European Journal of Cancer 119 (2019) 97–106

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Adverse events associated with encorafenib plus binimetinib in the COLUMBUS study: incidence, course and management

Helen J. Gogas [a,*], Keith T. Flaherty [b], Reinhard Dummer [c], Paolo A. Ascierto [d], Ana Arance [e], Mario Mandala [f], Gabriella Liszkay [g], Claus Garbe [h], Dirk Schadendorf [i], Ivana Krajsova [j], Ralf Gutzmer [k], Vanna Chiarion Sileni [l], Caroline Dutriaux [m], Jan Willem B. de Groot [n], Naoya Yamazaki [o], Carmen Loquai [p], Ashwin Gollerkeri [q], Michael D. Pickard [q], Caroline Robert [r]

[a] *Department of Internal Medicine, National and Kapodistrian University of Athens, Laikon Hospital, Athens, Greece*
[b] *Cancer Center, Massachusetts General Hospital, Boston, MA, USA*
[c] *Department of Dermatology, University Hospital Zürich Skin Cancer Center and University Zürich, Zürich, Switzerland*
[d] *Melanoma Unit, Cancer Immunotherapy and Innovative Therapies, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy*
[e] *Department of Medical Oncology, Hospital Clinic of Barcelona, Barcelona, Spain*
[f] *Department of Oncology and Haematology, Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy*
[g] *Department of Dermatology, National Institute of Oncology, Budapest, Hungary*
[h] *Department of Dermatology, University Hospital Tuebingen, Tuebingen, Germany*
[i] *Department of Dermatology, University Hospital Essen, Essen, Germany, and German Cancer Consortium, Heidelberg, Germany*
[j] *Department of Dermato-oncology, University Hospital Prague and Charles University First Medical Faculty, Prague, Czech Republic*
[k] *Department of Dermatology and Allergy, Skin Cancer Center Hannover, Hannover Medical School, Hannover, Germany*
[l] *Melanoma Cancer Unit, Oncology Institute of Veneto IRCCS, Padua, Italy*
[m] *Department of Oncologic Dermatology, Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France*
[n] *Department of Medical Oncology, Isala, Zwolle, Netherlands*
[o] *Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan*
[p] *Department of Dermatology, University Medical Center Mainz, Mainz, Germany*
[q] *Array BioPharma Inc., Boulder, CO, USA*
[r] *Service of Dermatology, Department of Medicine and Paris-Sud University, Gustave Roussy, Villejuif, France*

Received 28 May 2019; received in revised form 17 July 2019; accepted 19 July 2019
Available online 19 August 2019

* *Corresponding author*: First Department of Medicine, National and Kapodistrian University of Athens, 17 Ag. Thoma Str. Goudi, 11527, Greece. Fax: +30 2132061795.
E-mail address: helgogas@gmail.com (H.J. Gogas).

https://doi.org/10.1016/j.ejca.2019.07.016

KEYWORDS
Melanoma;
Safety;
Encorafenib;
Binimetinib;
Vemurafenib

Abstract ***Background:*** Dual inhibition of the mitogen-activated protein kinase pathway with BRAF/MEK inhibitor (BRAFi/MEKi) therapy is a standard treatment for *BRAF*V600-mutant metastatic melanoma and has historically been associated with grade III pyrexia or photosensitivity depending on the combination used. The objective of this study was to fully describe adverse events from the COLUMBUS study evaluating the most recent BRAF/MEK inhibitor combination encorafenib+binimetinib.

Patients and methods: Patients with locally advanced, unresectable or metastatic *BRAF*V600-mutant melanoma were randomised to receive encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, encorafenib 300 mg once daily or vemurafenib 960 mg twice daily. Adverse events that represent known effects of available BRAFi and/or MEKi were evaluated.

Results: The safety population included a total of 570 patients (encorafenib+binimetinib = 192; encorafenib = 192; vemurafenib = 186). Median duration of exposure was longer with encorafenib+binimetinib (51 weeks) than with encorafenib (31 weeks) or vemurafenib (27 weeks). Common BRAFi/MEKi toxicities with encorafenib+binimetinib were generally manageable, reversible and infrequently associated with discontinuation. Pyrexia was less frequent with encorafenib+binimetinib (18%) and encorafenib (16%) than with vemurafenib (30%) and occurred later in the course of therapy with encorafenib+binimetinib (median time to first onset: 85 days versus 2.5 days and 19 days, respectively). The incidence of photosensitivity was lower with encorafenib+binimetinib (5%) and encorafenib (4%) than with vemurafenib (30%). The incidence of serous retinopathy was higher with encorafenib+binimetinib (20%) than with encorafenib (2%) or vemurafenib (2%), but no patients discontinued encorafenib+binimetinib because of this event.

