European Journal of Cancer 163 (2022) 79–87

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event management algorithm in patients treated with adjuvant dabrafenib plus trametinib: Primary results of COMBI-APlus

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Received 10 September 2021; received in revised form 12 November 2021; accepted 13 December 2021
Available online 14 January 2022

KEYWORDS
BRAF V600–mutant melanoma;

Abstract ***Background:*** COMBI-AD demonstrated long-term benefit of adjuvant dabrafenib plus trametinib in patients with resected stage III *BRAF* V600E/K–mutant melanoma; however, 9% of patients permanently discontinued therapy due to pyrexia. COMBI-APlus

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https://doi.org/10.1016/j.ejca.2021.12.015

Adjuvant;
Pyrexia;
BRAF inhibitor;
Dabrafenib;
MEK inhibitor;
Trametinib;
Targeted therapy

evaluated whether an adapted pyrexia management algorithm reduces high-grade pyrexia and pyrexia-related adverse outcomes.

Methods: COMBI-APlus is an open-label, phase IIIb trial evaluating an adapted pyrexia management algorithm in patients with high-risk resected stage III *BRAF* V600E/K–mutant melanoma treated with up to 12 months of adjuvant dabrafenib plus trametinib. Both drugs were interrupted for pyrexia (temperature ≥38°C) or the occurrence of pyrexia syndrome for suspected recurrent pyrexia. Treatment was restarted at the same dose once patients were symptom free for ≥24 h. The primary endpoint was the composite rate of grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent discontinuation due to pyrexia versus historical COMBI-AD control (20.0%; 95% confidence interval [CI], 16.3%–24.1%).

Results: At data cutoff (5 October 2020), COMBI-APlus met its primary endpoint of significant improvement in the composite rate of pyrexia (8.0% [95% CI, 5.9%–10.6%]), with rates of 3.8% for grade 3/4 pyrexia, 4.3% for hospitalisation due to pyrexia, and 2.4% for discontinuation due to pyrexia. Estimated 12-month relapse-free survival was 91.8% (95% CI, 89.0%–93.9%). The most common adverse events were consistent with those in COMBI-AD, and 14.7% of patients permanently discontinued treatment due to adverse events.

Conclusions: The adapted pyrexia management algorithm appears to reduce the incidence of severe pyrexia outcomes, enables patients to manage pyrexia at home, and helps patients remain on treatment.

Clinical trial registration: NCT03551626.

1. Introduction

Adjuvant treatment with either BRAF plus MEK inhibitors or immune checkpoint inhibitors has contributed to prolonged relapse-free survival in patients with high-risk resected melanoma [1–3]. With 5 years of follow-up (data cutoff, 8 November 2019), dabrafenib plus trametinib demonstrated long-term relapse-free survival benefit in the COMBI-AD trial, which evaluated 12 months of adjuvant treatment. Fifty-two percent of patients treated with dabrafenib plus trametinib were alive and relapse free at 5 years compared with 36% of patients who received placebo (hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.42–0.61). Kaplan–Meier curves for relapse-free survival appeared to plateau between years 4 and 5 in the COMBI-AD trial, suggesting prolonged benefit [1]. At the primary analysis for relapse-free survival, a preplanned interim analysis for overall survival (median follow-up, 2.8 years; data cutoff, 30 June 2017) demonstrated a clinically meaningful improvement in overall survival, with 86% of patients treated with dabrafenib plus trametinib alive versus 77% of patients who received placebo at 3 years [4].

The safety profile of dabrafenib plus trametinib is well characterised [1,4,5]. In COMBI-AD, pyrexia was the most common adverse event experienced by patients treated with dabrafenib plus trametinib. Sixty-three percent of patients experienced any-grade pyrexia, and 5% experienced grade 3/4 pyrexia in COMBI-AD [4]. Twenty-six percent of patients discontinued treatment with dabrafenib plus trametinib because of adverse events, and 9% of all patients discontinued treatment due to pyrexia [4,6]. Therefore, improved pyrexia management could potentially help mitigate the impact of severe pyrexia and enable more patients to continue receiving dabrafenib plus trametinib for the full 12-month course of adjuvant treatment.

