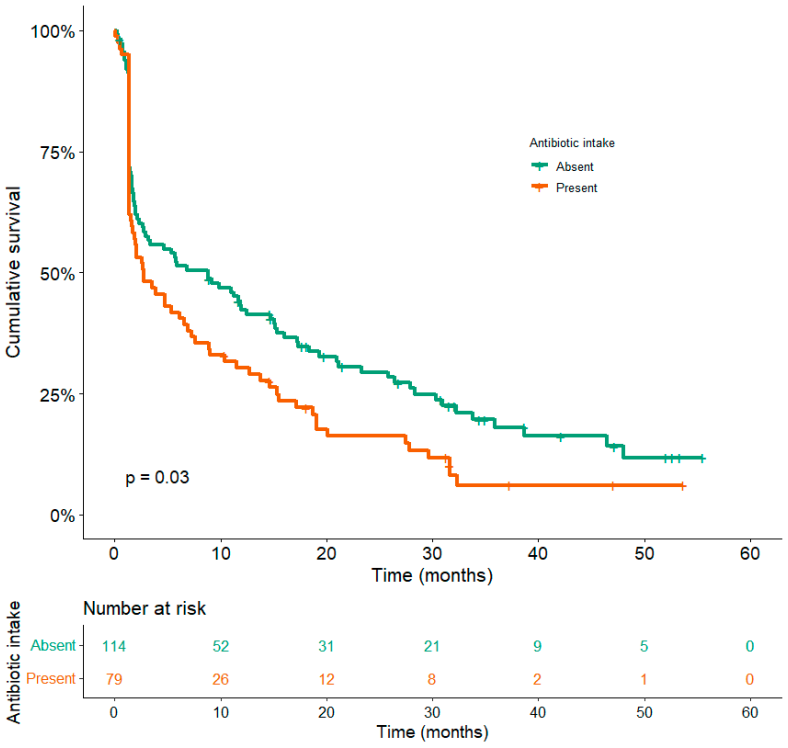
Supplementary Figure S1: TTNT in the entire population

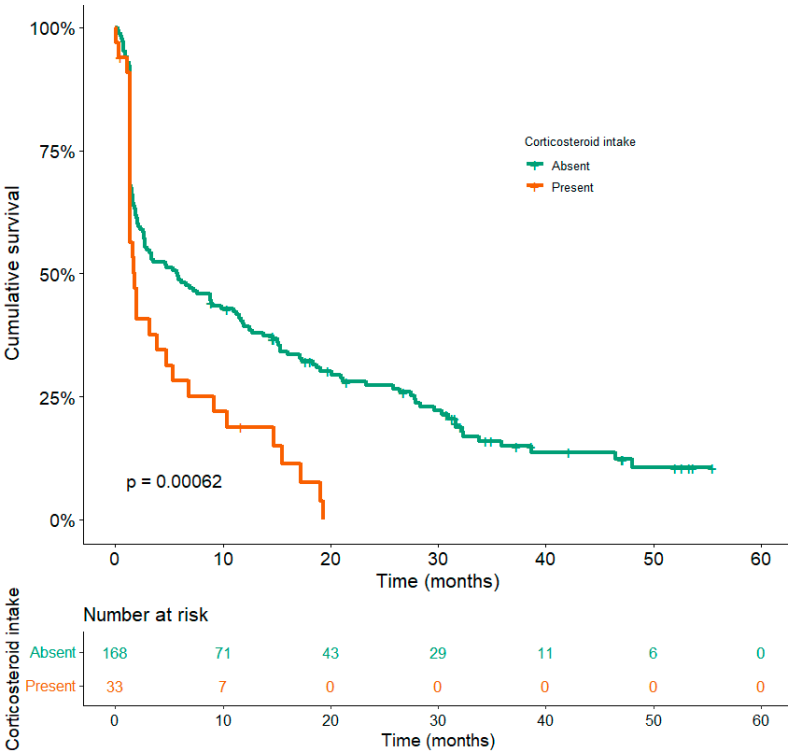


Supplementary Figure S2: TTNT according to treatment with antibiotics **(A),** corticosteroids **(B),** and LIPI score **(C).**