Conclusion: Encorafenib+binimetinib is generally well tolerated and has a low discontinuation rate in patients with *BRAF*V600-mutant melanoma, with a distinct safety profile as compared with other anti-BRAF/MEK targeted therapies.

Trial registration: ClinicalTrials.gov (Identifier: NCT01909453) and with EudraCT (number 2013-001176-38).

1. Introduction

Activating *BRAF*V600 mutations occur in ~50% of patients with melanoma [1]. These mutations drive constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in the development and progression of melanoma [2]. Dual inhibition of the MAPK pathway with combination BRAF/MEK inhibitor (BRAFi/MEKi) therapy is a standard treatment for patients with *BRAF*V600-mutant metastatic melanoma [3–6]. Compared with BRAFi monotherapy, BRAF/MEKi combination therapy improves survival while reducing BRAFi-associated toxicities resulting from paradoxical MAPK pathway activation [3–7]. BRAF/MEKi therapies are associated with characteristic adverse events (AEs), but each of the established combinations (dabrafenib plus trametinib and vemurafenib plus cobimetinib) has a distinct safety profile with unique toxicities that impact overall tolerability and may impact the ability to deliver optimal treatment. For example, pyrexia has been observed in 51–53% of patients treated with dabrafenib plus trametinib and has included serious febrile reactions and multiple episodes. It was the leading cause of dose interruption (30–32% of patients) or reduction (13–14% of patients) and discontinuation (2–3% of patients) [3,4]. Furthermore, photosensitivity has been commonly seen in patients treated with vemurafenib plus cobimetinib, occurring in 48% of patients, with 5% presenting with grade ≥3 photosensitivity [8].

The combination of encorafenib plus binimetinib has demonstrated clinical activity and tolerability in the Phase 3 COLUMBUS study in patients with *BRAF* V600–mutated melanoma [9,10]. This combination is distinct in that encorafenib is an adenosine triphosphate-competitive BRAF inhibitor that suppresses the MAPK pathway in tumour cells that express several mutated forms of BRAF kinase (eg, V600E,V600D and V600K mutations), with a dissociation half-life that is more than 10 times longer (>30 h) than either dabrafenib or vemurafenib [11]. Preclinical studies suggest that this property could allow for sustained target inhibition and enhance antitumour activity while reducing paradoxical activation of MAPK pathways in normal tissues [11,12]. Binimetinib is an orally available, non-ATP competitive, allosteric inhibitor of MEK1 and MEK2 [13]. Results from part 1 of the COLUMBUS study demonstrated encorafenib/binimetinib combination provides favourable efficacy and tolerability profile, as evidenced by the

achievement of higher median dose intensities and longer median treatment exposure [10].

These findings highlight the importance of defining the AE profiles of each combination to provide clinicians with information needed to optimise treatment for individual patients. The objective of this report was to describe the incidence, course and management of class-based AEs of from the COLUMBUS study.

2. Materials and methods

2.1. Study design and patients

COLUMBUS is a two-part, phase III, randomised, open-label study being conducted at 162 hospitals in 28 countries. A detailed description of the study design is provided in the original publications [10]. Briefly, patients with locally advanced or unresectable or metastatic melanoma with a *BRAF*V600E or *BRAF*V600K mutation and Eastern Cooperative Oncology Group performance status of 0 or 1 who were untreated or who had progressed on or after prior first-line immunotherapy were randomised 1:1:1 to receive encorafenib 450 mg once daily plus binimetinib 45 mg twice daily, encorafenib 300 mg once daily or vemurafenib 960 mg twice daily until disease progression (per central review), death, unacceptable toxic effects or withdrawal of consent. Throughout the study, dose modifications were permitted based on tolerability and AEs.

