

SUPPLEMENTARY MATERIALS

Supplementary Tables

Supplementary Table 1. Identification of covariates using hospital discharge diagnoses and long-term disease (LTD) diagnoses

Characteristics	Hospital discharge diagnoses and LTD diagnoses (ICD-10 codes) ^a Dispensed drugs (ATC codes) ^b Medical or surgical procedures ^c
Location of metastatic sites	
Brain	diagnosis: C793 C794
Lung	diagnosis: C780 C782 C783
Bone	diagnosis: C795
Liver	diagnosis: C787
Digestive system	diagnosis: C784 C785 C786 C788
Lymph node	diagnosis: C77 R590
Skin	diagnosis: C792
Mediastinum	diagnosis: C781
Urinary tract	diagnosis: C790 C791 C797
Others	diagnosis: C796 C798 C80.X except C80+0
Previous therapies	
Stereotactic radiotherapy	medical procedure - stereotactic radiotherapy
External beam radiotherapy	medical procedure - external beam radiotherapy
Lymphadenectomy	surgical procedure - lymphadenectomy
Surgical resection of distant metastases	surgical procedure - tumor resection in any organ except cutaneous or subcutaneous location
Comorbidities	
Cardiovascular and cerebrovascular disease	
Acute ischemic heart disease ^d	diagnosis: I200 I200+0 I201 I21-I24
Chronic ischemic heart disease ^e	diagnosis: I200 I200+0 I201 I21-I24 I208 I209 I25
Acute ischemic cerebrovascular disease ^d	diagnosis: I63 I64
Hemorrhagic stroke ^d	diagnosis: I61 I62
Sequelae or history of cerebrovascular disease ^e	diagnosis: I61-I64 I67 I69
Acute heart failure ^d	diagnosis: I110 I130 I132 I139 I50 K761 J81
Chronic heart failure ^e	diagnosis: I110 I130-I132 I139 I42 I43 I50 K761 J81 Q20-Q24
Cardiac arrhythmia	diagnosis: I471 I48
Cardiac valve disease	diagnosis: I05-I08 I34-I39 T820 T826 Z952-54
Acute peripheral vascular disease ^d	diagnosis: I710 I711 I713 I715 I718 I74 K550 or medical procedure of revascularization
Chronic peripheral vascular disease ^e	diagnosis: I70 I710-I716 I718 I719 I72 I731 I739 I74 I771-772 I775-779 I79 K550 K551 K558-559 Z958-959 I65 or medical procedure – revascularization

