Appendix

Supplementary methods

At baseline, patients underwent several assessments, including demographics, medical history, vital signs, Eastern Cooperative Oncology Group performance status, electrocardiogram, echocardiogram, ophthalmologic assessment, blood laboratory analysis, and physical examination with dermatologic assessment. Disease at baseline was assessed using contrast-enhanced brain magnetic resonance imaging (MRI), computed tomography (CT) scan of the chest, abdomen, and pelvis or MRI scan of the abdomen and pelvis; and clinical assessment for palpable and/or cutaneous lesions using callipers or photography.

All types of response rates (intracranial, extracranial, and overall) were defined as the percentage of patients achieving a confirmed complete or partial response from the start of treatment until disease progression or the start of new anti-cancer therapy.

Progression-free survival was defined as the interval of time (in months) between the date of first dose of study treatment and the earliest of the date of overall disease progression and the date of death due to any cause. Duration of intracranial/extracranial/overall response were summarised for patients with a confirmed intracranial complete or partial response and were defined as the time (in months) from the initial response to first documented intracranial/extracranial/overall response disease progression or death due to any cause.

The date of new anticancer therapy was defined as the earliest date of the initiation of on-study or post-study treatment systemic anticancer therapy, radiotherapy, and surgery. If anticancer therapy was started without documented overall disease progression or prior to documented overall disease progression, then progression-free survival was censored at the date of the last adequate assessment that was on or before the date of initiation of anticancer therapy (ie, if an assessment occurred on the same day as the start of new anticancer therapy, the assessment was used). The date of response at the last adequate assessment was used as the censoring value.

Supplementary data

Table S1: Key characteristics of patients with melanoma brain metastases by cohort in COMBI-MB

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
BRAF mutation genotype*	V600E	V600E	V600D/K/R	V600D/E/K/R
Symptom status of melanoma brain metastases	Asymptomatic	Asymptomatic	Asymptomatic	Symptomatic
Prior local therapy status	Without	With	With or without	With or without
ECOG performance status	0–1	0–1	0–1	0–2

ECOG=Eastern Cooperative Oncology Group.
*Locally confirmed for cohorts A (per latest protocol amendment) B, C, and D.

Table S2: Patient disposition

Patient status, n (%)	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)	Total (N=125)
Died	44 (58)	7 (44)	13 (81)	13 (76)	77 (62)
Ongoing	31 (41)	8 (50)	3 (19)	2 (12)	44 (35)
On-study treatment	14 (18)	2 (13)	0	0	16 (13)
In follow-up	17 (22)	6 (38)	3 (19)	2 (12)	28 (22)
Withdrawn from study	1 (1)	1 (6)	0	2 (12)	4 (3)

Table S3: Summary of proportion of responses (complete or partial) achieved by week 4 and week 8

	Cohort A	Cohort B	Cohort C	Cohort D
Intracranial response				
Total response observed, N*	44	9	7	10
Week 4, n (% of N)	39 (89)	3 (33)	3 (43)	7 (70)
Week 8, n (% of N)	4 (9)	2 (22)	3 (43)	0
Extracranial response				
Total response observed, N*	42	7	12	7
Week 4, n (% of N)	28 (67)	6 (86)	8 (67)	5 (71)
Week 8, n (% of N)	11 (26)	0	3 (25)	1 (14)
Overall response				
Total response observed, N*	44	9	7	11
Week 4, n (% of N)	36 (82)	4 (44)	4 (57)	8 (73)
Week 8, n (% of N)	7 (16)	1 (11)	2 (29)	0

*As of the data cutoff date.

Table S4: Patterns of disease progression

Progression category, n (%)	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)	Total (N=125)
Intracranial only	36 (47)	10 (63)	10 (63)	10 (59)	66 (53)
Extracranial only	7 (9)	1 (6)	3 (19)	0	11 (9)
Intracranial and extracranial	19 (25)	1 (6)	3 (19)	5 (29)	28 (22)
Neither intracranial nor extracranial*	14 (18)	4 (25)	0	2 (12)	20 (16)

*Patients did not have disease progression in intracranial nor extracranial lesions while on study treatment.