2.2. Safety evaluations

Safety assessments included AE monitoring, physical examinations and cardiac and clinical laboratory assessments. All patients in the encorafenib plus binimetinib group and only patients on the encorafenib and vemurafenib arms who had retinal abnormalities at baseline had routine ophthalmic testing at each regularly scheduled visit during the treatment period. For patients on the encorafenib and vemurafenib arms without retinal abnormalities at baseline, routine ophthalmic testing was performed at cycle 4 day 1 and every 12 weeks thereafter. Cardiac imaging by a multigated acquisition scan or echocardiogram to assess left ventricular dysfunction was performed at screening; at day 1 of cycle 2, 3, 6 and 9 and every 12 weeks thereafter. AE severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Individual AEs describing clinically significant risks identified in the non-clinical and clinical programs, as well-known class effects with BRAFi and MEKi were evaluated.

2.3. Statistical methods

All patients who received at least one dose of study drug and had at least one postbaseline safety assessment were included in the safety analysis set. AEs recorded on or before May 19, 2016 were included in the current analysis. Exposure-adjusted incidence rate (EAIR; per 100 patient-months of exposure to study drug) was calculated for each AE as the number of patients experiencing the AE divided by the total exposure time at risk for the AE, with the duration of study drug exposure contributed by an individual patient being truncated at the time of first onset of the AE. All safety assessments are described descriptively.

3. Results

A total of 577 patients were randomised; 570 received treatment and were included in the safety analysis set (encorafenib plus binimetinib = 192; encorafenib = 192; vemurafenib = 186).

Baseline characteristics were generally similar across treatment groups (Table 1). The median duration of exposure to study treatment was longer in the encorafenib plus binimetinib group (51 weeks for both components) than with encorafenib (31 weeks) or vemurafenib (27 weeks).

3.1. Adverse events

The incidence and EAIR of AEs are summarised in Table 2. The incidence and EAIR of selected AEs are presented in Figs. 1 and 2, respectively; discontinuation rates, dose

Table 1
Baseline demographics and clinical characteristics.

Characteristic	COMBO450 $n = 192$	ENCO300 $n = 192$	VEM $n = 186$
Mean (SD) age, y	56 (14)	55 (13)	55 (14)
Male sex, %	60	56	58
ECOG performance status 0,[a] %	71	72	73
LDH≥ULN, %	29	24	27
BRAF mutation status (V600E/V600K), %	89/11	89/10[b]	88/12
Tumour stage at study entry, %			
IIIB/IIIC	5	3	6
IVM1a	14	15	13
IVM1b	18	20	16
IVM1c	64	62	65
Number of organs involved, %			
1	24	29	24
2	30	27	31
≥3	45	44	46
Prior immunotherapy,[c] %	30	30	30
Ipilimumab	4	5	4
Prior anti–PD-1 or anti–PD-L1	1	1	0
Interferons/interleukins	27	26	27

COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ECOG, Eastern Cooperative Oncology Group; ENCO300, encorafenib 300 mg once daily; LDH, lactate dehydrogenase; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; ULN, upper limit of normal; VEM, vemurafenib 960 mg twice daily.

[a] All other patients had ECOG performance status of 1.

[b] Two observations were indeterminate.

[c] Includes adjuvant and metastatic settings.

Table 2
AEs by incidence and exposure-adjusted incidence rates.[a]