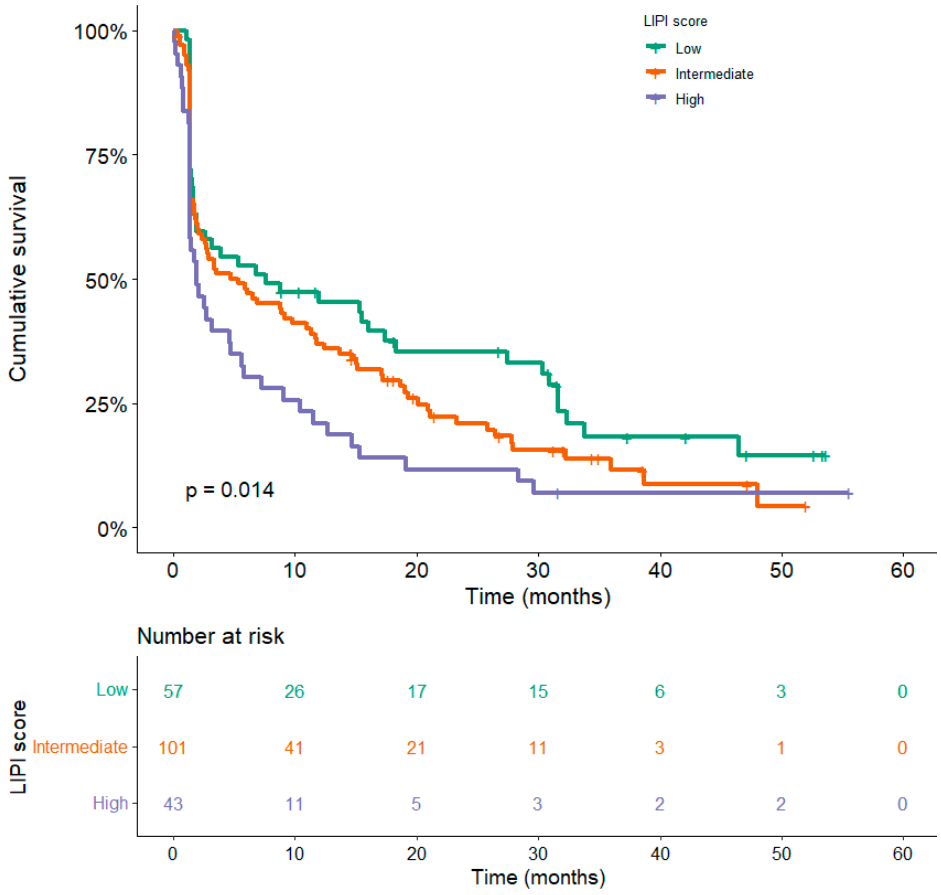
Suppl. Fig. S2A:



Suppl. Fig. S2B:



Suppl. Fig. S2C:



Supplementary Table S1 - Comparison of patients with Grade 3-4 immune-related adverse events with patients without Grade 3-4 irAEs

Variables	N	All patients (% of all patients)	N	Grade 3-4 irAEs		p
				No (% of patients in each variable)	Yes (% of patients in each variable)	
Age at ICI initiation (years) **Mean (SD)** **Median (IQR)**	201	63.3 (10.4) 64 (57 - 71)	201	62.9 (SD: 10.7) 63 (IQR: 56-70.5)	64.9 (SD: 9.4) 66.5 (IQR: 61-72)	0.24
Gender **Male** **Female**	201	130 (65) 69 (35)	201	110 (84.5.) 55 (80)	22 (17) 14 (20.5)	0.57
Healthcare center **Bichat – Claude Bernard AP-HP** **S^{t} Joseph Foundation Hospital**	201	162 (80.5) 39 (19.5)	201	131 (81) 34 (87)	31 (19.5) 5 (13)	0.37
Smoking status **Never-smokers** **Former smokers** **Smokers**	201	11 (5) 90 (45) 100 (50)	201	8 (73.0) 74 (82) 83 (83)	3 (27.5) 16 (18) 17 (17)	0.65
Histology **Squamous cell carcinoma** **Non-squamous cell carcinoma**	201	55 (27.5) 146 (72.5)	201	48 (87.5) 117 (80)	7 (13) 29 (20)	0.30
Performance status **0** **1** **2** **3**	201	27 (13.5) 94 (47) 69 (34) 11 (5.5)	199**	21 (78) 76 (81) 57 (82.5) 11 (100)	6 (22) 18 (19.5) 12 (17.5) 0 (0)	0.45
Metastatic sites count **< 3** **≥ 3**	201	102 (51.0) 99 (49.0)	199**	83 (81.5) 82 (83)	19 (19) 17 (17.5)	0.85
Brain metastasis **No** **Yes**	201	136 (68.0) 65 (32.0)	199**	108 (79.5) 57 (88)	28 (21) 8 (12.5)	0.17
Liver metastasis **No** **Yes**	201	168 (84.0) 33 (16.0)	199**	134 (80) 31 (94)	34 (20.5) 2 (6)	0.08

