

Supplementary Table 1. NM and SSM collected from participating centers and included in the study

Center	CM collected, n (%)						CM included			CM excluded		
	Total	NM	SSM	LMM	ALM	OTHER	Total	NM	SSM	Total	NM	SSM
All centers (EADO, Australia, USA)	25776*	5233 (20.3)*	15792 (61.3)*	4751 (18.4)*			20132	5062	15070	893‡	171	722
EADO (15 European Centers)	13243†	2451 (18.5) †	8730 (65.9) †	2062 (15.6) †			10400	2324	8076	781	127	654
Barcelona, Spain	1163	253 (21.8)	910 (78.2)	-	-	-	1158	251	907	5	2	3
Bucharest, Romania	786	42 (5.3)	176 (22.4)	568 (72.3)			195	40	155	23	2	21
Coimbra, Portugal	197	38 (19.3)	98 (49.7)	23 (11.7)	20 (10.2)	18 (9.1)	109	37	72	27	1	26
Frankfurt, Germany	972	291 (29.9)	473 (48.7)	140 (14.4)	68 (7.0)	-	744	280	464	20	11	9
Graz, Austria	66	37 (56.1)	29 (43.9)	-	-	-	66	37	29	0	0	0
Sevilla, Spain	550	94 (17.1)	257 (46.7)	39 (7.1)	23 (4.2)	137 (24.9)	292	79	213	59	15	44
Kiel, Germany	335	53 (15.8)	191 (57.0)	65 (19.4)	18 (5.4)	8 (2.4)	241	52	189	3	1	2
Belgrade, Serbia	845	172 (20.4)	593 (70.2)	21 (2.5)	13 (1.5)	46 (5.4)	696	157	539	69	15	54
Nantes, France	669	221 (33.0)	203 (30.3)	57 (8.5)	49 (7.3)	139 (20.8)	417	220	197	7	1	6
Roma, Italy	412	41 (10.0)	310 (75.2)	16 (3.9)	2 (0.0)	43 (10.4)	144	26	118	207	15	192
Athens, Greece	773	156 (20.2)	505 (65.3)	46 (6.0)	41 (5.3)	25 (3.2)	641	146	495	20	10	10
Tuebingen, Germany	4014	611 (15.2)	3403 (84.8)	-	-	-	3691	568	3123	323	43	280
Turin, Italy	1231	99 (8.0)	953 (77.4)	47 (3.8)	80 (6.5)	52 (4.2)	1052	99	953	0	0	0

Valencia, Spain	958	191 (19.9)	509 (53.1)	152 (15.9)	46 (4.8)	60 (6.3)	699	190	509	1	1	0
Zürich, Switzerland	272	152 (55.9)	120 (44.1)	-	-	-	255	142	113	17	10	7
MIA/Sydney, Australia	8211	1878 (22.9)	4296 (52.3)	537 (6.5)	125 (1.5)	1375 (16.7)	6109	1861	4248	65	17	48
MD Anderson, USA	4322	904 (20.9)	2766 (64.0)	447 (10.3)	178 (4.1)	27 (0.6)	3623	877	2746	47	27	20

EADO: European Academy of Dermatologic Oncology, NM: nodular melanoma, SSM: superficial spreading melanoma, LMM: lentigo maligna melanoma, ALM: acral lentiginous melanoma

(-): not available data

*summary data presented for 12 centers with available data on histological subtypes

†summary data presented for 10 centers with available data on histological subtypes

‡ Excluded: 20 cases with multiple primary melanomas (non-index cases), 188 cases with missing Breslow thickness or diagnosed as *in situ* melanomas, 465 cases with a date of diagnosis before 2006 or after 2015, 82 patients with missing age or age<16 years and 138 cases with missing values in all variables

Supplementary Table 2. Clinical and histological characteristics by Breslow thickness T1, T2, T3, T4 for NM and SSM from all centers (n=20132)

