

Supplementary Table S1. Overall survival according to the characteristics of the patient, the metastatic melanoma or prior therapies.

Adjusted hazard ratios were provided for characteristics retained in the backward stepwise model for overall survival.

	Crude HR (95%CI)	Adjusted HR (95%CI)¹
Sex, for women	0.93 (0.88-0.97)	0.95 (0.90-0.99)
Age, for 1 year	1.003 (1.002-1.005)	1.007 (1.005-1.009)
Comorbidities ²		
Congestive heart failure	1.41 (1.24-1.61)	1.37 (1.20-1.56)
Peripheral vascular disease	1.19 (1.05-1.35)	-
Cerebrovascular disease	1.51 (1.36-1.67)	1.22 (1.09-1.35)
Chronic pulmonary disease	1.11 (1.02-1.20)	1.12 (1.06-1.19)
Liver disease	1.24 (1.05-1.47)	-
Diabetes	1.01 (0.94-1.09)	-
Renal disease	1.33 (1.17-1.51)	1.25 (1.10-1.42)
Metastatic sites ³		
Lymph node	1.15 (1.09-1.20)	-
Lung	1.68 (1.61-1.77)	1.12 (1.06-1.19)
Liver	2.24 (2.13-2.36)	1.58 (1.48-1.67)
Brain	2.31 (2.20-2.43)	1.80 (1.69-1.91)
Bone	2.07 (1.96-2.19)	1.36 (1.28-1.46)
Number of metastatic sites ³	1.32 (1.31-1.34)	1.09 (1.07-1.12)
Surgical resection ⁴		
Lymphadenectomy	0.94 (0.89-0.99)	-
Subcutaneous metastases	0.86 (0.81-0.91)	-
Distant metastases ⁵	1.03 (0.96-1.11)	0.83 (0.76-0.89)
Radiotherapy ⁴	1.45 (1.35-1.55)	1.13 (1.05-1.21)

CI: confidence interval. HR: hazard ratio.

¹adjusted on cohort, age, sex, history of congestive heart failure, cerebrovascular disease, chronic pulmonary disease, renal disease, metastases of the lung, liver, brain, bone and number of metastatic sites, surgical resection of distant metastases and radiotherapy in the year preceding the initiation of the first-line therapy.

²recorded over the 12 months before initiation of the first-line treatment, using the algorithm developed by Bannay et al. for use of the Charlson comorbidity index with Electronic Health Care database (Bannay et al. 2016)

³identified from the hospitalisation discharge codes in the 3 months before and after initiation of the first-line treatment

⁴within the 12 months before initiation of the first-line treatment

⁵including mainly brain, digestive, liver and pulmonary sites

Supplementary Table S2. Comparative overall survival for metastatic melanoma patients within cohorts, according to the treatment received as first-line therapy.

Overall survival	Cohort 2 Jan 2012 – Oct 2013		Cohort 3 Nov 2013 – Jun 2015		Cohort 4 Jul 2015 – Dec 2017	
	Targeted therapy N=706	Chemotherapy N=1290	Targeted therapy N=779	Ipilimumab N=832	Targeted therapy N=1527	Anti-PD-1 antibody N=2605
median OS months [95%CI]	10.6 [9.5-11.8]	7.7 [6.9-8.3]	12.7 [11.4-14.5]	16.3 [13.6-18.8]	15.9 [14.9-17.7]	22.5 [19.2-25.7]
12-month OS % [95%CI]	45.3 [41.7-49.0]	37.3 [34.6-39.9]	51.2 [47.7-54.7]	55.9 [52.5-59.3]	58.3 [55.5-61.0]	61.6 [59.4-63.7]
24-month OS % [95%CI]	24.4 [21.2-27.5]	23.8 [21.5-26.1]	34.4 [31.1-37.7]	42.2 [38.8-45.5]	39.6 [36.4-42.8]	48.4 [45.7-51.1]

OS: overall survival. CI: confidence interval.

Supplementary Table S3. The impact of the evolution in the profiles of patients receiving a systemic therapy for metastatic melanoma on the estimation of survival.