Pyrexia has historically been thought to be associated with dabrafenib; thus, in COMBI-AD, the dose of dabrafenib (150 mg twice daily), but not trametinib (2 mg once daily), was reduced and/or interrupted for management of pyrexia. However, given the higher rate of pyrexia observed with dabrafenib plus trametinib versus dabrafenib monotherapy in the COMBI-d trial (51% versus 28%), it is now thought that trametinib also contributes to the emergence of pyrexia [7,8]. Atkinson *et al.* [9] published an updated adapted pyrexia management protocol that calls for interrupting both dabrafenib and trametinib if patients develop signs and symptom(s) of possible treatment-emergent pyrexia syndrome, which is defined as one or more of the following symptoms: fever (≥38°C), chills, rigours, night sweats, and influenza-like symptoms. Both drugs were restarted at the full dose when patients were symptom free for ≥24 h. The objective of the COMBI-APlus study was to investigate whether a similar adapted pyrexia management algorithm could reduce serious pyrexia-related adverse outcomes, including treatment cessation and hospitalisation, in patients with *BRAF* V600 mutation–positive resected stage III melanoma.

2. Materials and methods

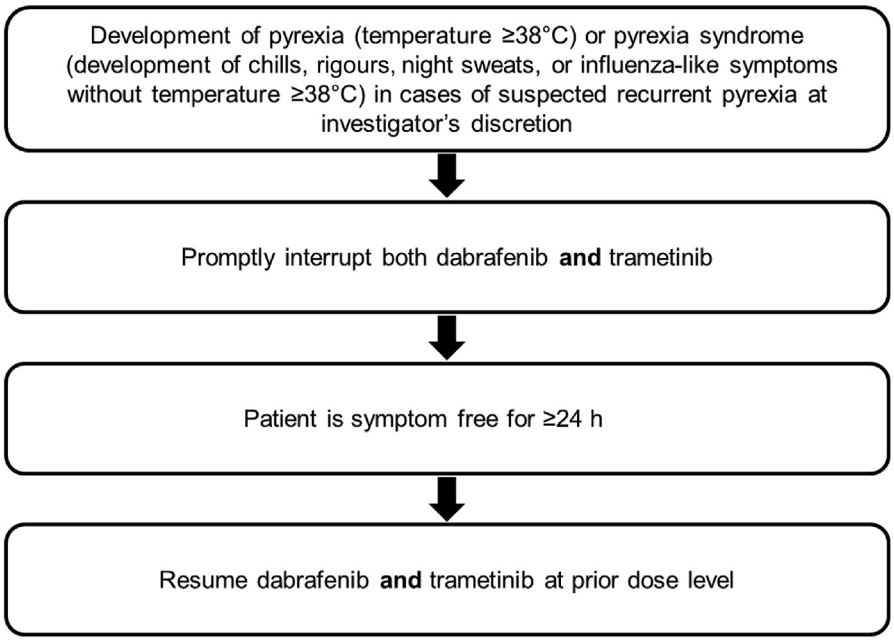
2.1. Study design and participants

COMBI-APlus (NCT03551626) is an open-label, multicentre, phase IIIb study of dabrafenib plus trametinib in the adjuvant treatment of stage III *BRAF* V600 mutation–positive melanoma after complete resection evaluating the impact of an adapted pyrexia adverse event management algorithm on pyrexia-related outcomes. Eligible patients (aged ≥18 years) had completely resected, histologically confirmed, *BRAF* V600 E/K mutation–positive cutaneous stage IIIA (lymph node metastasis >1 mm), IIIB, IIIC, or IIID melanoma according to the American Joint Committee on Cancer's (AJCC's) *Cancer Staging Manual,* 8th edition. Further details regarding inclusion and exclusion criteria are given in the Supplementary Material.

The sample size calculation was based on the primary variable, and the protocol provided justification for the planned sample size of 600. Based on the current sample size of 552, the study operating characteristics confirmed that the study achieved more than 90% power.

