European Journal of Cancer 109 (2019) 61–69

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Five-year outcomes from a phase 3 METRIC study in patients with *BRAF* V600 E/K–mutant advanced or metastatic melanoma☆

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Received 21 November 2018; received in revised form 30 November 2018; accepted 5 December 2018
Available online 25 January 2019

KEYWORDS
Trametinib;
MEK inhibitor;

Abstract ***Background:*** Primary findings from the METRIC (TMT212A2301) study demonstrated that trametinib improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy in patients with unresectable or metastatic cutaneous melanoma

☆ Presented in part at: European Society of Medical Oncology (ESMO) 2017, Madrid, Spain.

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https://doi.org/10.1016/j.ejca.2018.12.015

METRIC;
Survival;
Targeted therapy

with a *BRAF* V600 E/K mutation. However, clinical data characterising the long-term use of these therapies in combination with *BRAF* inhibitors or as monotherapies are limited.

Methods: In this open-label, phase 3 study, 322 patients with *BRAF* V600 E/K–mutant metastatic melanoma were randomised in a 2:1 ratio to receive trametinib (2 mg orally, once daily; n = 214) or chemotherapy (dacarbazine [1000 mg/m^2] or paclitaxel [175 mg/m^2] intravenously, every 3 weeks; n = 108). Patients who progressed on chemotherapy were allowed to cross over and receive trametinib. Five-year results of efficacy and safety analyses are reported.

Results: The median PFS was 4.9 months in the trametinib arm versus 1.5 months in the chemotherapy arm (hazard ratio, 0.54; 95% confidence interval, 0.41–0.73). Landmark OS rates for trametinib versus chemotherapy arms at 1 year, 2 years and 5 years were 60.9% versus 49.6%, 32.0% versus 29.4% and 13.3% versus 17.0%, respectively. Most patients (n = 70 [65%]) from the chemotherapy arm crossed over to the trametinib arm early in their treatment. No unexpected adverse events were reported.

Conclusions: This 5-year follow-up of patients with *BRAF* V600 E/K–mutant metastatic melanoma on a targeted therapy demonstrates that long-term use of trametinib is possible with no new or unexpected adverse events. Some patients experienced long-term survival benefit with trametinib monotherapy (METRIC ClinicalTrials.gov number, NCT01245062.).

1. Introduction

Recent advances in the treatment of patients with *BRAF* V600 E/K–mutant unresectable or metastatic melanoma have been associated with clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) [1–9]. Targeted therapies and immune checkpoint inhibitors now represent the standard of care for patients with advanced disease. Despite these advances, a significant proportion of patients on either targeted therapies or immune checkpoint inhibitors develop resistance. Long-term benefit from either targeted therapies or immune checkpoint inhibitors has been observed in a subgroup of patients [1,2,6,7].

Ipilimumab (anticytotoxic T-lymphocyte–associated protein 4) was the first drug to demonstrate a durable clinical benefit lasting ≥ 5 years in a small proportion of patients within a molecularly unselected advanced melanoma population [10]. Recently, 5-year landmark analysis from the randomised part (part C) of the phase 2 study (BRF113220) and 3-year landmark analysis from the randomised, phase 3, COMBI-d study reported long-term survival benefit with the combination therapy of dabrafenib (*BRAF* inhibitor) and trametinib (*MEK* inhibitor) in a subset of patients with *BRAF* V600–mutant metastatic melanoma [5,11]. The durable benefit observed in these long-term follow-up studies counters the idea that melanoma treatment with targeted therapies rapidly leads to deterioration after an initial response. A better understanding of the proportion and characteristics of patients who can derive long-term benefit and maintain tolerability is needed for optimal treatment strategies, which remains an unmet clinical need with the current therapies in this population.

In the current analysis of the phase 3 METRIC study (NCT01245062), we report a minimum 5-year follow-up data of trametinib (*MEK* inhibitor) monotherapy. At the time this trial was originally designed and implemented, the superiority of targeted combination (*BRAF* and *MEK* inhibitors) therapy over monotherapy had not been established. In a previously reported primary analysis, the median PFS was 4.8 months in the trametinib arm and 1.5 months in the chemotherapy arm (hazard ratio [HR], 0.45; 95% confidence interval [CI], 0.33–0.63; $P < 0.001$) in patients with unresectable stage IIIC or IV cutaneous melanoma with a *BRAF* V600 mutation [12]. At 6 months, the rate of OS was 81% in the trametinib arm and 67% in the chemotherapy arm. The HR was 0.54 (95% CI, 0.32–0.92; $P = 0.01$), despite 47% of patients in the chemotherapy group crossed over to receive trametinib at the time of the previously reported primary analysis [12]. In an extended analysis, trametinib showed durable clinical benefit lasting ≥2 years in a subset of patients [13]. The data from the patients who have responded to trametinib monotherapy in this study allow to better understand the efficacy and safety associated with the long-term use of a targeted combination (*BRAF* and *MEK* inhibitors) treatment.