ALL NM (n=5062)						
Variable	Breslow thickness					p-value
	T1: ≤1.0 (n=297)	T2: 1.1-2.0 (n=1082)	T3: 2.1-4.0 (n=1823)	T4: >4.0 (n=1860)	Total (n=5062)	
Age (years), median (IQR)	54.4 (43.0, 66.1)	58.4 (47.3, 69.0)	63.4 (50.0, 74.9)	65.8 (54.0, 76.6)	62.8 (50.1, 73.9)	<0.001*
Age, n (%)						
≤ 50 years	118 (39.7)	325 (30.0)	457 (25.1)	353 (19.0)	1253 (24.8)	<0.001†
>50 years	179 (60.3)	757 (70.0)	1366 (74.9)	1507 (81.0)	3809 (75.2)	
Gender, n (%)						
Male	155 (52.2)	599 (55.4)	1111 (60.9)	1186 (63.8)	3051 (60.3)	<0.001†
Female	142 (47.8)	483 (44.6)	712 (39.1)	674 (36.2)	2011 (39.7)	
Anatomic site of melanoma, n (%)						
head/neck	52 (17.7)	162 (15.1)	386 (21.4)	442 (24.1)	1042 (20.8)	<0.001†
trunk	102 (34.7)	395 (36.8)	659 (36.5)	686 (37.4)	1842 (36.8)	
upper extremities	74 (25.2)	263 (24.5)	369 (20.4)	332 (18.1)	1038 (20.7)	
lower extremities	66 (22.4)	253 (23.6)	391 (21.7)	372 (20.3)	1082 (21.6)	
Breslow thickness (mm), median (IQR)	0.9 (0.7, 1.0)	1.6 (1.3, 1.8)	2.9 (2.5, 3.5)	6.1 (5.0, 9.0)	3.1 (2.0, 5.2)	<0.001*
Ulceration, n (%)						
present	33 (11.7)	272 (26.7)	869 (49.6)	1196 (67.2)	2370 (49.0)	<0.001†
absent	250 (88.3)	745 (73.3)	884 (50.4)	585 (32.8)	2464 (51.0)	
Regression, n (%)						
present	41 (15.9)	98 (10.6)	144 (9.0)	137 (8.8)	420 (9.7)	0.002†
absent	217 (84.1)	830 (89.4)	1448 (91.0)	1423 (91.2)	3918 (90.3)	
Nevus remnants, n (%)						
present	68 (29.2)	190 (23.5)	228 (17.1)	141 (10.8)	627 (17.0)	<0.001†
absent	165 (70.8)	617 (76.5)	1109 (82.9)	1160 (89.2)	3051 (83.0)	
Mitoses, n (%)						
present	186 (76.9)	750 (93.1)	1312 (96.4)	1368 (97.7)	3616 (94.9)	<0.001†
absent	56 (23.1)	56 (6.9)	49 (3.6)	32 (2.3)	193 (5.1)	
Tumour spread (initial diagnosis), n (%)						
localized	212 (86.5)	765 (80.2)	1170 (72.9)	919 (57.8)	3066 (69.8)	<0.001†
satellite-/intransit metastasis	5 (2.0)	53 (5.6)	121 (7.5)	164 (10.3)	343 (7.8)	
regional lymph node metastasis	21 (8.6)	123 (12.9)	278 (17.3)	394 (24.8)	816 (18.6)	
distant metastasis	7 (2.9)	13 (1.4)	37 (2.3)	113 (7.1)	170 (3.9)	
ALL SSM (n=15070)						

Variable	Breslow thickness					p-value
	T1: ≤1.0 (n=9384)	T2: 1.1-2.0 (n=3484)	T3: 2.1-4.0 (n=1547)	T4: >4.0 (n=655)	Total (n=15070)	
Age, years, median (IQR)	53.7 (42.4, 65.0)	57.7 (46.0, 68.5)	61.4 (48.8, 72.3)	62.3 (49.0, 73.5)	55.8 (44.1, 67.1)	<0.001*
Age, n (%)						
≤ 50 years	3878 (41.3)	1186 (34.0)	419 (27.1)	173 (26.4)	5656 (37.5)	<0.001†
>50 years	5506 (58.7)	2298 (66.0)	1128 (72.9)	482 (73.6)	9414 (62.5)	
Gender, n (%)						
Male	4624 (49.3)	1906 (54.7)	925 (59.8)	425 (64.9)	7880 (52.3)	<0.001†
Female	4760 (50.7)	1578 (45.3)	622 (40.2)	230 (35.1)	7190 (47.7)	
Anatomic site of melanoma, n (%)						
head/neck	898 (9.6)	364 (10.6)	206 (13.6)	121 (19.0)	1589 (10.7)	<0.001†
trunk	4270 (45.8)	1499 (43.7)	674 (44.4)	291 (45.7)	6734 (45.2)	
upper extremities	1883 (20.2)	668 (19.5)	253 (16.7)	75 (11.8)	2879 (19.3)	
lower extremities	2262 (24.3)	902 (26.3)	386 (25.4)	150 (23.5)	3700 (24.8)	
Breslow thickness (mm), median (IQR)	0.6 (0.4, 0.8)	1.4 (1.2, 1.7)	2.7 (2.3, 3.2)	5.5 (4.8, 7.0)	0.8 (0.5, 1.4)	<0.001*
Ulceration, n (%)						
present	338 (3.8)	549 (16.5)	670 (44.9)	419 (66.6)	1976 (13.7)	<0.001†
absent	8616 (96.2)	2773 (83.5)	823 (55.1)	210 (33.4)	12422 (86.3)	
Regression, n (%)						
present	2631 (31.1)	744 (23.9)	282 (20.9)	125 (23.8)	3782 (28.1)	<0.001†
absent	5819 (68.9)	2368 (76.1)	1069 (79.1)	401 (76.2)	9657 (71.9)	
Nevus remnants, n (%)						
present	2762 (38.8)	881 (35.2)	285 (25.7)	86 (20.7)	4014 (36.0)	<0.001†
absent	4362 (61.2)	1623 (64.8)	825 (74.3)	330 (79.3)	7140 (64.0)	
Mitoses, n (%)						
present	2737 (45.8)	2123 (86.6)	1067 (96.6)	457 (97.2)	6384 (63.9)	<0.001†
absent	3234 (54.2)	329 (13.4)	37 (3.4)	13 (2.8)	3613 (36.1)	
Tumour spread (initial diagnosis), n (%)						
localized	7963 (95.4)	2611 (82.6)	938 (67.5)	290 (48.5)	11802 (87.5)	<0.001†
satellite-/intransit metastasis	52 (0.6)	122 (3.9)	100 (7.2)	50 (8.4)	324 (2.4)	
regional lymph node metastasis	299 (3.6)	403 (12.7)	333 (24.0)	233 (39.0)	1268 (9.4)	
distant metastasis	29 (0.3)	26 (0.8)	18 (1.3)	25 (4.2)	98 (0.7)	