***Table S5*: Summary of subsequent therapy**

Category, n (%)	**Cohort A (n=76)**	**Cohort B (n=16)**	**Cohort C (n=16)**	**Cohort D (n=17)**
Post-progression systemic therapy				
Immunotherapy	34 (45)	7 (44)	5 (31)	6 (35)
anti–CTLA-4	9 (12)	5 (31)	3 (19)	1 (6)
anti–PD-1	32 (42)	4 (25)	3 (19)	6 (35)
anti–PD-L1	0	0	0	0
Chemotherapy	8 (11)	0	2 (13)	2 (12)
Small-molecule targeted therapy	13 (17)	3 (19)	4 (25)	3 (18)
Dabrafenib	8 (11)	2 (13)	4 (25)	2 (12)
Trametinib	1 (1)	1 (6)	3 (19)	0
Biological	1 (1)	0	0	0
On-treatment or post-treatment therapy				
Anticancer surgical procedure	6 (8)	1 (1)	2 (13)	3 (18)
Radiotherapy procedure	35 (46)	10 (13)	9 (56)	9 (12)

***Table S6*: Serious adverse events (SAEs) experienced by at least 2 patients in any cohort**

SAE, n (%)	Cohort A (n=76)		Cohort B (n=16)		Cohort C (n=16)		Cohort D (n=17)		Total (N=125)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any	26 (34)	14 (18)	5 (31)	5 (31)	4 (25)	3 (19)	9 (53)	3 (18)	44 (35)	25 (20)
Pyrexia	4 (5)	0	1 (6)	0	2 (13)	0	2 (12)	0	9 (7)	0
Atrial fibrillation	2 (3)	0	0	0	0	0	0	0	2 (2)	0
Ejection fraction decreased	2 (3)	1 (1)	0	0	1 (6)	1 (6)	2 (12)	0	5 (4)	2 (2)
Epilepsy	2 (3)	1 (1)	0	0	0	0	0	0	2 (2)	1 (1)
Seizure	2 (3)	2 (3)	0	0	0	0	1 (6)	0	3 (2)	2 (2)
Syncope	2 (3)	0	0	0	0	0	0	0	2 (2)	0

***Table S7*: Summary of adverse events (AEs) leading to dose adjustments or permanent discontinuation**

Category, n (%)	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)	Total (N=125)
AEs	74 (97)	16 (100)	16 (100)	17 (100)	123 (98)
AEs related to study treatment	62 (82)	15 (94)	14 (88)	17 (100)	108 (86)
AEs leading to discontinuation	6 (8)	3 (19)	0	3 (18)	12 (10)
AEs leading to dose reduction	17 (22)	4 (25)	2 (13)	5 (29)	28 (22)
AEs leading to dose interruption	35 (46)	10 (63)	9 (56)	8 (47)	62 (50)
Serious AEs (SAEs)	26 (34)	5 (31)	4 (25)	9 (53)	44 (35)
SAEs related to study treatment	11 (14)	3 (19)	4 (25)	6 (35)	24 (19)
Fatal SAEs	1 (1)*	0	0	0	1 (<1)

*Intracranial tumour haemorrhage not related to study treatment.

***Table S8*: Serious adverse events (SAEs) related to dabrafenib or trametinib**

SAE (any grade), n (%)	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)	Total (N=125)
Dabrafenib-related					
Any	6 (8)	3 (19)	4 (25)	5 (29)	18 (14)
Pyrexia	3 (4)	1 (6)	2 (13)	2 (12)	8 (6)
Atrial fibrillation	2 (3)	0	0	0	2 (2)
Chills	0	0	1 (6)	1 (6)	2 (2)
Ejection fraction decreased	0	0	1 (6)	1 (6)	2 (2)
Acute kidney injury	1 (1)	0	0	0	1 (<1)
Cardiomyopathy	0	0	1 (6)	0	1 (<1)
Confusional state	0	1 (6)	0	0	1 (<1)
Dehydration	0	1 (6)	0	0	1 (<1)
Diarrhoea	0	0	1 (6)	0	1 (<1)
Fatigue	0	0	1 (6)	0	1 (<1)
Headache	0	0	0	1 (6)	1 (<1)
Hypotension	0	1 (6)	0	0	1 (<1)
Neck pain	0	0	0	1 (6)	1 (<1)
Pancreatitis	1 (1)	0	0	0	1 (<1)
Renal failure	0	0	0	1 (6)	1 (<1)
Transaminase increased	0	1 (6)	0	0	1 (<1)
Vomiting	1 (1)	0	0	0	1 (<1)
Trametinib-related					
Any	8 (11)	2 (13)	4 (25)	2 (12)	16 (13)
Ejection fraction increased	2 (3)	0	1 (6)	2 (12)	5 (4)
Atrial fibrillation	2 (3)	0	0	0	2 (2)
Cardiac failure	1 (1)	0	0	0	1 (<1)
Cardiomyopathy	0	0	1 (6)	0	1 (<1)
Chills	0	0	1 (6)	0	1 (<1)
Confusional state	0	1 (6)	0	0	1 (<1)
Detachment of retinal pigment epithelium	1 (1)	0	0	0	1 (<1)
Diarrhoea	0	0	1 (6)	0	1 (<1)
Fatigue	0	0	1 (6)	0	1 (<1)
Hypotension	0	1 (6)	0	0	1 (<1)
Myocarditis	1 (1)	0	0	0	1 (<1)
Pyrexia	0	1 (6)	0	0	1 (<1)
Squamous cell carcinoma	0	0	1 (6)	0	1 (<1)
Transaminases increased	0	1 (6)	0	0	1 (<1)
Troponin T increased	1 (1)	0	0	0	1 (<1)
Vomiting	1 (1)	0	0	0	1 (<1)