Respiratory disease	
Chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)	diagnosis: E84 I270 I27.9X.001 I28 G473 J41-47 J60-67 J684 J700 J701 J703 J841 J848 J982-983 or drug: R03AC12 R03AC13 R03AC18 R03AC19 R03AK06 R03AK07 R03AK08 R03AK09 R03AK10 R03AK11 R03AK12 R03AL R03BB
Metabolic disease	
Diabetes	diagnosis: E10-E14 G590, G730 G990 H280 H360 I792 M142 M146 N083 or drug: A10 except A10BX06
Liver and pancreatic disease	
Mild or moderate liver disease	diagnosis: B18 B942 K700-703 K709 K713-715 K717 K73 K74 or drug: J05AB04 J05AE11 J05AE12 J05AE14 J05AF05 J05AF07 J05AF08 J05AF09 J05AF10 J05AF11 J05AX14 J05AX15 J05AX16 J05AX65 J05AX67 L03AB09 L03AB10 L03AB11
Severe liver disease	diagnosis: I85 I864 I982 K704 K711 K721 K729 K762 K766-767
Pancreatic disease	diagnosis : K860 K861 K861+0 K861+8 K863 T86.8.1
Renal disease	
Chronic renal disease	diagnosis: I12 I13 N01 N03-05 N07 N081-085 N11 N161-168 N17 N183-189 N19 N250 N26 Q611-613 Q618-619
Dialysis ^d	diagnosis: Z49 Z992 or specific cost coding for dialysis or medical procedure – dialysis
Kidney transplant ^f	diagnosis: Z940 T861 or diagnosis-related-group for kidney transplant or surgical procedure - kidney transplant
Immunosuppression	
HIV infection	diagnosis: B20-B24 B24+0+1+9 F024 Z21 or drug: J05AF01 J05AF02 J05AF03 J05AF04 J05AF06 J05AF13 J05AG01 J05AG03 J05AG04 J05AG05 J05AR01 J05AR02 J05AR04 J05AE01 J05AE02 J05AE03 J05AE04 J05AE05 J05AE07 J05AE08 J05AE09 J05AE10 J05AR10 J05AR06 J05AR08 J05AR09 J05AR13 J05AR18 J05AX07 J05AX08 J05AX09 J05AX12
Solid organ transplant (except kidney) ^f	diagnosis: Z941-944 Z9481-9482 T862-864 or diagnosis-related-group for organ transplant or surgical procedure - organ transplant
Inflammatory and systemic disease	
Inflammatory bowel disease	diagnosis: K50-51 M074-075
Inflammatory rheumatic disorder or psoriasis requiring immunosuppressive or immunomodulating agents	diagnosis: L40 M05-09 M120 M123 M45 M460-461 M468-469 M797 and drug: oral formulation of corticosteroid or L04AA06 L04AA13 L04AA24 L04AA23 L04AA26 L04AA29 L04AA32 L04AA33 L04AA37 L04AB L04AC05 L04AC07 L04AC10 L04AC12 L04AC13 L04AC16 L04AD01 L04AX01 L04AX02 L04AX03 L01AA01 A07EC01
Connective tissue disease requiring immunosuppressive or immunomodulating agents	diagnosis: L942-944 M300-302 M308 M313-319 M32-34 M350-353 M359 M360 and drug: oral formulation of corticosteroid or L04AA06 L04AA13 L04AA24 L04AA23 L04AA26 L04AA29 L04AA32 L04AA33 L04AA37 L04AB L04AC05 L04AC07 L04AC10 L04AC12 L04AC13 L04AC16 L04AD01 L04AX01 L04AX02 L04AX03 L01AA01 A07EC01
Cancer	
Second cancer (other than melanoma)	diagnosis: Cxx except C43-44 C77-79 B21
Neurological disease	
Parkinson's disease and extrapyramidal syndromes	diagnosis: F023 G20 G213-219 G22 G23 G258-259 G26

Multiple sclerosis and related disorders	or drug: N04BA02 N04BA03 N04BC02 N04BD01 N04BD02 N04BX01 N04BX02 or certain formulations of bromocriptine, lisuride, apomorphine, piribedil, ropinirole, rotigotine diagnosis: G35 G360 G368-369 G370-371 G373-379 or drug: L03AB07 L03AB08 L03AB13 L03AX13 L04AA27 L04AA31 N07XX09
Paralysis	diagnosis: G041 G114 G80-G83
Neuromuscular disease	diagnosis: G60 G62 G631-638 G70-G72 G730-733 G735-737
Epilepsy	diagnosis: G40 G41 or drug: N03AA02 N03AA03 N03AF03 N03AF04 N03AD01 N03AD03 N03AX03 N03AX07 N03AX10 N03AX13 N03AX14 N03AX15 N03AX17 N03AX18 N03AX21 N03AX22 N03AB05 N03AG04 N03AG05 N03AG06
Dementia	diagnosis: F00-F01 F020-F022 F028 F03 F051 G30 G310 G311
Mental deficiency	diagnosis: F70-F73 F78 F79 F840-844 F848-849
Psychiatric disease	
Depression and mood disorders	diagnosis: F30-F34, F38-F48 or drug: N06A N05AN01 N03AG02 or certain formulations of valproic acid
Schizophrenia and delusional disorders	diagnosis: F20-F25 F28-F29 or drug: N05A except N05AN01 N05AL06 N05AA07
Alcohol abuse	diagnosis: E24 E512 F10 K70 T510 T519 G312 G621 G721 I426 K292 K860 Z502 Z714 Z721
Substance abuse	diagnosis: F11-F16 F18-F19 Z503 Z715 Z722 or drug: N07BB01 N07BB03 N07BB04

^a Long-term disease (LTD) diagnoses and hospitalization discharge diagnoses (main, related or associated diagnosis) were sought in the 4 years prior to the initiation of the anti-melanoma treatment for comorbidities, and in the year prior to the initiation of the anti-melanoma treatment for metastatic sites.