The trial was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board or independent ethics committee at each trial centre. All patients provided written

A



B

	COMBI-APlus	COMBI-AD[4]
Pyrexia definition	≥38.0°C	≥38.5°C
Action	Withhold dabrafenib and trametinib	Withhold dabrafenib and continue trametinib at the same dose
Additional pyrexia management instructions	• Initiate antipyretic treatment with NSAIDs or paracetamol • Consider corticosteroids in patients whose fever does not resolve with antipyretics	
Resumption of treatment	Upon resolution of pyrexia, resume dabrafenib and trametinib	Upon resolution of pyrexia, resume dabrafenib

Fig. 1. **Adapted pyrexia management algorithm (A) and comparison of pyrexia management strategies between COMBI-APlus and COMBI-AD (B)**. NSAID, nonsteroidal anti-inflammatory drug.

informed consent for data collection supporting these analyses.

2.2. Procedures

Patients received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily for up to 12 months or until discontinuation for disease recurrence, unacceptable toxicity, investigator's discretion, or withdrawal of consent. The total study duration for each patient was 24 months: up to 12 months of treatment followed by at least 12 months of follow-up. Further details on assessment schedules are given in the Supplementary Material.

In the adapted pyrexia management algorithm, dabrafenib and trametinib were interrupted promptly at the onset of pyrexia (≥38°C) and were restarted upon the improvement of symptoms at the same dose if patients remained symptom free (temperature <38°C) for at least 24 h. In addition, dabrafenib and trametinib could be interrupted in the presence of pyrexia syndrome (i.e. chills, rigours, night sweats, or influenza-like symptoms) without documented temperature ≥38°C for cases of suspected recurrent pyrexia, at the investigators' discretion, as shown in Fig. 1. The differences in pyrexia management between COMBI-APlus and COMBI-AD are also highlighted in Fig. 1.

Pyrexia events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 term for fever, which is classified by elevated body temperature as follows: grade 1, 38.0°C to 39.0°C; grade 2, >39.0°C to 40.0°C; grade 3, >40.0°C for ≤24 h; and grade 4, >40.0°C for >24 h.

2.3. Outcomes

The primary endpoint of the COMBI-APlus trial was the composite rate of grade 3/4 pyrexia, hospitalisation due to pyrexia, and/or permanent treatment discontinuation due to pyrexia compared with a historical control from COMBI-AD. Secondary endpoints included relapse-free survival, defined as the time from the first dose of the study medication to disease recurrence or death from any cause, at 12 months, and safety.

2.4. Statistical analysis

The primary statistical analysis was performed 12 months after the last patient's first visit and was based on the calculation of the observed pyrexia event rate up to 12 months of therapy (primary endpoint) using the full analysis set (all patients who received ≥1 dose of study treatment). Adverse events that occurred on treatment (i.e. between the date of first administration of study treatment until 30 days after the last administration of study treatment) were included in the analysis of adverse events. The observed pyrexia event rate was calculated using descriptive statistics (number and percentage of pyrexia events) along with its two-sided exact 95% CI using the Clopper-Pearson method. Evidence of treatment effect (improvement in pyrexia event rate using the adapted adverse event management algorithm) was concluded if the upper bound of the two-sided 95% CI was <20%. The historical control for comparison is based on the dabrafenib plus trametinib arm of COMBI-AD, in which 87 of 435 patients (20.0% [95% CI, 16.3%–24.1%]) had a composite pyrexia event [4]. Relapse-free survival was analysed descriptively in the full analysis set population, and the relapse-free survival distribution was estimated using the Kaplan–Meier method.

3. Results

Between 29 August 2018 and 26 September 2019, 552 patients from 23 countries were enrolled (Supplementary Table S1). At data cutoff (5 October 2020), all 552 patients had either completed 12 months of treatment or discontinued treatment. The median follow-up at the time of the analysis was 18.1 months. The most common reason for discontinuation of either drug was the development of adverse events (dabrafenib, 15.4%; trametinib, 16.1%; Table 1). The median age of enrolled patients was 53.0 years; 46.9% of the patients had primary tumour ulceration, and 15.2% had in-transit disease. Based on the AJCC's *Cancer Staging Manual,* 8th edition, 59 patients (10.7%) had stage IIIA disease, 176 patients (31.9%) had stage IIIB disease, 304 patients (55.1%) had stage IIIC disease, and 12 patients (2.2%) had stage IIID disease (Table 2).

