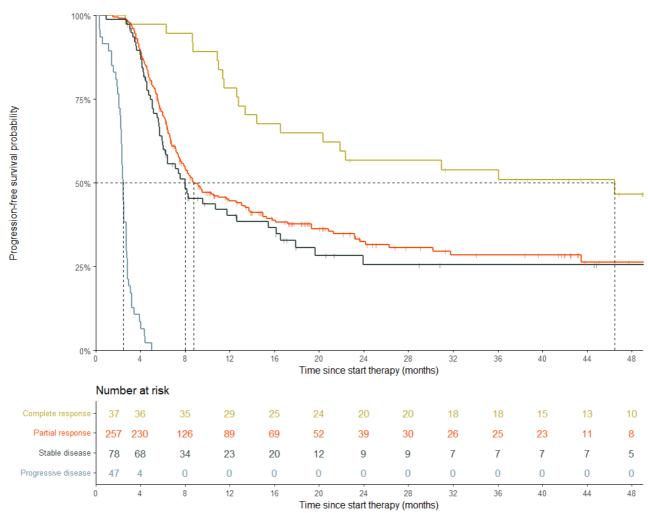
Variable		NE	vents	Hazard Ratio (HR)	HR (CI)	P-value
Age						
-	<50	84	62	•	Reference	
	50-59	92	73	·	1.00 (0.70, 1.42)	0.979
	60-69	94	81	·	1.23 (0.87, 1.73)	
	>70	77	70	· · · · · · · · · · · · · · · · · · ·	1.55 (1.08, 2.21)	0.016
Gender				1		
	Male	186	159	•	Reference	
	Female	161	127	i i i i i i i i i i i i i i i i i i i	0.90 (0.70, 1.15)	0.399
Stage						
č	Illc, IVm1a, IVm1	1b 25	12	•	Reference	
	IV-M1c	322	274	· · · · · · · · · · · · · · · · · · ·	1.72 (0.91, 3.24)	0.095
ECOG						
	0	130	101	•	Reference	
	1	134	110		1.17 (0.89, 1.54)	0.265
	2-4	83	75		1.06 (0.76, 1.49)	0.726
LDH						
	Normal	165	126	•	Reference	
	250-500	114	94	_ _	1.14 (0.85, 1.53)	0.382
	>500	68	66	· · · · · · · · · · · · · · · · · · ·	2.63 (1.82, 3.82)	< 0.001
Organsites				1		
5	<3	118	82	•	Reference	
	>2	229	204	· · · · · · · · · · · · · · · · · · ·	1.54 (1.15, 2.07)	0.004
Brainmetastasis				1		
	No	200	152	•	Reference	
	Asymptomatic	48	43	⊢	1.47 (1.02, 2.10)	0.037
	Symptomatic	99	91	· · · • · · · · · · · · · · · · · · · ·	1.78 (1.32, 2.39)	< 0.001
Livermetastasis						
	No	210	163	•	Reference	
	Yes	137	123	· · · · · · · · · · · · · · · · · · ·	1.09 (0.81, 1.45)	0.576
				1 1.5 2 2.533.5		

Supplement 1: Forest plot including multivariable Cox proportional hazard model for death within patients with advanced melanoma treated with first-line BRAF-MEK inhibitors.



- Complete response 🕂 Partial response 🕂 Stable disease 🕂 Progressive disease

Supplement 2: Kaplan-Meier estimates of median progression-free survival of patients with advanced melanoma treated with first-line BRAF-MEK inhibitors according to best-overall responses.

Fourteen patients were not evaluable for response, and two patients were excluded from this analysis because of missing data on progressive disease.

	Eligible	Ineligible	P-valu
Patients; n	208	227	
Median age, year (range)	60 (26-91)	59 (19-87)	0.98
Age categories; n (%)			0.58
<50yr	51 (24.5)	53 (23.3)	
50-59yr	52 (25.0)	65 (28.6)	
60-69yr	59 (28.4)	51 (22.5)	
70-79yr	33 (15.9)	44 (19.4)	
>80yr	13 (6.2)	14 (6.2)	
Gender; n (%)			0.70
Male	107 (51.4)	122 (53.7)	
Female	101 (48.6)	105 (46.3)	
ECOG PS; n (%)			
0	99 (47.6)	52 (22.9)	<0.00
1	87 (41.8)	64 (28.2)	
≥2	2 (1.0)	88 (38.8)	
Unknown	20 (9.6)	23 (10.1)	
LDH level (U/I); n (%)			0.10
Normal	102 (49.0)	107 (47.1)	
250-499	65 (31.2)	72 (31.7)	
>500	35 (16.8)	43 (19.0)	
Not determined	3 (1.4)	5 (2.2)	
Stage (AJCC 7 th); n (%)			<0.00
llic	28 (13.5)	3 (1.3)	
IV-M1a	13 (6.2)	1 (0.4)	
IV-M1b	9 (4.3)	3 (1.3)	
IV-M1c	158 (76.0)	220 (96.9)	
Metastasis in ≥3 organ sites; n (%)			<0.00
Yes	105 (50.5)	166 (73.1)	
Νο	103 (49.5)	61 (26.9)	
Brain metastasis; n (%)			<0.00
Νο	171 (82.2)	48 (21.1)	
Yes, asymptomatic	0 (0.0)	54 (23.8)	

Supplement 3: Patient- and tumor characteristics of patients treated with first-line BRAF-MEK inhibitors who are considered eligible and ineligible for phase III trial participation.

Yes, symptomatic	5 (2.4)	119 (52.4)	
Unknown	32 (15.4)	6 (2.6)	
Liver metastasis; n (%)	81 (38.9)	82 (36.1)	<0.001
Best overall response; n (%)			<0.001
Complete response	32 (15.4)	5 (2.2)	
Partial response	112 (53.8)	145 (63.9)	
Stable disease	39 (18.8)	39 (17.2)	
Progressive disease	22 (10.6)	27 (11.9)	
LTFU	3 (1.4)	11 (4.8)	
BRAF mutation; n (%)			0.002
V600E	177 (85.1)	184 (81.1)	
V600K	31 (14.9)	30 (13.2)	
Other	0	13 (5.7)	
Subsequent therapy after first-line BRAF/MEK; n (%)			0.388
No	87 (41.8)	105 (46.3)	
Immunotherapy	110 (52.9)	116 (51.1)	
Other	11 (5.3)	6 (2.6)	

Supplement 4: Therapy flow of long-term survivors who received BRAF-MEK inhibitors as first-line treatment