^b Dispensed drugs were sought in the year prior to the initiation of the anti-melanoma treatment (at least 3 dispensations), in the 4 years prior to initiation for immunosuppressive and immunomodulating agents (at least 1 dispensation), except for oral corticosteroids (at least 3 dispensations in the year).

^c Medical or surgical procedures were sought in the 4 years prior to the initiation of the anti-melanoma treatment for comorbidities, and in the year prior to the antibiotic timeframe for previous therapies.

^d in the year prior to the initiation of the anti-melanoma treatment

^e algorithm subject to a hierarchical rule, as follows: acute > chronic or sequelae

^f information was screened for until 2009.

Supplementary Table 2. Characteristics of patients receiving targeted therapy as a first-line treatment for metastatic melanoma and standardized mean differences according to antibiotic exposure

Characteristics	No. (%)	Standardized mean difference, % ^a	
		STD in the initial population	STD in the pseudo-population
Antibiotics			
Antibiotics in the 3 months before initiation of the first-line treatment	460 (30.1)	-	-
Antibiotics in the month before initiation of the first-line treatment	225 (14.7)	-	-
High-impact antibiotics in the 3 months before initiation of the first-line treatment ^a	233 (15.3)	-	-
Age, years			
Mean (SD)	60 (15)	-1.1	-1.1E-11
Range	18-95		
Sex			
Male	863 (56.5)	13.1	4.7E-12
Female	664 (43.5)	13.1	4.7E-12
Location of metastatic sites ^b			
Brain	320 (21.0)	-7.3	1.6E-11
Lung	418 (27.4)	11.1	5.6E-12
Bone	236 (15.5)	6.7	-7.3E-12
Liver	285 (18.7)	16.5	2.9E-12
Digestive system	176 (11.5)	8.6	1.2E-11
Lymph node	628 (41.1)	27.1	-6.8E-12
Skin	234 (15.3)	13.9	5.9E-12
Mediastinum	23 (1.5)	7.4	4.5E-12
Urinary tract	83 (5.4)	-5.6	-8.8E-12
Others	137 (9.0)	4.0	-1.7E-12
Number of metastatic sites ^b			
Mean (SD)	1.7 (1.7)	19.4	5.0E-12
Previous therapies ^c			
Stereotactic radiotherapy	71 (4.6)	-2.9	3.7E-12
External beam radiotherapy	104 (6.8)	7.1	5.7E-12
Lymphadenectomy	552 (36.1)	4.7	-3.0E-11
Surgical resection of distant metastases	139 (9.1)	3.4	6.8E-12
Comorbidities ^d			
Cardiovascular and cerebrovascular disease			
Recent acute ischemic heart disease ^c	13 (0.9)	3.5	-4.1E-11
Chronic ischemic heart disease	71 (4.6)	-0.6	7.2E-12
Recent acute ischemic cerebrovascular disease ^c	10 (0.7)	3.6	2.8E-12
Recent hemorrhagic stroke ^c	35 (2.3)	4.9	5.3E-12
Sequelae or history of cerebrovascular disease	31 (2.0)	1.4	4.8E-12
Recent acute heart failure ^c	21 (1.4)	6.8	-1.5E-11