Table 1
Reasons for treatment discontinuation.

Treatment discontinuation details	n (%)
Discontinued either of the two drugs	**128 (23.2)**
Discontinued dabrafenib	**125 (22.6)**
Reason for discontinuation	
Adverse events	85 (15.4)
Disease relapse	18 (3.3)
Loss to follow-up	3 (0.5)
Physician decision	4 (0.7)
Pregnancy	1 (0.2)
Protocol deviation	1 (0.2)
Patient decision	6 (1.1)
Technical problems	1 (0.2)
Withdrawal of informed consent	6 (1.1)
Discontinued trametinib	**128 (23.2)**
Reason for discontinuation	
Adverse events	89 (16.1)
Disease relapse	18 (3.3)
Loss to follow-up	3 (0.5)
Physician decision	4 (0.7)
Pregnancy	1 (0.2)
Protocol deviation	1 (0.2)
Patient decision	5 (0.9)
Technical problems	1 (0.2)
Withdrawal of informed consent	6 (1.1)

Table 2
Demographics and baseline disease characteristics.

Characteristics	$N = 552$
Age, years	
Median	53.0
IQR	45.0–63.0
Range	18–82
Sex, *n* (%)	
Female	255 (46.2)
Male	297 (53.8)
ECOG performance status, *n* (%)	
0	517 (93.7)
1	31 (5.6)
Missing	4 (0.7)
Time since initial diagnosis, months	
Median	5.0
IQR	3.6–16.1
Range	0.3–216.9
BRAF mutation status, *n* (%)	
V600E	520 (94.2)
V600K	31 (5.6)
Other (V600D)[a]	1 (0.2)
Primary tumour ulceration, *n* (%)	259 (46.9)
In-transit disease, *n* (%)	84 (15.2)
Tumour stage (AJCC 8), *n* (%)	
IIIA	59 (10.7)
IIIB	176 (31.9)
IIIC	304 (55.1)
IIID	12 (2.2)
Missing	1 (0.2)
Number of positive lymph nodes, *n* (%)	
0[b]	51 (9.2)
1	283 (51.3)
2–3	162 (29.3)
≥4	55 (10.0)
Unknown	1 (0.2)

AJCC 8, American Joint Committee on Cancer's *Cancer Staging Manual,* 8th edition; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

[a] Although only V600 E/K were permitted per protocol, one patient with a V600D mutation was included in the analysis per the statistical analysis plan.

[b] Patients with in-transit disease without lymph node involvement.

COMBI-APlus met its primary endpoint of improvement in the incidence of composite pyrexia events compared with a historical control from COMBI-AD. Grade 3/4 pyrexia, hospitalisation due to pyrexia, or permanent discontinuation of treatment due to pyrexia was experienced by 44 patients (8.0% [95% CI, 5.9%–10.6%]), compared with a historical control rate of 20.0% in COMBI-AD (Table 3). The rate of grade 3/4 pyrexia was 3.8% in COMBI-APlus versus 5.3% in COMBI-AD, the rate of hospitalisation due to pyrexia was 4.3% in COMBI-APlus versus 10.6% in COMBI-AD, and the discontinuation rate due to pyrexia was 2.4% in COMBI-APlus versus 8.7% in COMBI-AD [4,10]. These data are summarised in Supplementary Figure S1. Overall, 374 patients (67.8%) experienced any-grade pyrexia, and in total, there were 2068 on-treatment pyrexia events in the study. Among the 374 patients who experienced pyrexia, 194 (51.9%) had grade 1 pyrexia events, 159 (42.5%) had grade 2, 15 (4.0%) had grade 3, and six (1.6%) had grade 4. Pyrexia led to dose interruption of dabrafenib and trametinib in 61.6% and 60.9% of patients, respectively, and dose reduction of dabrafenib and trametinib in 5.8% and 4.3% of patients, respectively. The median time to the first onset of pyrexia was 22 days (interquartile range [IQR], 11–69 days), and the median duration of the first pyrexia event was 2.0 days (IQR, 2.0–4.0 days).