Adverse event	COMBO450 $n = 192$		ENCO300 $n = 192$		VEM $n = 186$	
	n (%)	EAIR[a]	n (%)	EAIR[a]	n (%)	EAIR[a]
General disorders and administration site conditions						
Fatigue[b]	83 (43)	5.5	80 (42)	6.8	86 (46)	9.1
Pyrexia[c]	35 (18)	1.7	30 (16)	1.9	55 (30)	5.1
Peripheral edema[d]	25 (13)	1.2	18 (9)	1.1	27 (15)	2.1
Erythema[e]	14 (7)	0.6	30 (16)	1.9	32 (17)	2.4
Gastrointestinal disorders						
Nausea	79 (41)	5.0	74 (39)	5.7	63 (34)	5.6
Diarrhoea	70 (37)	4.4	26 (14)	1.5	63 (34)	5.9
Vomiting[f]	57 (30)	3.1	52 (27)	3.4	29 (16)	2.1
Abdominal pain[g]	54 (28)	3.0	32 (17)	2.0	29 (16)	2.1
Constipation	42 (22)	2.1	27 (14)	1.6	12 (7)	0.8
Musculoskeletal and connective tissue disorders						
Arthralgia[h]	49 (26)	2.6	85 (44)	8.4	85 (46)	10.4
Myopathy[i]	45 (23)	2.2	64 (33)	5.0	41 (22)	3.3
Pain in extremity	21 (11)	1.0	42 (22)	2.8	25 (13)	1.9
Back pain	18 (9)	0.8	29 (15)	1.8	11 (6)	0.8
Skin and subcutaneous tissue disorders						
Hyperkeratosis[j]	44 (23)	2.3	110 (57)	14.6	92 (50)	12.1
Rash[k]	42 (22)	2.2	79 (41)	7.2	99 (53)	14.3
Dry skin[l]	31 (16)	1.5	72 (38)	6.2	49 (26)	4.2
Alopecia[l,m]	27 (14)	1.3	108 (56)	12.8	70 (38)	7.1
Pruritus[n]	24 (13)	1.1	59 (31)	4.6	39 (2.1)	3.4
PPE syndrome	13 (7)	0.6	98 (51)	9.8	26 (14)	1.9
Photosensitivity[o]	9 (5)	0.4	8 (4)	0.5	56 (30)	5.2
Nervous system disorders						
Headache[p]	42 (22)	2.0	54 (28)	3.9	37 (20)	3.0
Dizziness[q]	29 (15)	1.4	12 (6)	0.7	8 (4)	0.6
Neuropathy[r]	23 (12)	1.1	42 (22)	2.8	25 (13)	1.9
Eye disorders						
Visual impairment[s]	39 (20)	2.1	11 (6)	0.6	8 (4)	0.5
Serous retinopathy[t]	38 (20)	1.9	4 (2)	0.2	3 (2)	0.2
Vascular disorders						
Hemorrhage[u]	36 (19)	1.7	21 (11)	1.2	16 (9)	1.1
Hypertension[v]	22 (12)	1.0	11 (6)	0.6	21 (11)	1.5
Cardiac disorders						
Left ventricular dysfunction[w]	15 (8)	0.7	4 (2)	0.2	1 (1)	0.1
Neoplasms benign, malignant and unspecified disorders (of the skin)						
Skin papilloma[x]	14 (7)	0.6	20 (10)	1.2	36 (19)	2.9
CuSCC[y]	5 (3)	0.2	15 (8)	0.9	32 (17)	2.5
Basal cell carcinoma	3 (2)	0.1	2 (1)	0.1	3 (2)	0.2

AE, adverse event; COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; CuSCC, cutaneous squamous cell carcinoma; EAIR, exposure-adjusted incidence rates; ENCO300, encorafenib 300 mg once daily; PPE, palmar-plantar erythrodysesthesia; VEM, vemurafenib 960 mg twice daily.

[a] AE per 100 patient-months of exposure to study drug.
[b] Includes fatigue, asthenia.
[c] Includes pyrexia, body temperature increased, hyperpyrexia, hyperthermia.
[d] Includes peripheral edema, local swelling, localised edema, edema, peripheral swelling.
[e] Includes erythema, generalised erythema, plantar erythema.
[f] Includes vomiting, retching.
[g] Includes abdominal pain, abdominal discomfort, upper abdominal pain, epigastric discomfort, gastrointestinal pain.
[h] Includes arthralgia, arthropathy, joint stiffness.
[i] Includes muscle spasms, muscular weakness, myalgia, myositis.
[j] Includes hyperkeratosis, hyperkeratosis follicularis et parafollicularis, keratosis pilaris, lichenoid keratosis, palmoplantar keratoderma, parakeratosis, skin hyperplasia.
[k] Includes rash, exfoliative rash, erythematous rash, follicular rash, generalised rash, macular rash, maculopapular rash, papular rash, pruritic rash, vesicular rash.
[l] Includes dry skin, asteatosis, xeroderma, xerosis.
[m] Includes alopecia, alopecia totalis, diffuse alopecia.
[n] Includes pruritus, generalised pruritus, genital pruritus.
[o] Includes photosensitivity reaction, solar dermatitis.
[p] Includes headache, head discomfort, migraine.