*P value was calculated using a two-sided Kruskal Wallis test, †P value was calculated using a two-sided chi-squared test.

Supplementary Table 3. Multivariate logistic regression analysis of the characteristics of NM compared to SSM stratified by T3, T4 Breslow thickness

Variable	Breslow thickness			
	T3: 2.1-4.0 mm (n=1726)		T4: >4.0 mm (n=1216)	
	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Gender				
female	Ref		Ref	
male	1.02 (0.82, 1.27)	0.85	0.88 (0.65, 1.20)	0.42
Age, years				
≤50	Ref		Ref	
>50	0.87 (0.69, 1.09)	0.22	1.10 (0.78, 1.55)	0.59
Log Breslow thickness, mm	3.55 (2.13, 5.91)	<0.001	2.04 (1.41, 2.95)	<0.001
Anatomic site				
lower extremities	Ref		Ref	
head/neck	1.31 (0.95, 1.80)	0.10	1.10 (0.73, 1.67)	0.64
trunk	1.00 (0.76, 1.31)	0.97	1.06 (0.73, 1.55)	0.75
upper extremities	1.47 (1.07, 2.00)	0.02	1.81 (1.10, 2.95)	0.02
Ulceration				
absent	Ref		Ref	
present	1.12 (0.92, 1.37)	0.25	0.71 (0.53, 0.96)	0.03
Regression				
absent	Ref		Ref	
present	0.47 (0.35, 0.61)	<0.001	0.38 (0.26, 0.54)	<0.001
Nevus remnants				
absent	Ref		Ref	
present	0.61 (0.48, 0.78)	<0.001	0.47 (0.33, 0.68)	<0.001
Mitoses				
absent	Ref		Ref	
present	0.69 (0.36, 1.33)	0.27	1.57 (0.69, 3.59)	0.28
Tumor spread (initial diagnosis)				
localized	Ref		Ref	
regional metastasis	0.64 (0.52, 0.80)	<0.001	0.49 (0.36, 0.65)	<0.001
distant metastasis	1.07 (0.49, 2.33)	0.87	1.01 (0.53, 1.94)	0.98

Multivariate analysis adjusted for all variables included in Table.

* All statistical tests are two-sided.

Supplementary Table 4. Multivariate logistic regression analysis of the characteristics of NM compared to SSM stratified by T1, T2 Breslow thickness for localized melanomas

	Breslow thickness			
	T1: ≤ 1 mm (n=4044)		T2: 1.1-2.0 mm (n=1764)	
Variable	OR (95% CI)	p-value*	OR (95% CI)	p-value*
Gender				
female	Ref		Ref	
male	1.35 (0.93, 1.95)	0.11	1.13 (0.89, 1.43)	0.32
Age, years				
≤50	Ref		Ref	
>50	0.99 (0.68, 1.42)	0.93	0.95 (0.74, 1.23)	0.72
Log Breslow thickness, mm	22.53 (10.23, 49.60)	<0.001	7.18 (4.00, 12.91)	<0.001
Anatomic site				
lower extremities	Ref		Ref	
head/neck	1.81 (1.02, 3.22)	0.04	1.52 (1.03, 2.22)	0.03
trunk	1.03 (0.63, 1.68)	0.92	1.14 (0.83, 1.55)	0.42
upper extremities	1.16 (0.69, 1.93)	0.58	1.51 (1.10, 2.06)	0.01
Ulceration				
absent	Ref		Ref	
present	1.18 (0.62, 2.26)	0.609	1.19 (0.90, 1.58)	0.225
Regression				
absent	Ref		Ref	
present	0.45 (0.27, 0.74)	0.002	0.47 (0.34, 0.64)	<0.001
Nevus remnants				
absent	Ref		Ref	
present	0.62 (0.43, 0.90)	0.01	0.56 (0.44, 0.72)	<0.001
Mitoses				
absent	Ref		Ref	
present	1.97 (1.29, 3.02)	0.002	2.60 (1.62, 4.17)	<0.001

Multivariate analysis adjusted for all variables included in Table.