Overall safety is shown in Table 4. A total of 541 patients (98.0%) experienced adverse events, and 226 patients (40.9%) experienced grade ≥3 adverse events. Adverse events led to discontinuation of both dabrafenib and trametinib in 81 patients (14.7%). The most common adverse events (≥20% of all patients [N = 552]) were pyrexia (374 patients [67.8%]), headache (175 patients [31.7%]), asymptomatic blood creatine phosphokinase increase (154 patients [27.9%]), diarrhoea (149 patients [27.0%]), chills (146 patients [26.4%]), fatigue (142 patients [25.7%]), asthenia (130 patients [23.6%]), nausea (129 patients [23.4%]), rash (118 patients [21.4%]), and arthralgia (116 patients [21.0%]). A total of 23 deaths (4.2%) were reported in the study. The cause of 20 deaths (3.6%) was melanoma disease progression. Two patients (0.4%) died on treatment, one because of disease progression and one because of sepsis, which was determined to not be treatment related.

The median duration of treatment was 11.0 months for both dabrafenib and trametinib, and the median relative dose intensity for both dabrafenib and trametinib was 94.5% (Table 5). At the data cutoff, 83 patients (15.0%) had experienced a relapse-free survival event, including 79 relapses (14.3%) and four deaths before documented disease progression (0.7%). At 12 months, 91.8% of patients were alive and relapse free (95% CI, 89.0%–93.9%).

4. Discussion

Pyrexia is an adverse event associated with BRAF and MEK inhibitor therapy; however, rates appear higher with the combination of dabrafenib and trametinib relative to other targeted therapies [1,5,11,12]. Atkinson *et al.* [9] published guidance on managing adverse events associated with dabrafenib plus trametinib, particularly pyrexia syndrome. COMBI-APlus investigated a similar pyrexia management algorithm and met its primary endpoint of significant reduction in composite pyrexia events compared with a historical control from COMBI-AD. The rates of grade 3/4 pyrexia, hospitalisation due to pyrexia, and discontinuation due to pyrexia were lower in COMBI-APlus compared with COMBI-AD [4,10]. Baseline patient and disease characteristics were similar between both studies [4], suggesting that the improvement in outcomes are due to the adapted

Table 3
Characterisation of pyrexia events.

Pyrexia characteristics	$N = 552$
Incidence of composite pyrexia events, *n* (%)[a]	**44 (8.0)**
95% CI	**5.9–10.6**
Grade 3/4 pyrexia	21 (3.8)
Hospitalisation due to pyrexia	24 (4.3)
Permanent treatment discontinuation due to pyrexia	13 (2.4)
Incidence of pyrexia, any grade, *n* (%)	**374 (67.8)**
Total number of pyrexia events	2068
Maximum grade, *n* (%)[b,c]	
1	194 (51.9)
2	159 (42.5)
3	15 (4.0)
4	6 (1.6)
Outcome, *n* (%)[b]	
Recovered/resolved	336 (89.8)
Not recovered/not resolved[d]	38 (10.2)
Recovered/resolved with sequelae	0
Fatal	0
Number of occurrences of pyrexia, *n* (%)[b]	
1	113 (30.2)
2	53 (14.2)
≥3	208 (55.6)
Time to first occurrence of pyrexia, days	
Mean (SD)	52.7 (66.4)
Median	22.0
IQR	11.0–69.0
Range	1–357
Duration of first occurrence of pyrexia, days	
Mean (SD)	3.3 (3.4)
Median	2.0
IQR	2.0–4.0
Range	1–32

IQR, interquartile range.
[a] The incidence of composite pyrexia events in COMBI-APlus was compared with the historical control rate of 20.0% (95% CI, 16.3%–24.1%) in the COMBI-AD trial.
[b] The percentage is calculated based on the 374 patients who developed pyrexia.
[c] A patient with multiple severity grades for an adverse event is only counted under the maximum grade.
[d] At the time of the data cutoff of 5 October 2020.