[q] Includes dizziness, balance disorder, vertigo.
[r] Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, sciatica, sensory disturbance, sensory loss.
[s] Includes visual impairment, blurred vision, reduced visual acuity.
[t] Includes retinal detachment, chorioretinitis, chorioretinopathy, cystoid macular edema, macular retinal pigment epithelium detachment, retinal pigment epithelium detachment, macular detachment, macular edema, metamorphopsia, retinal disorder, retinal exudates, retinal edema, retinal pigment epitheliopathy, retinopathy, subretinal fluid.
[u] Includes rectal haemorrhage, hematochezia, haematuria, cerebral haemorrhage, epistaxis, haemorrhoidal haemorrhage, menorrhagia, metrorrhagia, retinal haemorrhage, conjunctival haemorrhage, gastric ulcer haemorrhage, gastrointestinal haemorrhage, haematospermia, haemorrhagic cyst, intracranial tumour haemorrhage, polymenorrhea, subdural haematoma, uterine haemorrhage, haemorrhagic diarrhoea, haemoptysis, mucosal haemorrhage, occult blood, postprocedural haemorrhage, postmenopausal haemorrhage, pulmonary alveolar haemorrhage, tumour haemorrhage, vaginal haemorrhage, wound haemorrhage.
[v] Includes hypertension, essential hypertension, hypertensive crisis.
[w] Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction and ejection fraction abnormal.
[x] Includes skin papilloma, papilloma, blepharal papilloma, oral papilloma.
[y] Includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma, squamous cell carcinoma of skin.

modification rates, and time to first onset are summarised in Table 3. EAIRs were included to account for differences in the duration of exposure among the treatment groups. As can be seen in Table 2, the EAIRs for the encorafenib plus binimetinib group were generally lower relative to the other treatment groups. Additional event characteristics are detailed in the following section.

3.2. Pyrexia

Pyrexia was less frequent with encorafenib plus binimetinib (18%) and encorafenib (16%) than with vemurafenib (30%), and events with encorafenib plus binimetinib occurred later in the course of therapy (median [range] time to first onset, 85 [2–545] days versus 2.5 [1–560] days and 19 [2–619] days, respectively). Pyrexia was mild (grade I) for most of the patients in the encorafenib plus binimetinib group who experienced it (23/35; 66%). No patients in the encorafenib plus binimetinib group experienced grade IV pyrexia, and a minority (10/192; 5%) experienced more than one episode. Pyrexia led to discontinuation in only one of 192 (<1%) patients receiving encorafenib plus binimetinib, and pyrexia-related dose interruptions/adjustments were uncommon (8/192; 4%).

The six serious AEs of pyrexia that occurred with encorafenib plus binimetinib were not associated with hypotension, chills/rigors, dehydration, renal failure or syncope and were usually associated with concurrent contributory factors such as disease progression or underlying infection.

3.3. Gastrointestinal AEs (nausea, diarrhoea and vomiting)

The incidence of nausea was similar across treatment groups (encorafenib plus binimetinib: 41%; encorafenib: 39% and vemurafenib: 34%). In the encorafenib plus binimetinib treatment group, 24% of patients experienced grade I nausea; 15% grade II and 2% grade III.

Diarrhoea was reported in more number of patients who receive encorafenib plus binimetinib (36%) and vemurafenib (34%) than those who receive encorafenib (14%). In the encorafenib plus binimetinib group, 24% of patients experienced grade I diarrhoea; 10% grade II; 2% grade III and 0.5% grade IV.

The incidence of vomiting was 30% with encorafenib plus binimetinib, 27% with encorafenib and 16% with vemurafenib. In the encorafenib plus binimetinib group, 18% of patients experienced grade I vomiting; 10% grade II and 2% grade III.

In the encorafenib plus binimetinib group, nausea, diarrhoea and vomiting occasionally led to dose modification (8%, 4% and 7%, respectively); diarrhoea led to study discontinuation in 1% of patients. The median time to first onset was 29 days for both nausea (range: 1–614 days) and diarrhoea (range: 1–534 days) and 57 days for vomiting (range: 1–607 days).

3.4. Arthralgia

The incidence of arthralgia was lower with encorafenib plus binimetinib (26%) than with encorafenib (44%) or vemurafenib (46%), with a median (range) time to first onset with combination therapy of 85 (1–708) days. In the encorafenib plus binimetinib group, severe arthralgia was uncommon; the incidence of grade I, grade II and grade III events was 19%, 6% and 1%, respectively. A minority of patients in the encorafenib plus binimetinib group (2%) required dose interruption or adjustment, and no patient discontinued because of arthralgia.