*All statistical tests are two-sided.

Supplementary Table 5. In localized melanomas: Mitotic rate for NM (median and adjusted geometric mean) compared with SSM stratified for T1, T2, T3 and T4 melanomas. Normal regression analysis restricted to cases from MD Anderson and MIA/Sydney

	Mitotic rate per mm ²				
	NM		SSM		p-value*†
	n	GM* (95% CI) Median (25 th , 75 th)	n	GM* (95% CI) Median (25 th , 75 th)	
Breslow thickness					
T1: ≤1.0 mm (n=1531)	107	2.1 (1.9, 2.4) 2.0 (1.0, 3.0)	1424	1.5 (1.5, 1.6) 0.0 (0.0, 1.0)	<0.001
T2: 1.1-2.0 mm (n=1428)	411	3.1 (2.8, 3.4) 3.0 (2.0, 5.0)	1017	2.5 (2.3, 2.8) 2.0 (1.0, 5.0)	<0.001
T3: 2.1-4.0 mm (n=1051)	615	4.3 (3.8, 4.9) 6.0 (3.0, 10.0)	436	3.7 (3.2, 4.3) 5.0 (3.0, 9.0)	0.003
T4: >4.0 mm (n=528)	435	6.5 (5.1, 8.4) 9.0 (5.0, 15.0)	93	5.9 (4.3, 8.0) 10.0 (5.0, 14.0)	0.27

GM: geometric mean, CI: confidence intervals

*Normal regression analysis adjusted for gender, age, ulceration

†All statistical tests are two-sided.

Supplementary Table 6. Five -year melanoma specific survival (MSS) rates and associated prognostic factors in univariate Kaplan-Meier analysis

Variable			Melanoma-specific survival rate, %	
	N	Melanoma deaths	5-Year (95% CI)	p-value #
All melanomas	18373	1567	86.9 (86.2, 87.6)	
Histological subtype				
SSM	13726	800	91.0 (90.3, 91.6)	<0.001
NM	4647	767	75.4 (73.6, 77.1)	
Year at diagnosis				
2006-2010	9252	1035	87.0 (86.2, 87.8)	0.37
2011-2015	9121	532	86.6 (85.2, 88.0)	
Age, years				
≤ 50	6673	475	89.8 (88.7, 90.7)	<0.001
51-60	3600	281	88.6 (87.0, 89.9)	
60-69	3950	358	86.1 (84.5, 87.5)	
≥70	4150	453	80.6 (78.7, 82.3)	
Gender				
Female	8333	549	90.2 (89.3, 91.1)	<0.001
Male	10040	1018	84.1 (83.1, 85.1)	
Anatomical site *				
head/neck	2451	299	79.5 (77.1, 81.7)	<0.001
trunk	7880	706	86.7 (85.6, 87.7)	
upper extremities	3560	204	91.1 (89.7, 92.4)	
lower extremities	4347	334	88.5 (87.1, 89.8)	
Breslow thickness (mm)				
≤1.0	8748	202	96.4 (95.8, 97.0)	<0.001
1.1-2.0	4170	320	89.0 (87.6, 90.3)	
2.1-4.0	3135	455	78.2 (76.2, 80.1)	
>4.0	2320	590	61.8 (59.0, 64.6)	
Ulceration †				
absent	13600	717	91.7 (91.1, 92.4)	<0.001
present	4000	766	71.6 (69.6, 73.5)	
Regression ‡				
absent	12465	1062	87.0 (86.1, 87.8)	<0.001
present	3767	218	90.9 (89.5, 92.3)	
Nevus remnants §				
absent	9689	849	86.8 (85.9, 87.7)	<0.001
present	4300	256	90.6 (89.2, 91.7)	
Mitoses				
absent	3322	54	96.9 (95.9, 97.8)	<0.001
present	9204	1045	82.0 (80.9, 83.1)	

Tumor spread (at diagnosis) †				
Localized	13463	617	92.8 (92.1, 93.4)	<0.001
Regional metastasis	2674	635	67.5 (65.1, 69.8)	
Distant metastasis	257	119	33.4 (25.2, 41.8)	
Region				
EADO	9228	812	87.4 (86.5, 88.3)	<0.001
MIA/Sydney	5553	461	84.1 (82.5, 85.6)	
Region				
EADO	9228	812	87.4 (86.5, 88.3)	0.13
MD Anderson, USA	3592	294	88.4 (87.0, 89.8)	