2. Methods

2.1. Study design and treatment

METRIC (TMT212A2301; NCT01245062) was a randomised, open-label, multicentre, phase 3 study to evaluate the efficacy and safety of trametinib monotherapy versus chemotherapy (dacarbazine or paclitaxel). The study design, treatment regimen, patient population and endpoints have been reported previously [12]. Patients with unresectable or metastatic cutaneous melanoma with a *BRAF* V600 E/K mutation were randomised in a 2:1 ratio to receive either oral trametinib (2 mg once daily) or intravenous chemotherapy consisting of either

dacarbazine (1000 mg/m^2 of body surface area) or paclitaxel (175 mg/m^2), every 3 weeks, at the discretion of the investigator.

Patients were stratified by the baseline lactate dehydrogenase (LDH) levels (normal vs elevated) and prior chemotherapy for advanced disease (yes or no). Patients in the chemotherapy arm, who did not receive any further anticancer treatment after discontinuing chemotherapy and eventually had disease progression as per Response Evaluation Criteria in Solid Tumours, version 1.1, were allowed to cross over to the trametinib arm. All patients were followed for survival, irrespective of the initiation of crossover therapy and/or subsequent therapies. The endpoints evaluated in this analysis included PFS, OS, objective response rate, duration of response (DOR) and safety. The primary efficacy analysis was restricted to patients with the *BRAF* V600 E mutation who did not have brain metastases at the baseline.

The protocol was approved by the institutional review boards at each study centre and complied with country-specific regulatory requirements. All patients provided written informed consent at screening. The study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Assessments and statistical methods

Efficacy analyses were carried out in the intention-to-treat (ITT) population and in the primary efficacy population (PEP). PFS and OS were estimated using the Kaplan–Meier (K–M) method. Response rates and 95% CI are reported for the study groups. We used the K–M method to calculate medians and interquartile ranges (IQRs) to summarise the DOR. The patients who crossed over to receive trametinib after initial chemotherapy treatment were included in the chemotherapy arm for updated OS analysis. PFS was recorded separately during the crossover phase.

Safety analyses included all patients who had received at least one dose of the study drug. Safety assessments included physical examinations, vital signs, adverse events (AEs), serious AEs (SAEs), laboratory measurements, electrocardiograms and echocardiograms/multigated acquisition for the determination of the left ventricular ejection fraction and are summarised according to the frequency of AEs in the total population.

3. Results

3.1. Patient disposition

A total of 322 patients were randomised in a 2:1 ratio to receive trametinib (2 mg orally, once daily; n = 214) or chemotherapy (dacarbazine [1000 mg/m^2] or paclitaxel [175 mg/m^2] intravenously, every 3 weeks; n = 108). The first patient was randomised on December 24, 2010, and the last patient, on July 05, 2011. Forty-one patients (19%) in the trametinib arm withdrew from the study compared with 31 (29%) in the chemotherapy arm (Fig. 1). At data