Disease stage at ICI initiation **Non metastatic** **Metastatic**	201	25 (12.5) 176 (87.5)	199**	19 (76) 146 (83)	6 (24) 30 (17)	0.41
History of CRD **No** **Yes**	192	131 (68.0) 61 (32.0)	191#	107 (82) 50 (82)	24 (18.5) 11 (18.5)	1.00
History of CVD **No** **Yes**	195	94 (48.2) 101 (51.8)	194##	82 (87) 77 (76)	12 (13) 24 (24)	0.06
PPI intake* **No** **Yes**	182	109 (59.9) 73 (40.1)	181‡	94 (86) 53 (72.5)	15 (14) 20 (27.5)	**0.034**
Corticosteroids intake* **No** **Yes**	201	168 (83.6) 33 (16.4)	199**	136 (81) 29 (88)	32 (19) 4 (12.5)	0.46
Antibiotics intake* **No** **Yes**	193	114 (59.1) 79 (40.9)	192‡‡	93 (81.5) 64 (81)	21 (18.5) 15 (19)	1.00
ICI sequence **First-line** **Following chemotherapy**	201	61 (30.3) 140 (69.7)	199**	49 (80.5) 116 (83)	12 (20) 24 (17.5)	0.84
ICI type **Nivolumab** **Pembrolizumab** **Nivolumab + Ipilimumab**	201	138 (68.7) 51 (25.4) 12 (6.0)	199**	116 (84) 43 (84.5) 6 (50)	22 (16) 8 (16) 6 (50)	**0.023**
PD-L1 TPS **<1 %** **1-49 %** **≥50 %**	158	33 (20.9) 37 (23.4) 88 (55.7)	156‡‡‡	31 (94) 30 (81) 68 (77.5)	2 (6) 7 (20) 20 (23)	0.11

SD, standard deviation; IQR, interquartile range; irAEs, immune-related adverse events; ICI, immune checkpoint inhibitor; CRD, chronic respiratory disease; CVD, cardiovascular disease; PPI, proton pump inhibitor; TPS, tumor proportion score.

* during the month preceding and/or the three first months following the initiation of ICI treatment.

** missing data in 2 patients; # missing data in 10 patients; ## missing data in 7 patients; ‡ missing data in 20 patients

‡‡missing data in 9 patients; ‡‡‡missing data in 45 patients

Supplementary Table S2 – Univariable ~~(Kaplan-Meier)~~ and multivariable analyses (Cox proportional hazards) for time to new treatment (TTNT)