* 135 missing values, † 773 missing values, ‡ 2141 missing values, § 4384 missing values, || 5847 missing values, ¶ 1979 missing values, #P-values were calculated using a two-sided long-rank test

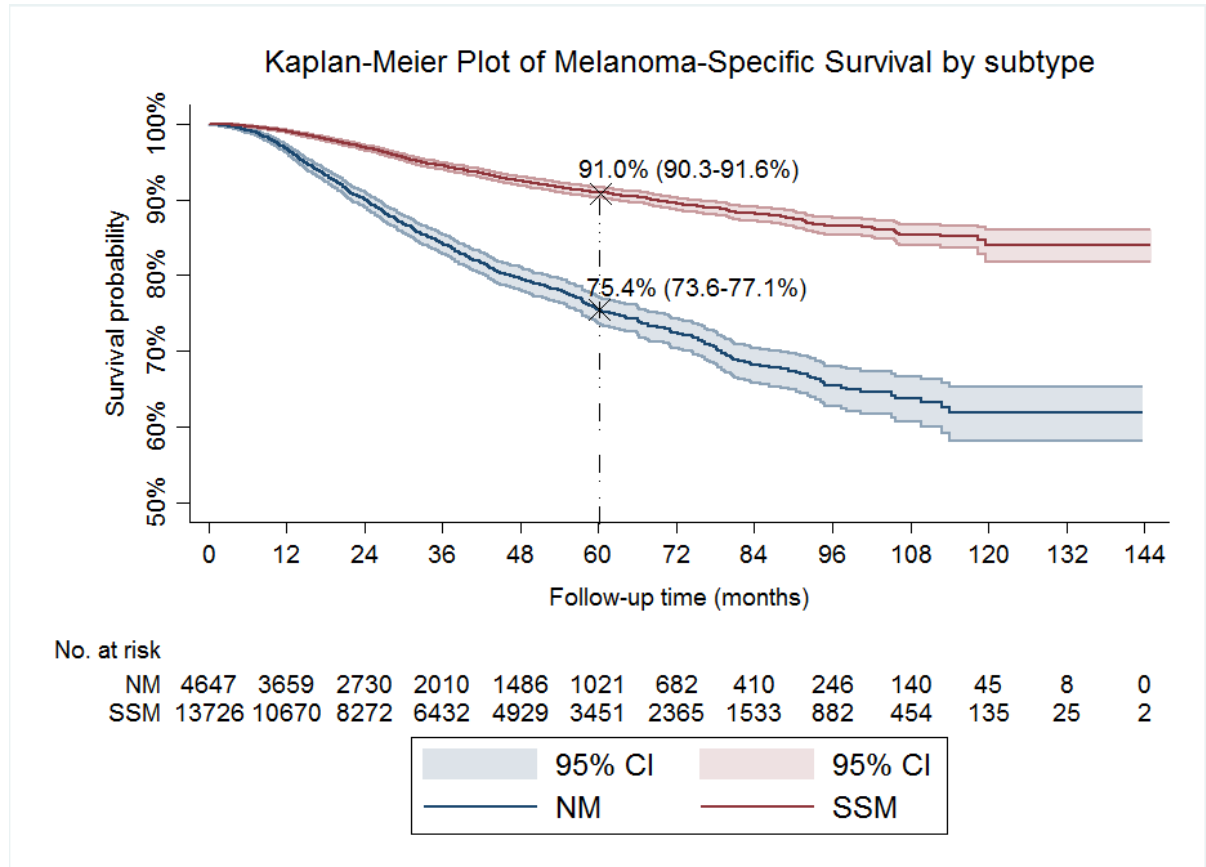
Supplementary Table 7. Cox Proportional Hazard Models comparisons according to AIC and BIC criterion

	T1		T2		T3		T4	
Cox regression models	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
All cases								
Multivariate 2 (adjusted for age, sex, Breslow thickness, ulceration)	3036.941	3086.168	4321.371	4365.389	6286.222	6328.32	7839.198	7879.166
Multivariate 2 with frailty for center	3016.431	3065.658	4298.707	4342.725	6250.082	6292.18	7817.814	7857.782
Stratified: localized melanomas								
Multivariate 2 (adjusted for age, sex, Breslow thickness, ulceration)	1790.649	1838.765	1919.922	1961.763	2304.208	2342.996	1892.203	1926.939
Multivariate 2 with frailty for center	1782.961	1831.077	1896.406	1938.247	2267.966	2306.754	1864.944	1899.68