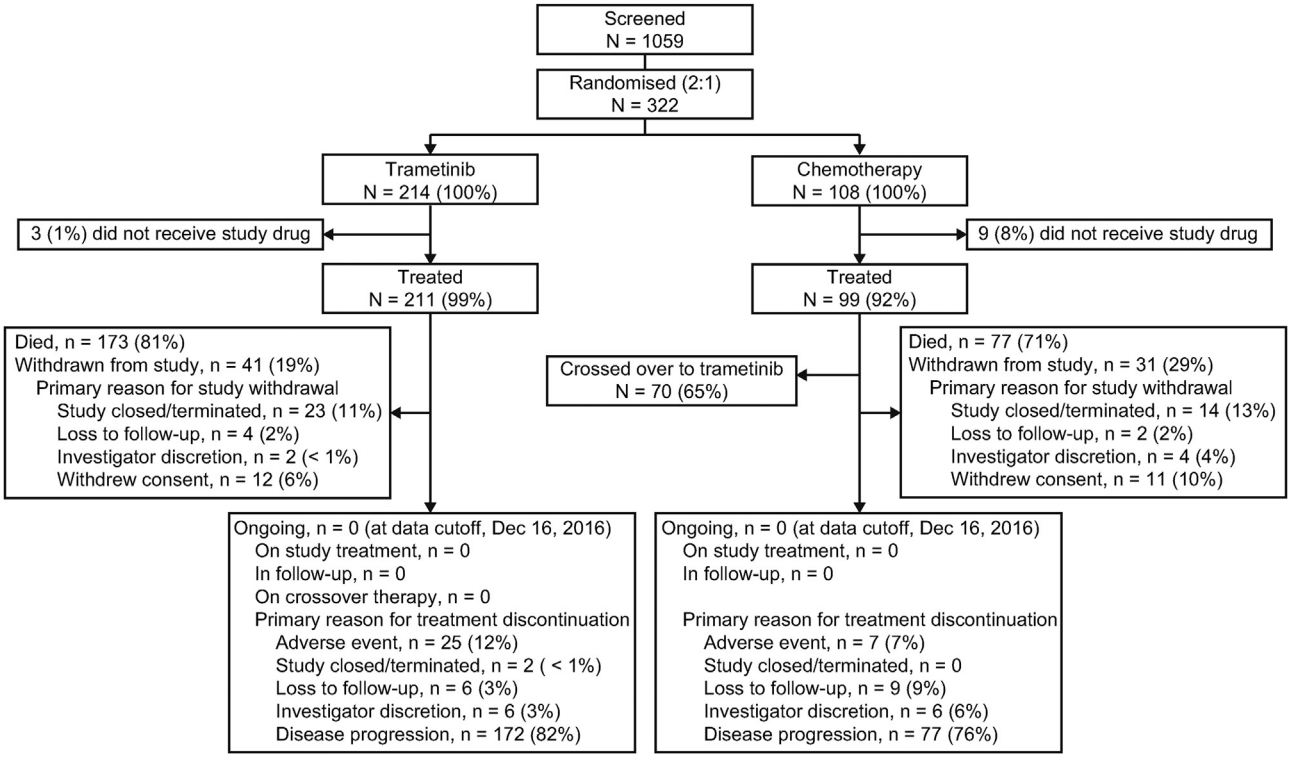

Fig. 1. METRIC study schema.

cut-off (December 16, 2016), 23 (11%) patients in the trametinib arm versus 14 (13%) in the chemotherapy arm withdrew from the study owing to study closure/termination. No patients were on randomised chemotherapy at data cut-off; however, two patients were still receiving trametinib monotherapy at data cut-off in the randomised phase, and three patients were still receiving trametinib monotherapy at data cut-off in the crossover phase.

At the final data cut-off, the median (range) follow-up was 14.7 months (0–70) in the trametinib arm and 8.7 months (0–70) in the chemotherapy arm. The median (range) time to crossover was 3.1 months (1–20), and the median (range) duration of follow-up after crossover was 8.8 months (0–67).

3.2. Baseline demographics and characteristics

Among the 322 patients, 281 had *BRAF* V600 E mutation, 40 had *BRAF* V600 K mutation and one had *BRAF* V600 E/K mutation. Prior anticancer therapy was received by 301 patients (93%). Patient demographics and baseline characteristics were consistent between the treatment arms (Table 1). As expected in a general metastatic melanoma population, 65% of patients had stage IV M1c disease, of which 37% of patients had elevated LDH. A total of 179 patients (56%) had ≥ 3 metastatic organ sites involved, and >50% patients had metastasis in lung and lymph nodes. In the chemotherapy arm, 70 patients (65%) crossed over to receive trametinib. The demographic and baseline prognostic characteristics of the crossover population were similar to the ITT population.

3.3. Efficacy

The median OS was 15.6 months in the trametinib arm versus 11.3 months in the chemotherapy arm (HR, 0.84; 95% CI, 0.63–1.11; Fig. 2). The landmark OS rates for the trametinib arm versus the chemotherapy arm at 1 year, 2 years, 3 years, 4 years and 5 years were 60.9% versus 49.6%, 32.0% versus 29.4%, 20.6% versus 22.6%, 14.9% versus 20.4% and 13.3% versus 17.0%, respectively (Fig. 2).

In the ITT population, the median PFS was 4.9 months in the trametinib arm compared with 1.5 months in the chemotherapy arm. Trametinib was associated with a 46% reduction in the estimated risk of progression or death (HR, 0.54; 95% CI, 0.41–0.73; Fig. 3A). The median PFS in the PEP was similar to that in the ITT population (Fig. 3B). In the crossover population, the median PFS was 3.0 months (95% CI, 2.7–4.8; Fig. 3C).