pyrexia management algorithm. The overall safety profile of COMBI-APlus was similar to that observed in COMBI-AD with the exception of 27.9% of patients with increased blood creatine phosphokinase levels, a parameter that was not required to be routinely assessed in COMBI-AD [4]. Together, these data demonstrate that the effect of the algorithm is primarily on the composite rate of pyrexia. The algorithm tested in COMBI-APlus was not intended to reduce the overall incidence of pyrexia (COMBI-AD, 63% versus COMBI-APlus, 67.8%) but to mitigate severe pyrexia episodes to keep more patients on treatment [4]. With a median duration of exposure of 11.0 months for dabrafenib and trametinib in both COMBI-APlus and COMBI-AD, patients in COMBI-APlus had fewer treatment discontinuations and a similar duration of pyrexia [4,13]. While a small number of patients dose reduced dabrafenib and/or trametinib due to recurrent pyrexia that did not respond to dose interruption and corticosteroids, the adapted pyrexia algorithm was associated with a marked decrease in dose reduction compared with COMBI-AD.

Several studies have suggested the benefit of using a similar pyrexia management approach to that evaluated in COMBI-APlus. Recent data from a pooled analysis of 1076 patients treated in registrational trials of dabrafenib plus trametinib demonstrated that temporary dose interruption of dabrafenib or trametinib was the most common and effective pyrexia management strategy [14]. A modified pyrexia management algorithm involving withholding both dabrafenib and trametinib at the earliest onset of pyrexia was also evaluated in the phase III COMBI-i trial of spartalizumab or placebo plus dabrafenib and trametinib in the metastatic setting. In the placebo plus dabrafenib and trametinib arm of COMBI-i, fewer patients experienced grade ≥3 pyrexia adverse events of special interest, hospitalisation because of pyrexia adverse events of special interest, or complicated pyrexia (defined as pyrexia accompanied by chills grade ≥3, hypotension, dehydration, syncope, or renal dysfunction) compared with COMBI-d/v [15]. The Summary of Product Characteristics for dabrafenib and trametinib was updated in September 2021 to include a pyrexia management strategy involving interruption of both dabrafenib and trametinib at the first sign of pyrexia, then restarting treatment once the patient is symptom free for ≥24 h, which is aligned with the algorithms used in COMBI-APlus and COMBI-i [16,17]. The COMBI-APlus algorithm is simple and easy to follow, and the ability of patients to manage pyrexia at

Table 4
Adverse events (≥10% of patients).

Adverse events	$N = 552$	
	All grades	Grade ≥3
Any adverse event (all-cause), *n* (%)	541 (98.0)	226 (40.9)
Pyrexia	374 (67.8)	21 (3.8)
Headache	175 (31.7)	2 (0.4)
Blood CPK increased	154 (27.9)	32 (5.8)
Diarrhoea	149 (27.0)	7 (1.3)
Chills	146 (26.4)	2 (0.4)
Fatigue	142 (25.7)	6 (1.1)
Asthenia	130 (23.6)	2 (0.4)
Nausea	129 (23.4)	0
Rash	118 (21.4)	3 (0.5)
Arthralgia	116 (21.0)	2 (0.4)
Vomiting	84 (15.2)	2 (0.4)
Myalgia	83 (15.0)	3 (0.5)
Cough	79 (14.3)	1 (0.2)
ALT increased	75 (13.6)	10 (1.8)
AST increased	74 (13.4)	8 (1.4)
Lipase increased	71 (12.9)	39 (7.1)
Influenza-like illness	67 (12.1)	2 (0.4)
Oedema peripheral	65 (11.8)	1 (0.2)
Any treatment-related adverse event	515 (93.3)	166 (30.1)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

Table 5
Drug exposure.