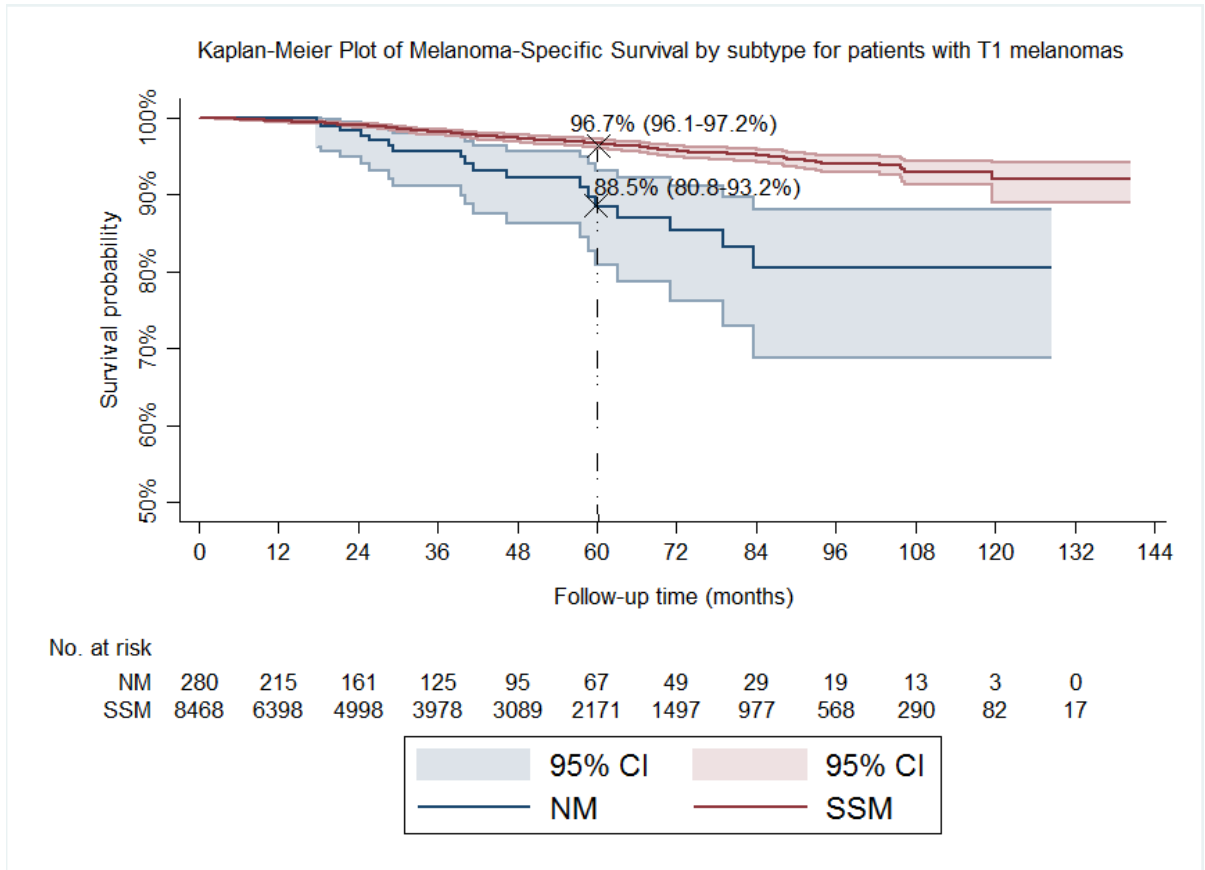
AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion

Supplementary Figure 1. Kaplan-Meier plots for melanoma-specific survival rates for NM compared to SSM. A. for all cases with known survival (n=18373) (p<0.001), B. for T1 (n=8748), (p < 0.001), C. for T2 (p=0.009), D. for T3/T4 melanomas (p=0.15). P values were calculated by a two-sided log-rank test. Shaded areas indicate 95% confidence intervals. Dashed line indicates 5-year rates.