***Figure S1*: Duration of intracranial response in cohort A by independent assessment**

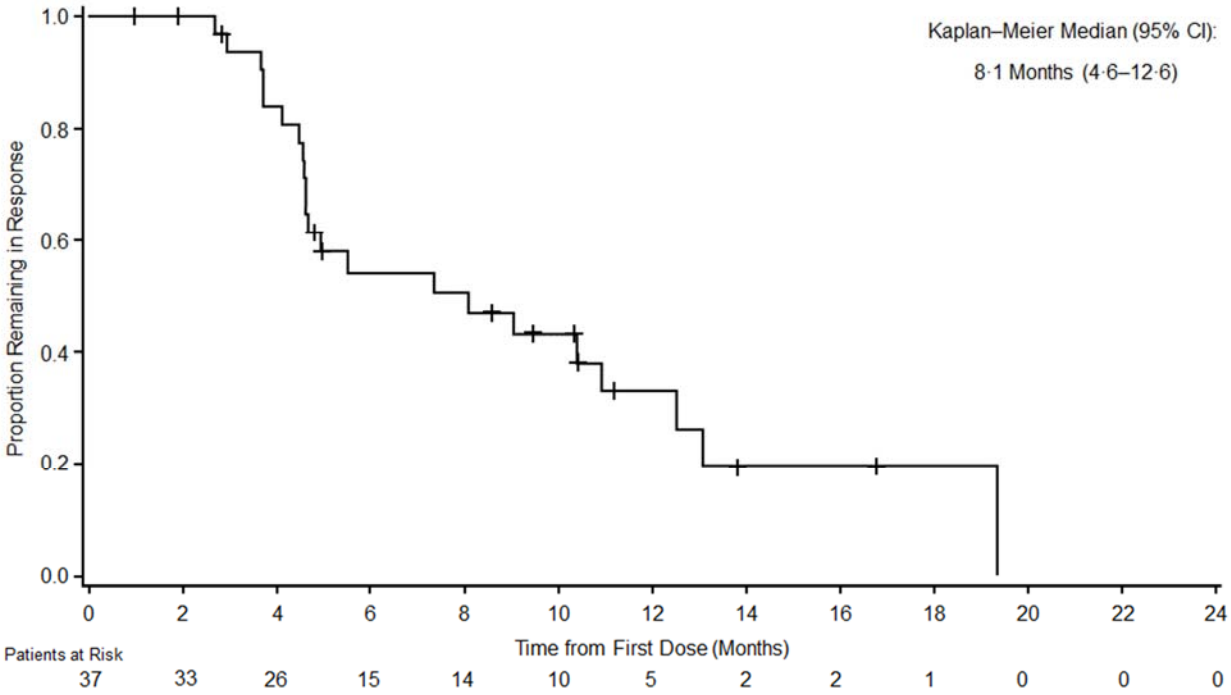