In the ITT population, 61 patients treated with trametinib had a confirmed response of either complete or partial response (29%; 95% CI, 22.6–35.1) and 109 (51%) had stable disease (SD) compared with ten patients treated with chemotherapy who had confirmed complete or partial response (9%; 95% CI, 4.5–16.4) and 33 (31%) who had SD. The unconfirmed response rate in the ITT population in the trametinib arm was 40% (95% CI, 33.6–47.1) compared with 14% (95% CI, 8.0–21.9) in the chemotherapy arm (Table 2). In the crossover population, the unconfirmed response rate

Table 1
Baseline patient characteristics.

Parameters	Trametinib (N = 214)	Chemotherapy (N = 108)
Age, years		
Mean (SD)	54.3 (12.97)	52.8 (13.56)
Median (min–max)	54.5 (23–85)	54.0 (21–77)
Age group, n (%)		
<65	165 (77)	86 (80)
≥65	49 (23)	22 (20)
Gender, n (%)		
Female/male	94 (44)/120 (56)	55 (51)/53 (49)
Ethnicity, n (%)		
White	214 (100)	108 (100)
ECOG PS, n (%)		
0	136 (64)	69 (64)
≥1	78 (36)	39 (36)
Unknown	0	0
TNM staging at screening, distant metastasis, n (%)		
M0	8 (4)	5 (5)
M1a	25 (12)	16 (15)
M1b	35 (16)	22 (20)
M1c	145 (68)	65 (60)
Missing	1 (<1)	0
LDH level, n (%)		
Elevated (>ULN)	77 (36)	42 (39)
Normal (≤ULN)	134 (63)	66 (61)
Missing	3 (1)	0
Number of organs involved (investigator assessed), n (%)		
1	36 (17)	22 (20)
2	55 (26)	30 (28)
≥3	123 (57)	56 (52)
History of brain metastases, n (%)		
No/yes	205 (96)/9 (4)	106 (98)/2 (2)
Prior treatment for brain metastases, n (%)		
Missing	205 (96)	106 (98)
No/yes	3 (1)/6 (3)	1 (<1)/1 (<1)
Prior treatment, n (%)		
Surgery	193 (90)	98 (91)
Chemotherapy	74 (35)	39 (36)
Immunotherapy	68 (32)	30 (28)
Radiotherapy	53 (25)	21 (19)
Biologic therapy (monoclonal antibodies, vaccines)	16 (7)	13 (12)
Hormonal therapy	1 (<1)	0
Small molecule targeted therapy	0	1 (<1)
V600 E no brain metastases, n	178	95
V600 E no brain metastases/prior chemotherapy	64	33
V600 E no brain metastases/no prior chemotherapy	114	62
BRAF mutation,[a] n		
V600 E/K	184/29	97/11

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; SD, standard deviation; TNM, tumour/node/metastasis; ULN, upper limit of the normal.
[a] One patient had V600 E/K mutation.