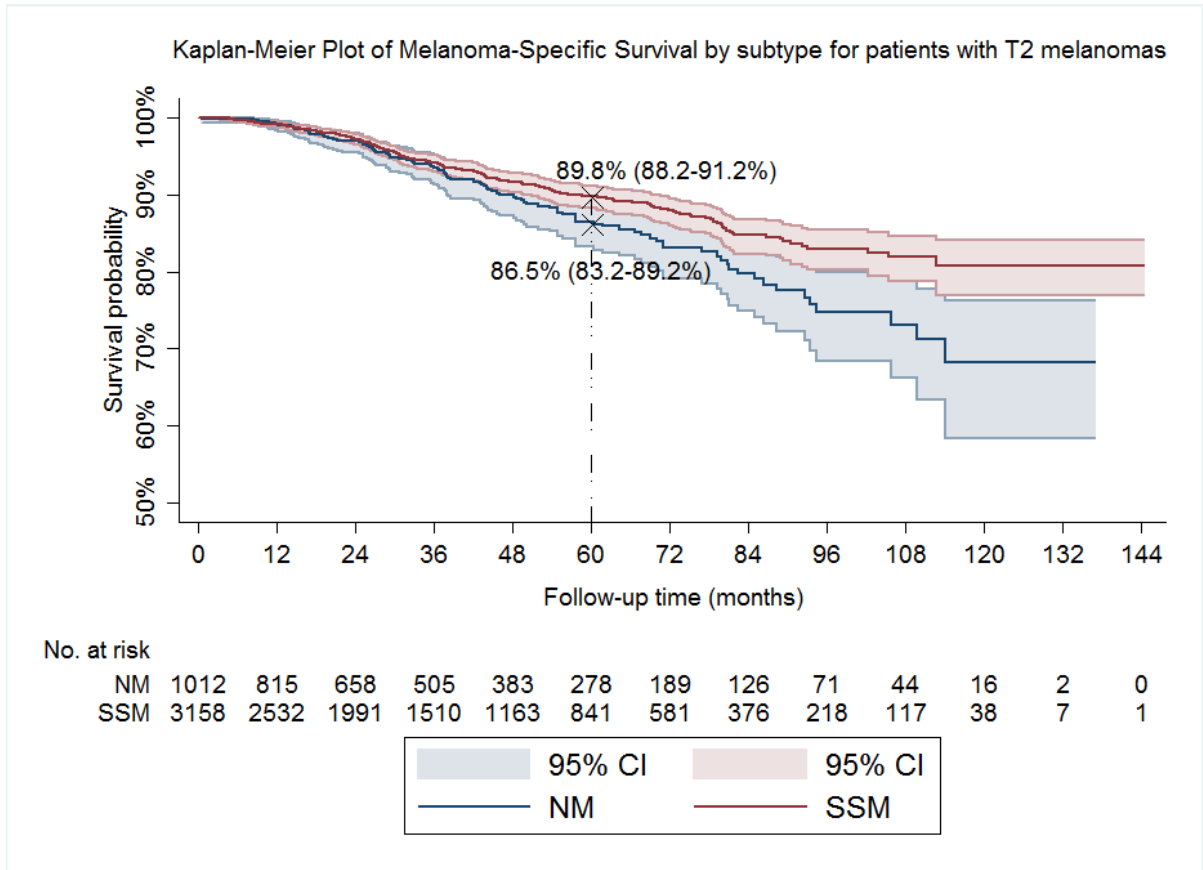
A.