***Figure S2*: Progression-free survival in cohort A by independent assessment**

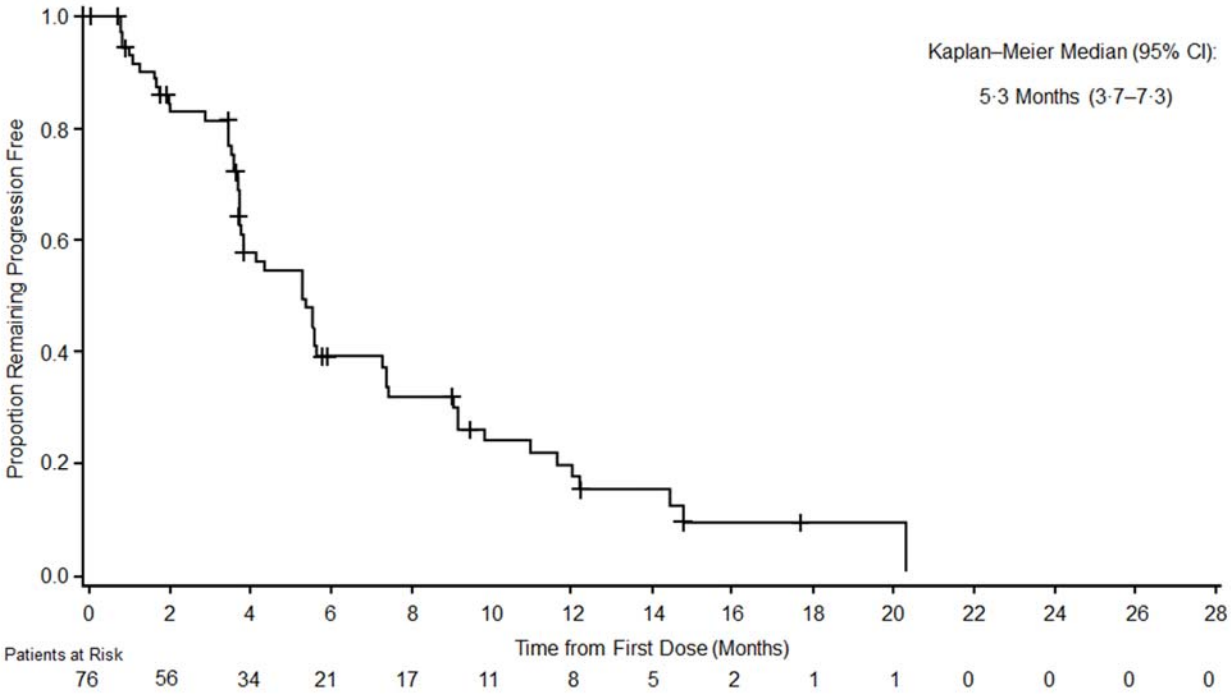


***Figure S3*: Progression-free survival in cohort