3.5. Hyperkeratosis

The incidence of hyperkeratosis was lower with encorafenib plus binimetinib (23%) than with encorafenib (57%) or vemurafenib (49%), with a median (range) time to first onset in the combination group of 77 (1–408) days. With encorafenib plus binimetinib, severe hyperkeratosis was uncommon; the incidence of grade I, grade II and grade III events was 17%, 5% and 1%, respectively. A minority of patients in the encorafenib plus binimetinib group (2%) required dose interruption or

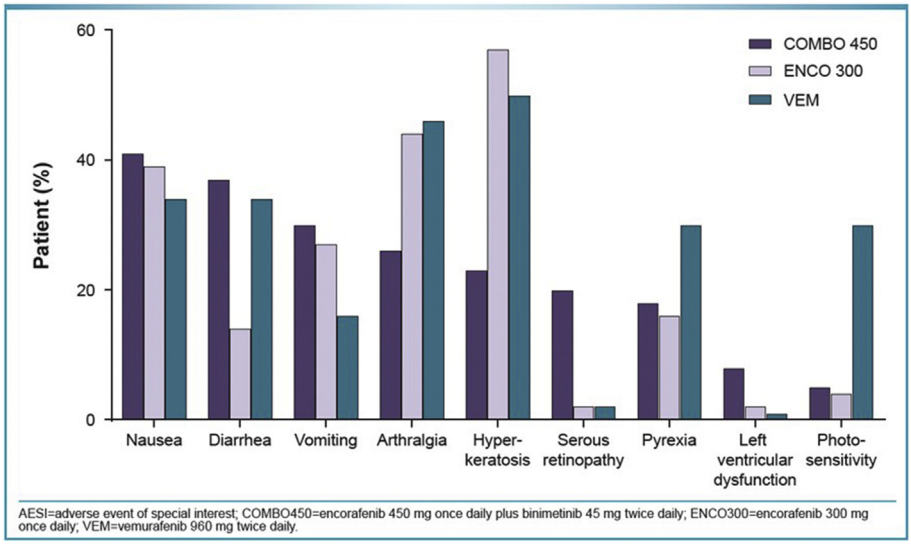

Fig. 1. Selected AEs occurring in patients (all grades) in any study group. AESI, adverse event of special interest; COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300, encorafenib 300 mg once daily; VEM, vemurafenib 960 mg twice daily.