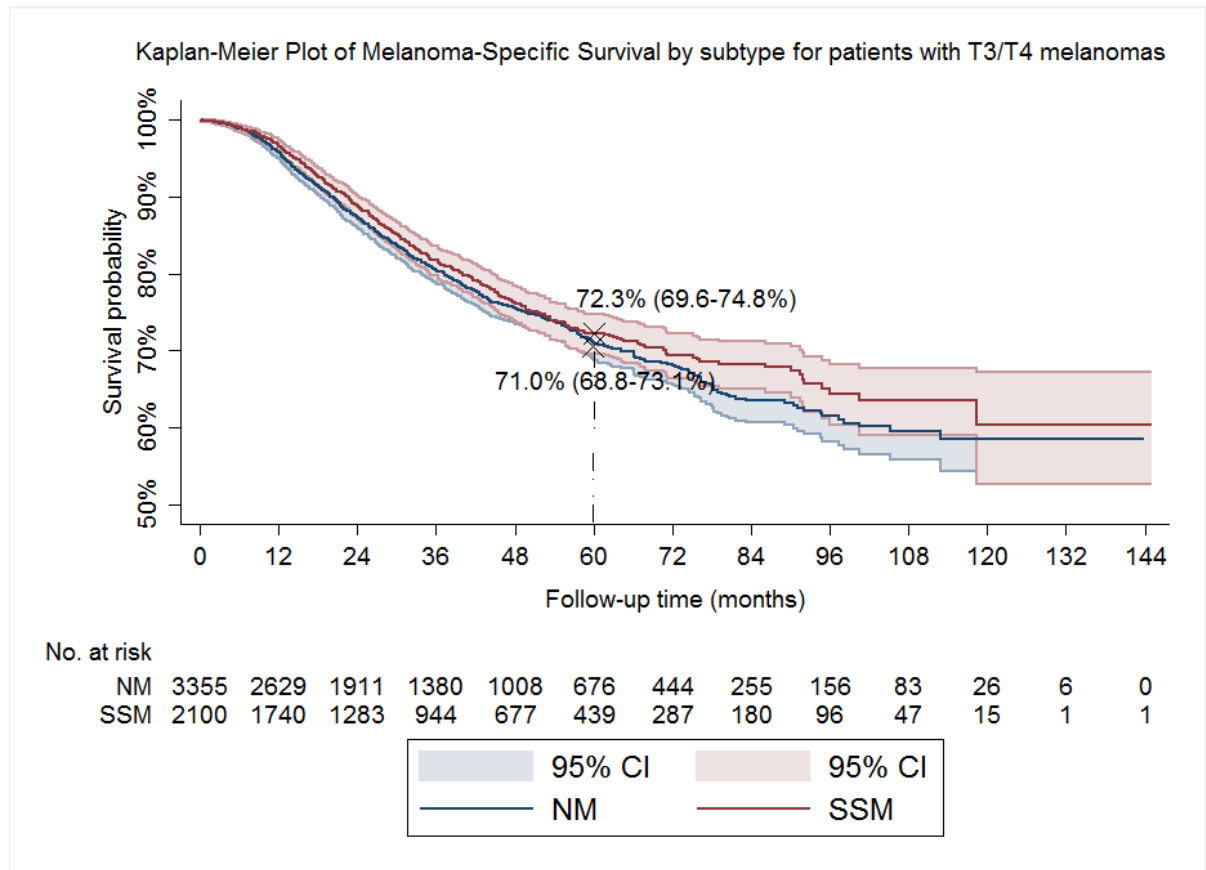
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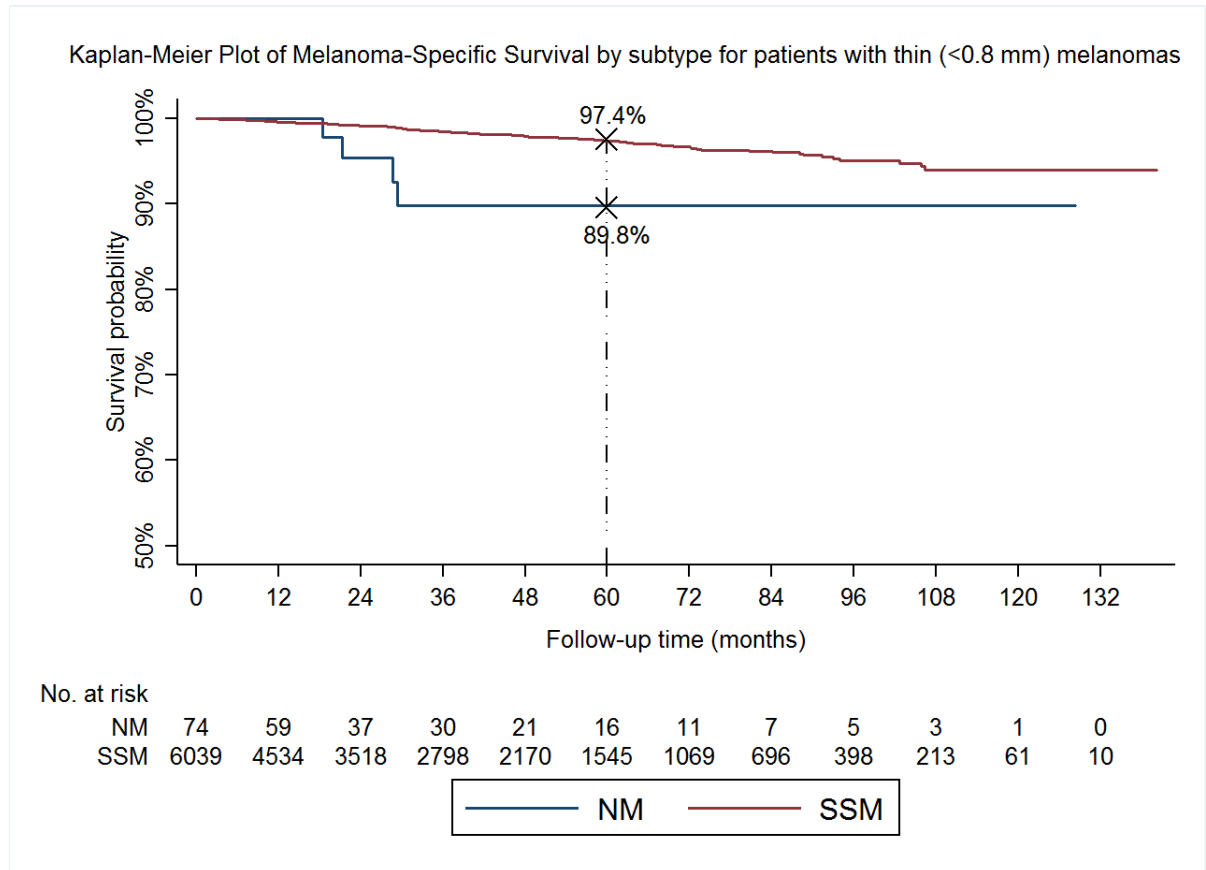


D.



Supplementary Figure 2. Kaplan-Meier plots for melanoma-specific survival rates for NM compared to SSM in T1 melanomas by thickness at 0.8 mm
 A. for thickness <0.8 mm (p=0.01), B. for thickness 0.8-1.00 mm (p=0.006).
 P values were calculated using a two-sided log-rank test. Shaded areas indicate 95% confidence intervals. Dashed line indicates 5-year rates.

A.



B.

