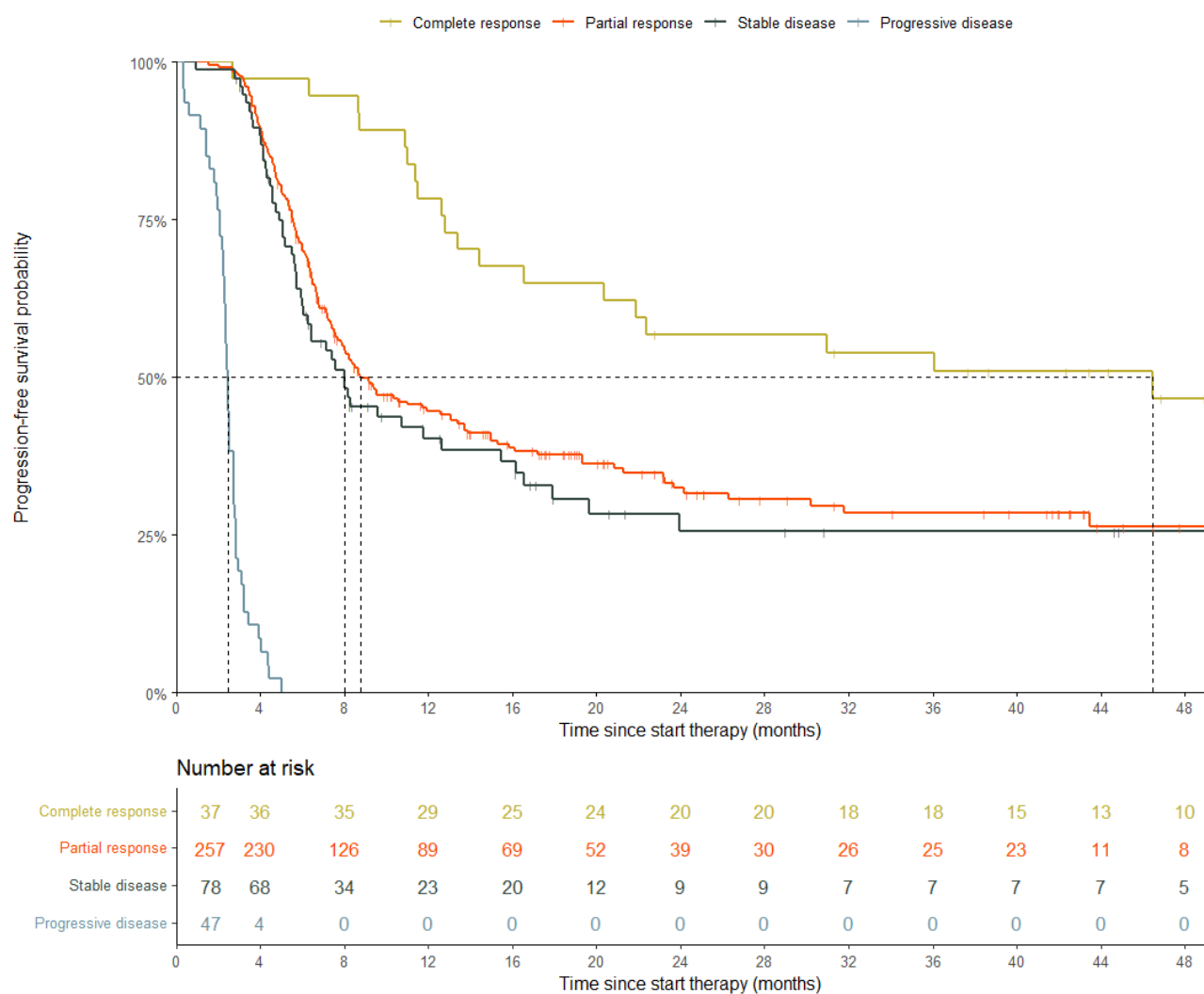


Supplement 1: Forest plot including multivariable Cox proportional hazard model for death within patients with advanced melanoma treated with first-line BRAF-MEK inhibitors.



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.

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.

	Eligible	Ineligible	P-value
Patients; n	208	227	
Median age, year (range)	60 (26-91)	59 (19-87)	0.981
Age categories; n (%)			0.583
<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 (%)			0.701
Male	107 (51.4)	122 (53.7)	
Female	101 (48.6)	105 (46.3)	
ECOG PS; n (%)			
0	99 (47.6)	52 (22.9)	<0.001
1	87 (41.8)	64 (28.2)	
≥2	2 (1.0)	88 (38.8)	
Unknown	20 (9.6)	23 (10.1)	
LDH level (U/l); n (%)			0.103
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 7th); n (%)			<0.001
IIIc	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 (%)			<0.001
Yes	105 (50.5)	166 (73.1)	
No	103 (49.5)	61 (26.9)	
Brain metastasis; n (%)			<0.001
No	171 (82.2)	48 (21.1)	
Yes, asymptomatic	0 (0.0)	54 (23.8)	

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