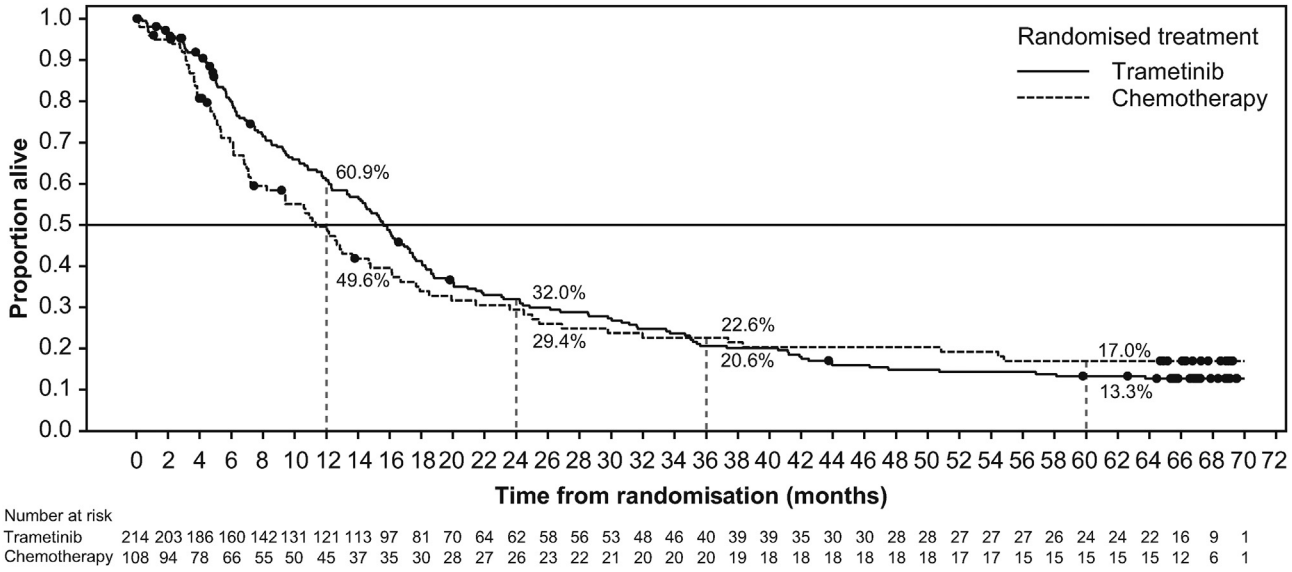

Fig. 2. Overall survival in the intent-to-treat population.

was 44% (95% CI, 32.4–56.7; Table 2). The median DOR in patients receiving trametinib was 5.3 months (95% CI, 3.6–6.9) compared with 8.1 months (95% CI, 3.5–11.1) in patients receiving chemotherapy.

The median time from study treatment discontinuation to start of subsequent anticancer therapy was 24 days (IQR range, 9–41) in the trametinib arm versus 35 days (IQR range, 30–49) in the chemotherapy arm. Follow-up anticancer therapy other than crossover therapy for patients in the chemotherapy arm was received by 208 patients: 158 (74%) in the trametinib arm and 50 (46%) in the chemotherapy arm (Table 3).

3.4. Safety

Safety was evaluated in 310 patients in the randomised phase (trametinib, n = 211; chemotherapy, n = 99) and in 70 patients in the crossover phase. In the randomised phase, the median duration of trametinib exposure was 4.8 months, and 23 patients (11%) continued trametinib beyond 12 months. The median (range) daily dose of trametinib administered in the study was 2 mg (0.5–2.0 mg).

The incidence of AEs was similar to that observed in the primary analysis [12]. In the randomised phase, the most common AEs irrespective of study drug relationship were rash, diarrhoea, fatigue, peripheral oedema, nausea and dermatitis acneiform in the trametinib arm (Table 4). Rash, diarrhoea and fatigue were the most common drug-related AEs for trametinib in the randomised phase (Table 5). The most common AEs reported in the crossover phase were similar to those reported in the randomised phase.

Drug-related SAEs were observed in 37 patients (26 [12%] in the trametinib arm and 11 [11%] in the chemotherapy arm). A total of six fatal SAEs (trametinib, n = 4 versus chemotherapy, n = 2) were reported in the randomised phase, of which, one SAE (renal failure) in the trametinib arm was suspected to be treatment related. In the crossover phase, two instances of fatal SAEs were reported and one (pneumonitis) was suspected to be treatment related.

4. Discussion

In this study, an OS of at least 5 years was observed in approximately 13% of patients who received trametinib monotherapy. Trametinib was associated with a 16% reduction in the risk of death compared with chemotherapy, despite crossover of approximately 65% of patients in the chemotherapy arm. The lack of statistically significant difference in the OS rates between trametinib and chemotherapy could be attributed to the crossover study design. In the absence of crossover, the between-group difference in the OS can be expected to be larger. Another potential reason could be the imbalance in the follow-up anticancer therapies between the treatment arms, as approximately 65% of patients received postprogression therapies.

This 5-year landmark analysis did not show any unexpected AEs. The most common AEs of any grade irrespective of the study drug relationship included rash, diarrhoea, fatigue, peripheral oedema and nausea. Trametinib was well tolerated, and the long-term safety findings were consistent with the results from previous analyses [12,14,15].

The results of long-term analyses from studies of dabrafenib and trametinib combination therapy in patients with unresectable or metastatic melanoma suggest that some patients can experience long-term responses. Patients with good baseline prognostic features (normal