Drug exposure details	N = 552	
	Dabrafenib	Trametinib
Duration of exposure, months		
Mean (SD)	9.7 (3.0)	9.7 (3.0)
Median	11.0	11.0
IQR	10.9–11.1	10.9–11.1
Range	0.03–14.4	0.03–12.4
Average daily dose, mg/day[a]		
Mean (SD)	273.9 (41.6)	1.9 (0.2)
Median	297.1	2.0
IQR	264.5–299.6	1.9–2.0
Range	123.9–315.3	0.9–2.1
Dose intensity, mg/day[b]		
Mean (SD)	256.7 (54.3)	1.7 (0.3)
Median	283.4	1.9
IQR	222.7–296.4	1.6–2.0
Range	82.1–481.9	0.7–2.0
Relative dose intensity, %[c]		
Mean (SD)	85.6 (18.1)	86.8 (16.1)
Median	94.5	94.5
IQR	74.2–98.8	77.7–98.8
Range	27.4–160.6	33.6–101.1

IQR, interquartile range.
[a] Average dose does not consider drug-free days, whereas dose intensity and relative dose intensity include days of zero dose in the calculation.
[b] Dose intensity (mg/day) = actual cumulative dose (mg)/duration of exposure to study treatment (day).
[c] Relative dose intensity = dose intensity (mg/day)/planned dose intensity (mg/day).

home without the need to visit a healthcare provider may be beneficial for patient quality of life. Furthermore, evidence suggests that patients with cancer are at increased risk of severe COVID-19–related illness and poor clinical outcomes [18], so the ability to manage pyrexia from home is of potential increased importance during the COVID-19 pandemic.

Preliminary efficacy data suggest a relapse-free survival rate in COMBI-APlus comparable with that observed in COMBI-AD. The estimated 12-month relapse-free survival rate was 91.8% in COMBI-APlus compared with 88% in COMBI-AD [4,19]. Follow-up was longer in the COMBI-AD trial, and continued follow-up of patients in COMBI-APlus will provide insight into whether patients who managed pyrexia with the adapted algorithm will have similar or potentially improved relapse-free survival benefit, and follow-up is ongoing for overall survival and health-related quality of life.

A limitation of this analysis is that it was not a randomised study. The open-label design using an approved therapy with demonstrated efficacy could have positively impacted patients' willingness to stay on treatment. We cannot rule out that this may have contributed to the difference in discontinuation rates between COMBI-AD (26%), which was a randomised trial, versus COMBI-APlus (14.7%) [4]. Healthcare provider experience with dabrafenib plus trametinib also could have affected adverse event management, as physicians are now more experienced with the safety profile of targeted therapy [20,21]. Furthermore, as a single-arm study, a historical control was used rather than a direct comparison with a control arm. Because patient populations and inclusion/exclusion criteria were similar between COMBI-AD and COMBI-APlus, we were able to use a historical control, which allowed us to decrease the sample size and increase the power of COMBI-APlus.

The choice of which adjuvant therapy to use is based on several factors, amongst which risk versus benefit is important. Both targeted and immune checkpoint inhibitor therapy have demonstrated benefit in the adjuvant treatment setting and have distinct safety profiles [1,2,22]. Targeted therapy is associated with acute adverse events, such as pyrexia, that largely resolve following discontinuation, whereas immune checkpoint inhibitors are associated with some long-term adverse events, which may require ongoing management, such as hypothyroidism and, rarely, diabetes mellitus [1,4,23,24]. Therefore, reducing the burden of serious pyrexia-related events helps to improve the risk–benefit profile of adjuvant dabrafenib plus trametinib.

5. Conclusions

The COMBI-APlus trial met its primary endpoint, and this primary analysis demonstrates that the adapted pyrexia management algorithm enables more patients to remain on adjuvant dabrafenib plus trametinib treatment with less impact of severe pyrexia outcomes, such as high-grade pyrexia and hospitalisation or discontinuation due to pyrexia. This adapted pyrexia management algorithm may be easier to follow than the previous approach to managing pyrexia and allow patients to manage pyrexia at home without the need to visit a healthcare provider, which may provide an advantage during the current COVID-19 pandemic. Early relapse-free survival data demonstrate benefit, and the ability to remain on treatment could enable more patients to derive long-term benefit. The effect of the adapted pyrexia management algorithm on long-term relapse-free and overall survival is a topic of ongoing investigation.