B (A), cohort C (B), and cohort D (C) by investigator assessment**

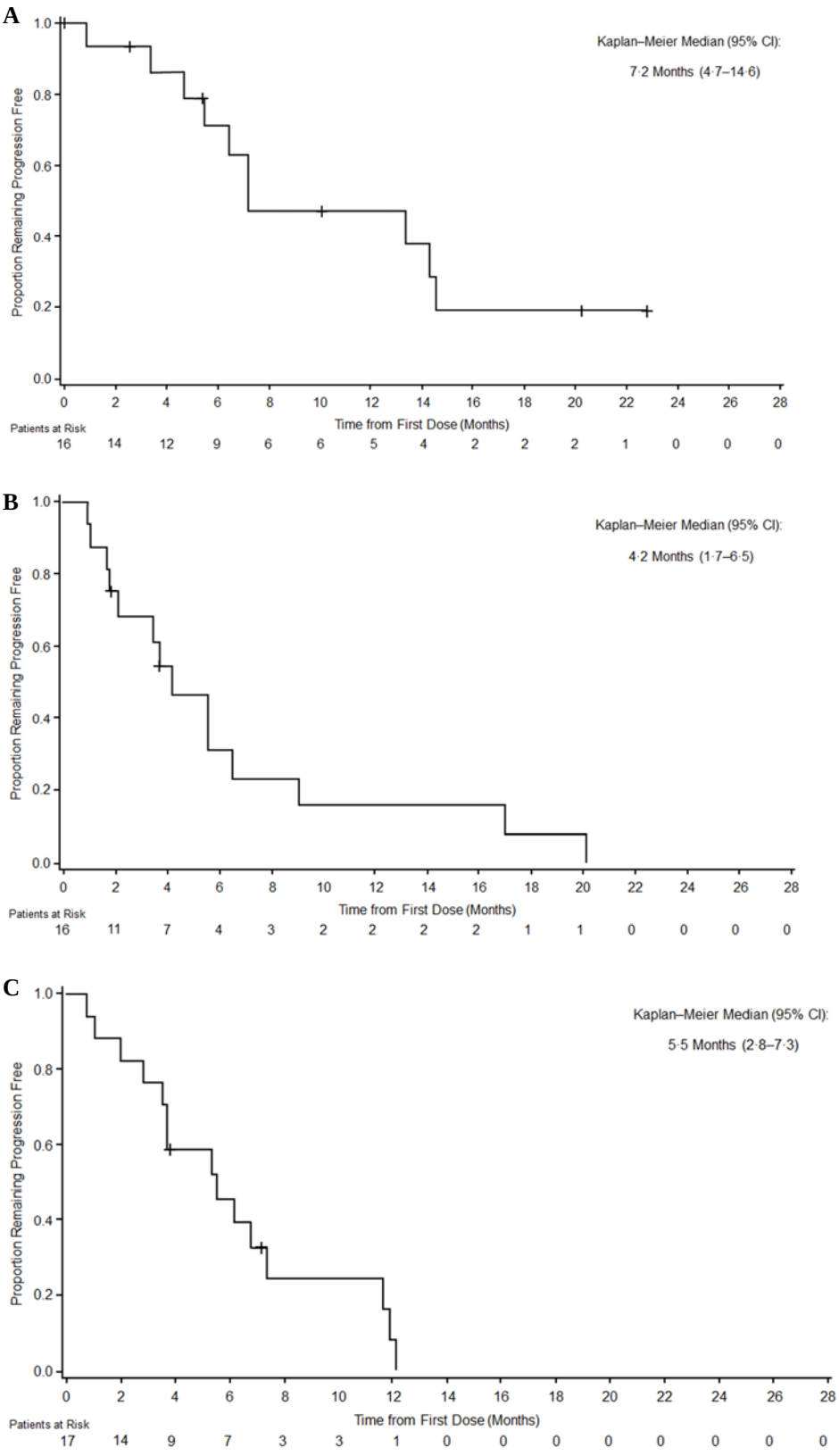
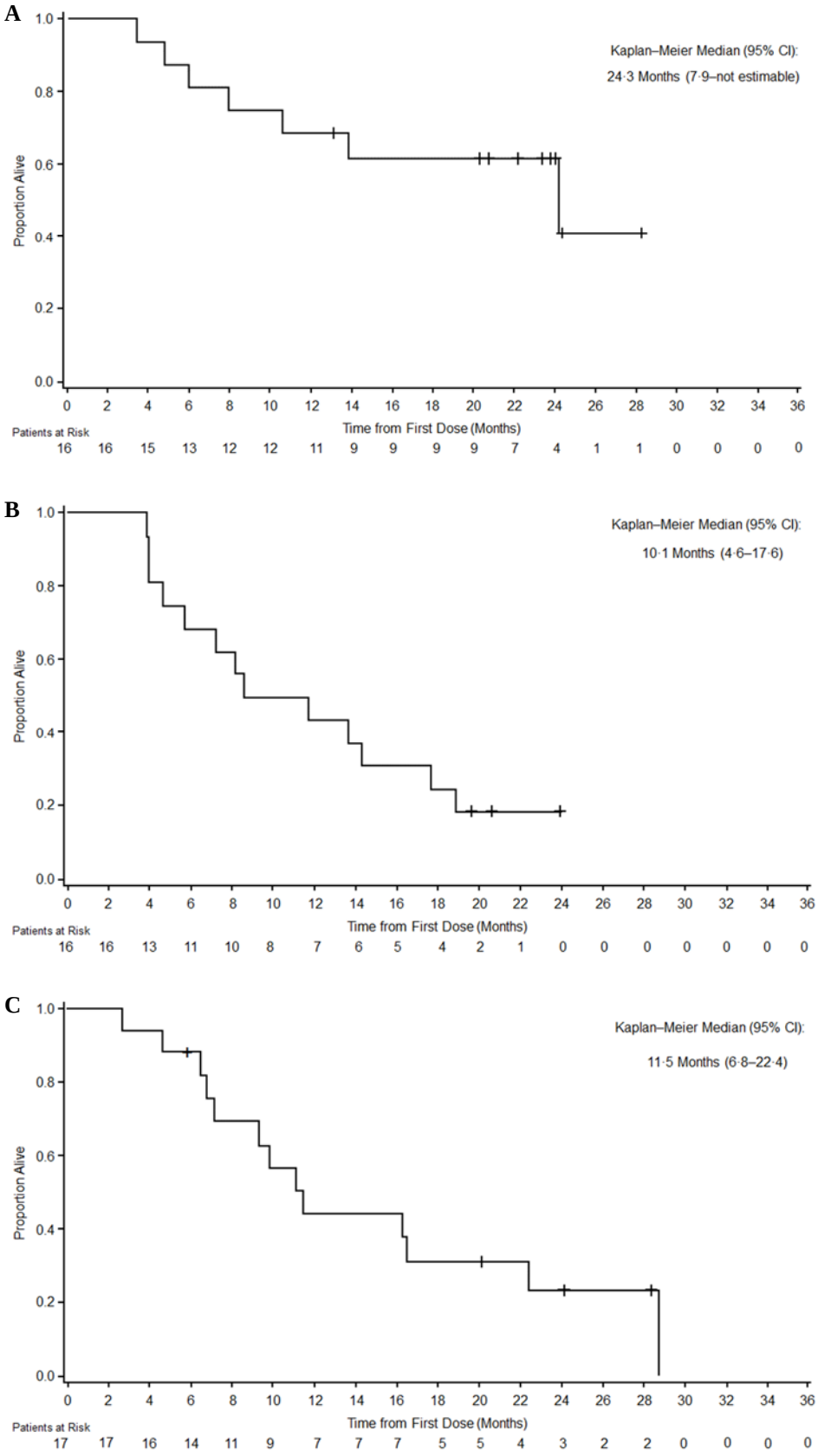