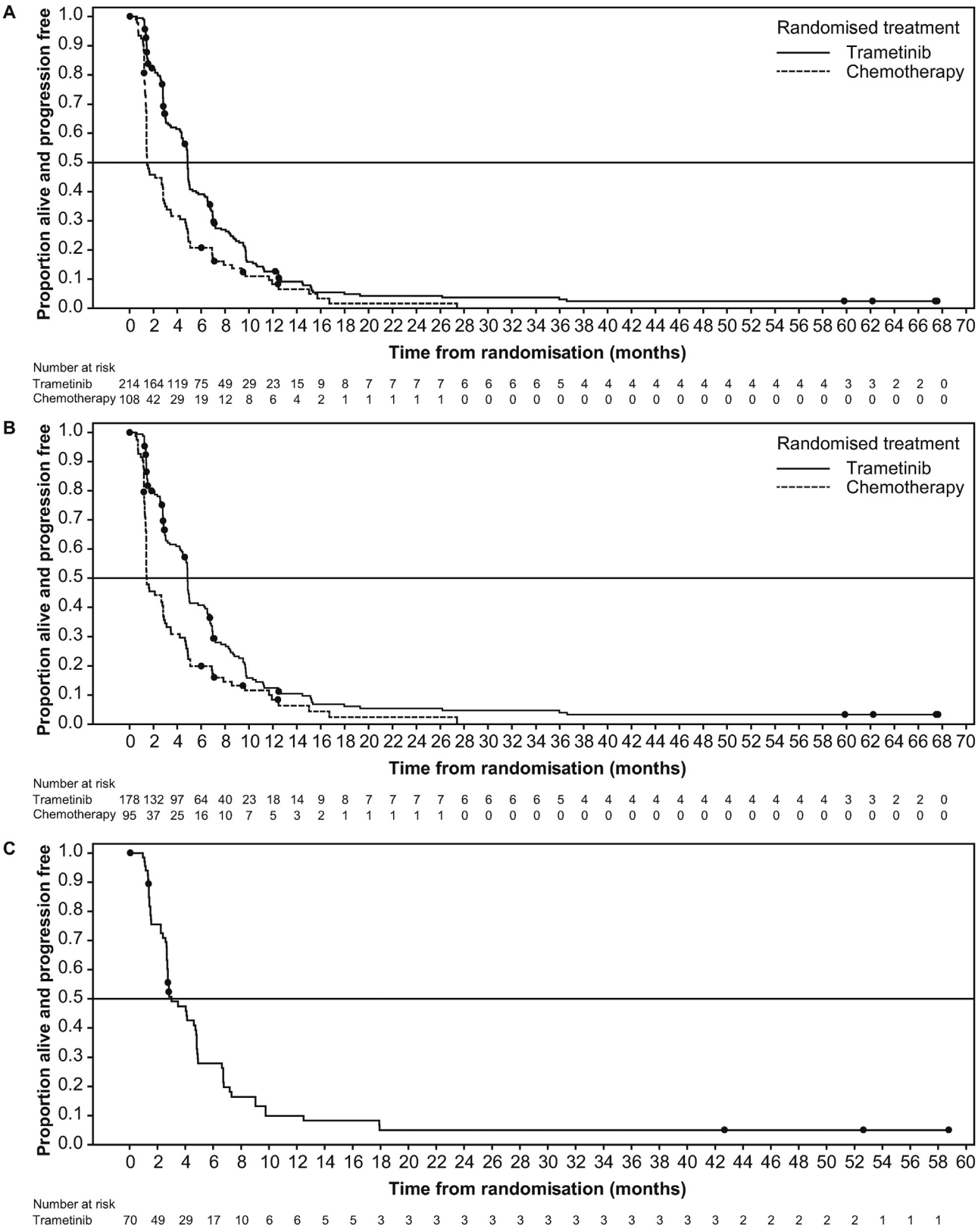

Fig. 3. Progression-free survival: (A) investigator-assessed PFS in the intent-to-treat population, (B) investigator-assessed PFS in the primary efficacy population and (C) investigator-assessed PFS in the crossover population. PFS, progression-free survival.

Table 2
Investigator-assessed best response with or without confirmation.

Parameters	Randomised phase		Crossover to trametinib (N = 70)
	Trametinib (N = 214)	Chemotherapy (N = 108)	
Best response, n (%)			
Complete response	9 (4)	3 (3)	2 (3)
Partial response	77 (36)	12 (11)	29 (41)
Stable disease	84 (39)	28 (26)	25 (36)
Progressive disease	36 (17)	50 (46)	14 (20)
Not evaluable	8 (4)	15 (14)	0
Response rate, n (%)			
Complete response + partial response	86 (40)	15 (14)	31 (44)
95% confidence interval	33.6–47.1	8.0–21.9	32.4–56.7

Table 3
Follow-up anticancer therapy.