Authors' contributions

All the authors developed the initial draft of the article and made the decision to submit it for publication; all the authors contributed to subsequent drafts. The authors affirm the accuracy and completeness of the data and adherence of the trial to the protocol. Conception or design of the work; acquisition, analysis, or interpretation of data; and drafting or revision of the work were done by V.A., M.D.V., B.R., J.G., and A.M.

Acquisition, analysis, or interpretation of data and drafting or revising of the work were done by C.R., H.G., C.D., L.D., A.G., F.M., H.B., and M.L.

Funding

This work was supported by Novartis Pharmaceuticals Corporation (no grant number). The study was designed by the academic authors in conjunction with representatives of the sponsor. Data were collected by the sponsor and analysed and interpreted in collaboration with the authors. The sponsor was involved in the writing of the report and the decision to submit for publication. All authors had full access to all the data in the study and accept responsibility to submit for publication.

Conflict of interest statement

V.A. reports advisory relationships with Bristol Myers Squibb, MSD, Merck, Nektar, Novartis, Pierre Fabre, Provectus, QBiotics, and Roche; travel expenses paid by Bristol Myers Squibb and OncoSec; and speaker fees from MSD, Merck, Novartis, Pierre Fabre, and Roche. C.R. reports consulting or advisory relationships with Bristol Myers Squibb, Roche, Pierre Fabre, Novartis, Amgen, Sanofi, Merck, MSD, and AstraZeneca. J.J.G. reports receipt of honoraria from and consulting or advisory relationships with Roche, Novartis, Bristol Myers Squibb, MSD, Amgen, Pierre Fabre, Sanofi, Merck, and Pfizer; and travel, accommodations, or other expenses paid by Roche, Novartis, Bristol Myers Squibb, MSD, and Pierre Fabre. H.G. reports receipt of honoraria from Bristol Myers Squibb, MSD, Novartis, and Pierre Fabre; consulting or advisory relationships with Bristol Myers Squibb, MSD, and Amgen; and travel, accommodations, or other expenses paid by Bristol Myers Squibb, MSD, and Pierre Fabre. C.D. reports consulting or advisory relationships with and travel, accommodations, or other expenses paid by Bristol Myers Squibb, MSD, Pierre Fabre, and Novartis. L.D. reports receipt of honoraria from, consulting or advisory relationships with, participation in speakers bureaus with, and provision of expert testimony for Roche, Novartis, MSD, Bristol Myers Squibb, and BIOCAD; and research funding from Roche, Novartis, MSD, Bristol Myers Squibb, BIOCAD, Array BioPharma, Amgen, and Pfizer. A.G. reports consulting or advisory relationships with Amgen, Bristol Myers Squibb, and Novartis and payment or honoraria from Bristol Myers Squibb and Novartis. A.M.M. reports consulting or advisory relationships with Bristol Myers Squibb, MSD, Novartis, Roche, Pierre Fabre, and QBiotics. B.R. reports consulting fees from Amgen, Bristol Myers Squibb, Clinigen, MSD, Novartis, and Roche and honoraria from MSD and Pfizer. F.M. reports employment with and stock or other ownership in Novartis Pharmaceuticals Corporation. H.B. reports employment with Novartis Pharmaceuticals Corporation and stock or other ownership in Bristol Myers Squibb. M.L. reports employment with and stock or other ownership in Novartis Pharma AG. M.D.V. reports receipt of honoraria from and consulting or advisory relationships with Merck, Novartis, Bristol Myers Squibb, Sanofi, and Pierre Fabre; and research funding from Bristol Myers Squibb.

Acknowledgements

The study in this analysis was sponsored by Novartis Pharmaceuticals Corporation; dabrafenib and trametinib are assets of Novartis Pharmaceuticals Corporation as of 2 March 2015. The authors thank the patients and their families for their participation. The authors thank the study site staff and additional investigators for their contributions. Editorial assistance was provided by Sandra Haberthuer (Novartis Pharmaceuticals Corporation). Medical writing assistance was provided by Alana Reed, PhD (ArticulateScience LLC), and was funded by Novartis Pharmaceuticals Corporation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.12.015.

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