In this box, we explore how the decision for prototypic melanoma patients may have been different in a period when few efficacious treatments were available (“earlier years”) and in a period when several efficacious treatments had been released (“later years”). For different disease and prognostic profiles, we show how a typical therapeutic decision in the earlier years could have been different in the later years; in each situation we state whether the patient would have been included in our cohorts 1 to 4, since metastatic melanoma patients were included from the initiation of the first-line anticancer drug. By changing the time of inclusion in the cohort, the prognosis at inclusion also changes, and consequently so does the length of survival; in each situation we mention the type of bias involved and in which direction it might take.

Patient severity profile	Earlier years		Later years		Type of bias	Direction of the potential bias on the HR
	Therapeutic decision	Inclusion in the cohort	Therapeutic decision	Inclusion in the cohort		
Patients with a good prognosis						
Asymptomatic metastatic disease	Cytotoxic chemotherapy delayed until symptomatic	No, or delayed	Novel therapies	Yes	Selection bias if not included in earlier years; immortal-time bias if the inclusion was delayed in earlier years	Toward the null
Oligometastatic disease	Surgery and radiotherapy alone	No, or delayed	Surgery and radiotherapy associated with novel therapies	Yes	Selection bias if not included in earlier years; immortal-time bias if the inclusion was delayed in earlier years	Toward the null
Patients with a poor prognosis						
Aggressive multimetastatic disease	Palliative care	No	Novel therapies	Yes	Selection bias	Away from the null
Patients with an intermediate prognosis						
Symptomatic metastatic disease	Cytotoxic chemotherapy	Yes	Novel therapies	Yes	Absence of bias	Measure of the efficacy of novel therapies

OS: Overall Survival

Supplementary Table S4. Constitution of the study cohort

The study cohort was selected through successive steps of inclusion (I) or exclusion (E) of patients.

Step	Target	I/E	Condition	Codes	Patients (n)
1	Melanoma 2009-2017				
		I	all-stage melanoma	ICD-10 "melanoma": C43 D03	187,541
2	Systemic treatment 2009-2017				
		I	at least 1 issue of recorded drugs	CIP/UCD codes for ipilimumab, pembrolizumab, nivolumab, vemurafenib, dabrafenib, cobimetinib, trametinib, temozolomide, fotemustine	12,217
		I	at least one hospitalization for "chemo & other"	ICD-10 "chemo & other": Z511 without the issue of a recorded drug (list above)	13,220
3	Another contemporaneous cancer or mucous melanoma 2009-2017				
	Among patients with at least one issue of recorded drugs	E	MD "therapy session" RD "other cancer" ²	ICD-10 "therapy session": Z511 Z512 with an issue of a recorded drug (list above)	1620
		E	MD "therapy session" RD "metastasis" AD "other cancer"		220
		E	no MD "therapy session" and MD/RD/AD "other cancer" ²	ICD-10 "other cancer": D46, Cxx except C43 C44 C76 C77 C78 C79 C80	533
	Among patients receiving only "chemo & other"	E	MD "chemo & other" RD "other cancer"	ICD-10 "metastasis": C77 C78 C79	8422
		I	MD "chemo & other" RD "melanoma"		2903
		E	MD "chemo & other" RD "metastasis" AD "other cancer"		107
		I	MD "chemo & other" RD "metastasis" AD "melanoma" and no hospitalization with "other cancer" code		151
		E	MD "chemo & other" AD "other cancer"		53
		I	MD "chemo & other" AD "melanoma"		39
		I	MD "chemo & other" RD or AD "metastasis" and no hospitalization with "other cancer" code		394
		I	MD "chemo & other" no RD and no hospitalization with "other cancer" code		13
		E	no AD "chemo & other"		772
		I	AD "chemo & other" MD melanoma		5
		I	AD "chemo & other" RD melanoma		2
E		AD/RD "chemo & other" not included previously		359	
4	Previous systemic treatment for melanoma				
		E	First-line treatment started in 2009		2341
5	"chemo & other" used for other treatments ²				

		E	less than 3 times in 4 months (except if interrupted by death)		1004
		E	sentinel lymph node or lymphadenectomy within 3 months; "chemo & other" followed by an issue of interferon		1411

I: Inclusion; E: Exclusion.

MD: main diagnosis; RD: related diagnosis; AD: associated diagnosis.

CIP: Code identifiant de presentation ; ICD-10 : International classification of disease, 10th edition ; UCD : unité commune de dispensation

¹no "therapy session" for oral treatments

²exclusion of Z511 code used wrongly for treatment other than chemotherapy (blood transfusion, adjuvant treatment...)

Journal Pre-proof