Category	Trametinib (N = 214)[a]	Chemotherapy (N = 108)[a]	Crossover to trametinib (N = 70)
Any anticancer therapy, n (%)[b]			
Yes	158 (74)	50 (46)	41 (59)
No	56 (26)	58 (54)	29 (41)
Type of anticancer therapy			
Small molecule targeted therapy	88 (41)	30 (28)	25 (36)
Dabrafenib	7 (3)	5 (5)	4 (6)
Dabrafenib + trametinib	6 (3)	2 (2)	1 (1)
Vemurafenib	82 (38)	26 (24)	19 (27)
Radiotherapy	86 (40)	27 (25)	20 (29)
Immunotherapy	69 (32)	20 (19)	17 (24)
Ipilimumab	60 (28)	19 (18)	17 (24)
Nivolumab	3 (1)	3 (3)	2 (3)
Pembrolizumab	11 (5)	5 (5)	4 (6)
IL2	2 (1)	1 (1)	1 (1)
IFN	5 (2)	0	0
Chemotherapy	69 (32)	15 (14)	9 (13)
Surgery	50 (23)	21 (19)	16 (23)
Biologic therapy	9 (4)	3 (3)	2 (3)
Unknown	0	1 (<1)	1 (1)
Hormonal therapy	0	0	0
Time from study treatment discontinuation to start of subsequent anticancer therapy (days)[c]			
n	158	79	40
First quartile	9.0	30.0	9.0
Median	24.0	35.0	27.0
Third quartile	41.0	49.0	42.0

IFN, interferon; IL, interleukin.
[a] This reflects the number of randomised patients in the trial.
[b] The chemotherapy arm includes any anticancer therapy other than crossover therapy.
[c] Time from study treatment discontinuation to start of subsequent anticancer therapy: includes crossover therapy in the chemotherapy column.

LDH levels, earlier stage melanoma, fewer organ sites with metastases and lower sum of lesion diameters) are associated with both durable responses and prolonged survival [16,17]. Additional analyses are needed to better understand the characteristics of patients who are likely to experience long-term benefit from treatment with targeted therapies. The results from this 5-year follow-up of patients in the METRIC trial are important as they will allow conducting indirect comparisons with planned 5-year analyses of dabrafenib and trametinib combination therapy in the COMBI-d and COMBI-v studies.

In conclusion, this is the longest reported follow-up for trametinib monotherapy in patients with *BRAF* V600 E/K–mutant metastatic melanoma. Some patients experienced long-term survival benefit with trametinib. Because 65% patients in the chemotherapy arm were permitted to cross over and receive trametinib, it is expected that this active treatment also contributed to the long-term survival of patients in the chemotherapy arm. Trametinib monotherapy might be an alternative and a reasonable therapeutic option for patients who are intolerant to anti-BRAF monotherapy and who progressed after immunotherapy. The findings from this

Table 4
Adverse events occurring in >15% of patients irrespective of study drug relationship (randomised and crossover phase).

Adverse event, n (%)	Trametinib (N = 211)			Chemotherapy (N = 99)			Crossover to trametinib (N = 70)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Total	209 (>99)	97 (46)	14 (7)	92 (93)	33 (33)	5 (5)	69 (99)	22 (31)	5 (7)
Rash	124 (59)	17 (8)	1 (<1)	10 (10)	0	0	37 (53)	2 (3)	0
Diarrhoea	94 (45)	1 (<1)	0	17 (17)	1 (1)	1 (1)	24 (34)	0	0
Fatigue	62 (29)	9 (4)	0	29 (29)	3 (3)	0	8 (11)	1 (1)	0
Peripheral oedema	55 (26)	2 (<1)	0	2 (2)	0	0	16 (23)	0	0
Nausea	48 (23)	2 (<1)	0	40 (40)	1 (1)	0	12 (17)	0	0
Dermatitis acneiform	42 (20)	2 (<1)	0	2 (2)	0	0	10 (14)	1 (1)	0
Hypertension	40 (19)	32 (15)	0	9 (9)	6 (6)	0	9 (13)	4 (6)	0
Alopecia	38 (18)	2 (<1)	0	19 (19)	0	0	7 (10)	0	0
Constipation	35 (17)	1 (<1)	0	24 (24)	1 (1)	0	12 (17)	0	0
Vomiting	33 (16)	3 (1)	0	21 (21)	2 (2)	0	16 (23)	1 (1)	0
Pruritus	25 (12)	4 (2)	0	1 (1)	0	0	11 (16)	0	0

Table 5
Adverse events related to the study drug, occurring in >15% of patients (randomised and crossover phase).

Adverse event, n (%)	Trametinib (N = 211)	Chemotherapy (N = 99)	Crossover to trametinib (N = 70)
Rash	121 (57)	3 (3)	36 (51)
Diarrhoea	70 (33)	12 (12)	15 (21)
Fatigue	42 (20)	22 (22)	5 (7)
Alopecia	34 (16)	19 (19)	6 (9)
Peripheral oedema	34 (16)	0	7 (10)
Nausea	30 (14)	31 (31)	7 (10)
Dermatitis acneiform	41 (19)	0	10 (14)
Vomiting	13 (6)	16 (16)	8 (11)

extended analysis of trametinib monotherapy may serve as the basis for future indirect comparisons against long-term findings from other ongoing trials of dabrafenib and trametinib combination therapy.