		Univariable analysis			Multivariable analysis		
Variables	**N (events)**	**HR**	**95% CI**	**P value**	**aHR**	**95% CI**	**P value**
Age at ICI initiation (years)	201 (169)						
> 65	91 (75)	-		0.286			
≤ 65	110 (94)	1.2	0.9-1.6				
Gender	201 (169)						
Female	69 (51)	-		**0.018**	1.5	1.1-2.1	**0.020**
Male	132 (118)	1.5	1.1-2.1				
PS at ICI initiation	201 (169)						
0-1	121 (94)	-		**<0.0001**	1.5	1.1-2.1	**0.010**
≥ 2	80 (75)	1.9	1.4-2.6				
Antibiotic intake*	193 (161)						
No	114 (90)	-		**0.039**	1.4	1.0-1.9	0.062
Yes	79 (71)	1.4	1.0-1.9				
Corticosteroid intake*	201 (169)						
No	168 (138)	-		**0.002**	1.6	1.0-2.4	**0.034**
Yes	33 (31)	1.9	1.3-2.8				
Histological type	201 (169)						
Squamous	55 (49)	-		0.597			
Non-squamous	146 (120)	0.9	0.7-1.3				
Number of metastatic sites	201 (169)						
< 3	102 (78)	-		**<0.0001**	1.6	1.1-2.2	**0.017**
≥ 3	99 (91)	1.9	1.4-2.6				
PD-L1 status (TPS)	158 (129)			0.108			
≥ 50	88 (67)	-		-			
0	33 (31)	1.5	1.0-2.4	0.048			
1-49	37 (31)	1.3	0.9-2.0	0.189			
Disease stage at ICI initiation	201 (169)						
Non metastatic	25 (21)	-		0.133			
Metastatic	176 (148)	1.4	0.9-2.3				
Brain metastasis	201 (169)						
No	136 (107)	-		**<0.001**			
Yes	65 (62)	1.8	1.3-2.5				
Liver metastasis	201 (169)						
No	168 (137)	-		**<0.0001**	1.9	1.2-2.9	**0.006**
Yes	33 (32)	2.4	1.6-3.5				
ICI sequence	201 (169)						
First-line	61 (49)	-		0.828			
Following chemotherapy	140 (120)	1.0	0.7-1.4				
ICI type	201 (169)						
Nivolumab and Ipilimumab	12 (10)	-		0.328			
Nivolumab or Pembrolizumab	189 (159)	1.4	0.7-2.6				
LIPI score	201 (169)			**0.022**			**0.023**
0	57 (44)	-		-	-		-
1	101 (85)	1.3	0.9-1.9	0.155	1.7	1.1-2.5	**0.010**
2	43 (40)	1.8	1.2-2.8	**0.006**	1.7	1.1-2.7	**0.023**
Grade 3-4 irAEs	201 (169)						
Yes	36 (25)	-		**<0.0001**	2.4	1.6-3.8	**<0.0001**
No	165 (144)	2.4	1.6-3.7				

* During the month preceding and/or the three first months following the initiation of ICI treatment. 95% CI, 95% confidence interval; aHR, adjusted hazard ratio; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; PD-L1, programmed death ligand 1; PS, performance status, TPS, tumor proportion score; TTNT, time to new treatment.

The multivariable analysis included 193 patients with all available data, accounting for 161 events.

Supplementary Table S3 – Multivariable analysis by Cox proportional hazards for overall survival (OS), including PD-L1

Multivariable analysis (events = 102/151)			
Variables	**aHR**	**95% CI**	**P value**
Gender			
Female	1.8	1.1-2.8	**0.014**
Male			
PS at ICI initiation			
0-1	1.9	1.2-2.9	**0.005**
≥ 2			
Antibiotic intake*			
No	1.7	1.1-2.6	**0.017**
Yes			
Corticosteroid intake*			
No	2.2	1.2-3.9	**0.010**
Yes			
Number of metastatic sites			
< 3	1.6	0.9-2.6	0.088
≥ 3			
Brain metastasis			
No	1.7	1.0-2.9	**0.035**
Yes			
Liver metastasis			
No	2.5	1.4-4.2	**0.001**
Yes			
LIPI score			**<0.001**
0	-		-
1	3.2	1.8-5.6	**<0.0001**
2	2.2	1.2-4.0	**0.007**
Grade 3-4 irAEs			
No	3.4	1.9-6.4	**<0.0001**
Yes			

* During the month preceding and/or the three first months following the initiation of ICI treatment.

95% CI, 95% confidence interval; aHR, adjusted hazard ratio; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse events; PS, performance status.

PD-L1 was included in the modeling procedure, the multivariable analysis including 151 patients with all available data accounting for 102 events. PD-L1 is not retained in the final model. Stage was excluded either from the model since tightly linked to brain, liver and number of metastases variables.