Chronic heart failure	40 (2.6)	5.6	-8.2E-12
Cardiac arrhythmia	100 (6.5)	3.6	9.1E-12
Cardiac valve disease	33 (2.2)	-6.6	-1.3E-11
Recent acute peripheral vascular disease ^c	13 (0.9)	3.5	3.2E-12
Chronic peripheral vascular disease	55 (3.6)	7.1	-1.3E-11
Respiratory disease			
Chronic respiratory disease (including asthma and chronic obstructive pulmonary disease)	142 (9.3)	11.7	-3.0E-11
Metabolic disease			
Diabetes	160 (10.5)	1.8	-1.8E-11
Liver and pancreatic disease			
Mild or moderate liver disease	13 (0.9)	0.3	3.0E-12
Severe liver disease	11 (0.7)	5.8	3.2E-12
Pancreatic disease	1 (0.1)	-	-
Renal disease			
Chronic renal disease	67 (4.4)	8.5	7.7E-12
Dialysis ^c	2 (0.1)	3.1	1.3E-12
Kidney transplant ^c	1 (0.1)	-	-
Immunosuppression			
HIV infection	2 (0.1)	-	-
Solid organ transplant (except kidney) ^c	1 (0.1)	-	-
Inflammatory and systemic disease			
Inflammatory bowel disease	6 (0.4)	5.4	-7.9E-11
Inflammatory rheumatic disorder or psoriasis requiring immunosuppressive or immunomodulating agents	12 (0.8)	-10.3	-6.5E-10
Connective tissue disease requiring immunosuppressive or immunomodulating agents	6 (0.4)	5.4	-1.1E-10
Cancer			
Second cancer (other than melanoma)	160 (10.5)	3.8	1.2E-11
Neurological disease			
Parkinson's disease and extrapyramidal syndromes	17 (1.1)	5.3	3.8E-12
Multiple sclerosis and related disorders	4 (0.3)	-	-
Paralysis	84 (5.5)	-8.9	7.2E-12
Neuromuscular disease	17 (1.1)	2.5	-3.2E-11
Epilepsy	59 (3.9)	-6.3	6.0E-12
Dementia	13 (0.9)	-3.2	2.8E-12
Mental deficiency	3 (0.2)	0.7	1.7E-12
Psychiatric disease			
Hospitalization in a psychiatric hospital	26 (1.7)	-12.8	-2.7E-12
Depression and mood disorders	250 (16.4)	8.0	-7.5E-12
Schizophrenia and delusional disorders	44 (2.9)	6.7	5.7E-12
Alcohol abuse	70 (4.6)	-4.7	-5.0E-12
Substance abuse	10 (0.7)	0.0	2.7E-12

^a Standardized mean differences (STD) are provided for the initial populations (before overlap weighting), and for the pseudo-populations (after overlap weighting).

- : covariates with zero values (no exposed or unexposed individual) were not included in the calculation of the propensity score

Supplementary Table 3. Crude and weighted hazard ratios estimating the association between antibiotic use and the outcome following anti-melanoma treatment

Analyses	Anti-PD-1 antibody cohort		Targeted therapy cohort	
	Crude HR (95%CI)	Weighted HR (95%CI)	Crude HR (95%CI)	Weighted HR (95%CI)
Antibiotic use in the 3 months before initiation of the first-line treatment				
Overall survival	1.01 (0.88-1.16)	1.01 (0.88-1.17)	1.14 (0.98-1.34)	1.08 (0.92-1.27)
Time-to-treatment discontinuation	1.00 (0.90-1.11)	1.00 (0.89-1.11)	1.07 (0.94-1.22)	1.04 (0.91-1.18)
Antibiotic use in the month before initiation of the first-line treatment				
Overall survival	0.97 (0.80-1.17)	0.92 (0.76-1.11)	1.31 (1.08-1.59)	1.21 (0.99-1.49)
Time-to-treatment discontinuation	1.00 (0.87-1.16)	0.96 (0.83-1.12)	1.16 (0.99-1.37)	1.12 (0.95-1.33)
High-impact antibiotics ^a				
Overall survival	1.09 (0.92-1.29)	1.07 (0.89-1.27)	1.23 (1.01-1.50)	1.15 (0.93-1.41)
Time-to-treatment discontinuation	1.08 (0.94-1.23)	1.06 (0.92-1.21)	1.10 (0.93-1.30)	1.05 (0.88-1.25)
Excluding patients with infection requiring hospitalization				
Overall survival	0.98 (0.84-1.14)	0.98 (0.84-1.14)	1.15 (0.97-1.36)	1.10 (0.92-1.31)
Time-to-treatment discontinuation	0.99 (0.88-1.11)	0.99 (0.88-1.11)	1.06 (0.92-1.22)	1.04 (0.90-1.20)

^a including second- and third-generation cephalosporins, penicillins associated with β -lactamase inhibitors and fluoroquinolones. CI = confidence interval; HR = hazard ratio.