Funding

This trial was initially sponsored by GSK. Trametinib was designated as an asset of Novartis as of March 2, 2015, and Novartis took over the sponsorship of the trial after March 2, 2015.

Conflict of interest statement

C.R. reports personal fees for participating as consultant in advisory boards for Roche, Pierre Fabre, Merck, Novartis, Amgen and BMS, outside the submitted work. K.F. served as a consultant and received grant support and personal fees from Novartis, during the conduct of the study. He serves on the board of directors for Loxo Oncology, Clovis Oncology, Strata Oncology and Vivid Biosciences; corporate advisory boards for X4 Pharmaceuticals and PIC Therapeutics; scientific advisory boards for Sanofi, Amgen, Asana, Adaptimmune, Fount, Aeglea, Array BioPharma, Shattuck Labs, Arch Oncology, Tolero, Apricity, Oncoceutics, Fog Pharma and Tvardi and a consultant to Genentech, BMS, Merck, Takeda, Verastem, Checkmate, and Boston Biomedical. P.N. reports personal fees from Novartis for participating in advisory board and being speaker, outside the submitted work. C.G. reports receiving grant and personal fees from Novartis for advisory role, during the conduct of the study; personal fees from Amgen, MSD, Philogen and grant and personal fees from BMS and Roche for advisory role, outside the submitted work. M.M. was an advisory board member of Amgen and Blueprint Medicines, outside the submitted work. L.D. reports receiving grant from Novartis and personal fees from Novartis, Roche, BMS, MSD and BIOCAD, outside the submitted work. P.M. was an advisory board member of Novartis, BMS, GSK, MSD, Roche, Pierre Fabre and Amgen and also received grant from BMS and MSD, outside the submitted work. J.C.H. reports receiving fees from Novartis for patient treatment inside this clinical trial; grant from BMS for translational research trial and personal fees from BMS, MSD, Roche, Novartis and Pfizer for participating in talks, outside the submitted work. P.R. received honoraria for lectures and advisory board from Novartis, MSD, BMS, Roche and Amgen, honoraria for lectures from Pfizer and honoraria for advisory board from Blueprint Medicines, outside the submitted work. R.D. has intermittent, project focused consulting and/or advisory relationships with Novartis, MSD, BMS, Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma and Sanofi, outside the submitted work. J.U. reports receiving fees from GSK/Novartis to conduct this clinical trial and is on the advisory board or has received honoraria and travel support from Amgen, BMS, GSK, Leo Pharma, MSD, Novartis, Pierre Fabre, and Roche. J.L. reports receiving grant and personal fees from Achilles Therapeutics, BMS, MSD, Nektar, Novartis, Pfizer, Roche/Genentech, Covance, and Immunocore for consultancy and research; personal fees from AstraZeneca, Boston

Biomedical, Eisai, EUSA Pharma, GSK, Ipsen, Imugene, Incyte, iOnctura, Kymab, Merck Serono, Pierre Fabre, Secarna, and Vitaccess for consultancy; grant from Aveo and Pharmacyclics for consultancy, outside the submitted work. A.D. Jr. is an employee of Novartis and owns stock of Novartis and GSK, outside the submitted work. B.M. is an employee of Novartis and owns stock of Novartis, GSK and AstraZeneca, outside the submitted work. D.S. reports receiving grant, personal fees for adboard and patients' fees from Novartis, during the conduct of the study; personal fees from Amgen, Boehringer Ingelheim, Leo Pharma, Incyte, 4SC, AstraZeneca, Immunocore, Pierre Fabre, Pfizer and Array for adboard; grant, personal fees for adboard and patients' fees from BMS; personal fees for adboard and patient's fees from MSD, Regeneron, Merck-EMD, Philogen and Roche, outside the submitted work. All remaining authors have declared no conflicts of interest.

Acknowledgements

The authors acknowledge the patients, their families and their caregivers, as well as all the investigators. The METRIC study group is grateful to all the physicians who contributed to the present study, the worldwide network of research nurses, trial coordinators and operations staff for their contributions. They appreciate the support of the colleagues of the METRIC Study Team who contributed to the presented data. In addition, they thank Rajasree Solipuram, Rohitbhai Kachhadiya and Sharol Janice Rodrigues of Novartis Healthcare Pvt. Ltd. for providing medical editorial assistance with this manuscript.

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