***Figure S4*: Overall survival in cohort B (A), cohort C (B), and cohort D (C) by investigator assessment**



Supplementary information

Study site enrolment information

Principal Investigator	Study Site, City, Country	Patients enrolled, n
Saiag, Philippe	Hopital Ambroise Pare, Boulogne-Billancourt, France	13
Arance Fernández, Ana	Hospital Clinic i Provincial, Barcelona, Spain	11
Robert, Caroline	Institut Gustave Roussy, Villejuif, France	11
Chiarion Sileni, Vanna	Istituto Oncologico Veneto, Padova PD, Italy	8
Thomas, Luc	Centre Hospitalier Lyon Sud, Pierre-Bénite, France	8
Lesimple, Thierry	Centre Eugène Marquis, Rennes, France	6
Mortier, Laurent	CHRU de Lille - Hôpital Claude Huriez, Lille, France	6
Moschos, Stergios	University of North Carolina at Chapel Hill, Chapel Hill, NC, USA	6
Hogg, David	Princess Margaret Hospital, University Health Network, Toronto, ON, Canada	5
Marquez Rodas, Ivan	Hospital General Universatario Gregorio Maranon, Madrid, Spain	5
Del Vecchio, Michele	Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy	4
Lebbé, Céleste	Hôpital Saint Louis, Paris, France	4
Meyer, Nicolas	Institut Claudius Regaud, Toulouse, France	4
Hassel, Jessica	Universitaetsklinikum Heidelberg, Heidelberg, Germany	3
Long, Georgina	Melanoma Institute Australia, Wollstonecraft NSW, Australia	3
Miller, Wilson	McGill University, Montreal, QC, Canada	3
Walker, John	Cross Cancer Institute, Edmonton, AB, Canada	3
Conry, Robert	University of Alabama at Birmingham, Birmingham, AL, USA	2
Ferrucci, Pier Francesco	Istituto Europeo di Oncologia-IRCCS, Milano, Italy	2
Grob, Jean-Jacques	CHU de Marseille - Hôpital de la Timone, Marseille, France	2
Hauschild, Axel	Universitaetsklinikum Schleswig-Holstein, Kiel, Germany	2
Haydon, Andrew	Alfred Health, Melbourne VIC, Australia	2
Montesa Pino, Álvaro	Hospital Carlos Haya, Málaga, Spain	2
Rodríguez Abreu, Delvys	Hospital Insular, Las Palmas, Spain	2
Davies, Michael	University of Texas MD Anderson Cancer Center, Houston, TX, USA	1
Flaherty, Keith	Massachusetts General Hospital, Boston, MA, USA	1
Hainaut-Wierzbicka, Ewa	CHU de Poitiers - La Milétrie, Poitiers, France	1
Kaatz, Martin	SRH Wald-Klinikum Gera gGmbH, Gera, Germany	1
Kudchadkar, Ragini	Winship Cancer Institute, Emory University, Atlanta, GA, USA	1
Martín Algarra, Salvador	Clinica Universidad de Navarra, Navarra, Spain	1
Soriano Teruel, Virtudes	Instituto Valenciano de Oncologia, València, Spain	1
Alizadeh, Aaron	Georgia Cancer Specialists, Decatur, GA	1