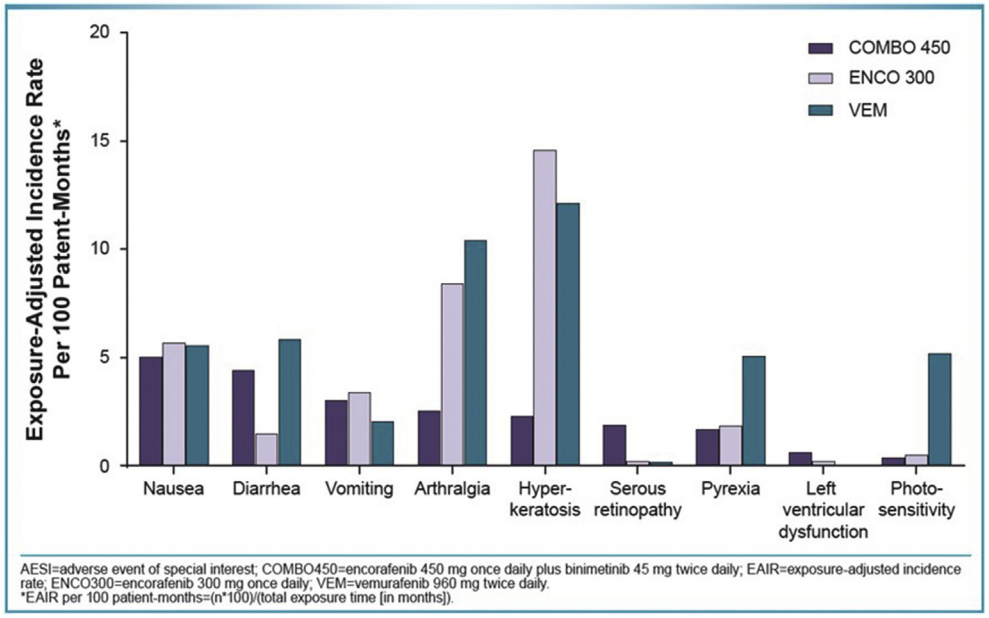

Fig. 2. Selected AEs by exposure-adjusted incidence rate. AESI, adverse event of special interest; COMBO450, encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; EAIR, exposure-adjusted incidence rates; ENCO300, encorafenib 300 mg once daily; VEM, vemurafenib 960 mg twice daily. *EAIR per 100 patient-months = (n*100)/(total exposure time [in months]).

adjustment, and no patient discontinued because of hyperkeratosis.

3.6. Photosensitivity

The incidence of photosensitivity was lower with encorafenib plus binimetinib (5%) and encorafenib (4%) than with vemurafenib (30%) despite advice on minimizing sun exposure [14], with a median (range) time to first onset in the combination group of 84 (1–677) days. With encorafenib plus binimetinib, all events were of grade I or II, except for one grade III event. Only 1 patient (1%) in the combination group required dose interruption or adjustment, and no patient discontinued because of photosensitivity.

3.7. Serous retinopathy

The incidence of serous retinopathy was higher with encorafenib plus binimetinib (20%) than with

Table 3
Characteristics of selected AEs in the combination encorafenib plus binimetinib treatment group, by time to first onset.

AEs	Median time to first onset, days (range)	Discontinuation, %	Dose modification,[a] %
Nausea	29 (1–614)	0	8
Diarrhoea	29 (1–534)	1	4
Serous retinopathy	38 (1–532)	0	6
Vomiting	57 (1–607)	0	7
Hyperkeratosis	77 (1–408)	0	2
Photosensitivity	84 (1–677)	0	1
Pyrexia	85 (2–545)	<1	4
Arthralgia	85 (1–708)	0	2
Left ventricular dysfunction	109 (1–648)	0	6

AE, adverse event.
Median times to first onset are calculated only for those experiencing the event. Discontinuation and dose modification percentages are calculated using the number of patients in the combination encorafenib plus binimetinib treatment group with the safety population as the denominator (n = 192).
[a] Dose modifications include dose interruptions and dose adjustments.

encorafenib (2%) or vemurafenib (2%), with a median (range) time to first onset in the combination group of 38 (1–532) days. With encorafenib plus binimetinib, severe serous retinopathy was uncommon; the incidence of grade I (asymptomatic), grade II and grade III events was 12%, 5% and 3%, respectively. Six percent of patients with encorafenib plus binimetinib required dose interruption or adjustment, and no patient discontinued because of serous retinopathy. Clinical review of serous retinopathy events indicated that these events were generally reversible, with 31/38 (82%) of events reported as 'recovered' and 1/38 (3%) as 'recovering'.

3.8. Left ventricular dysfunction

The incidence of left ventricular dysfunction (LVD) was higher with encorafenib plus binimetinib (8%) than with encorafenib (2%) or vemurafenib (1%), with a median (range) time to first onset in the combination group of 109 (1–648) days. With encorafenib plus binimetinib, severe LVD was uncommon; the incidence of grade I, grade II and grade III events was 2%, 4% and 2%, respectively. Six percent of patients receiving encorafenib plus binimetinib required dose interruption or adjustment, and no patient discontinued because of LVD. Clinical review of LVD events indicated that these events were generally reversible upon dose reduction or discontinuation, with 14/15 (93%) events reported as 'recovered' and one as 'resolved with sequelae'.

4. Discussion

The results of the current analysis of safety data from the COLUMBUS study suggest that common BRAFi/MEKi AEs of interest evaluated in this article with encorafenib plus binimetinib were generally manageable, reversible and infrequently associated with treatment discontinuation. No serious unexpected AEs were observed. Since the median duration of exposure was nearly twice as long as in the encorafenib plus binimetinib group (51 weeks) compared with the vemurafenib group (27 weeks) or the encorafenib group (31 weeks), the EAIRs provide additional context when comparing the incidence of AEs by accounting for how long a patient was exposed to the study treatment before experiencing an AE, if at all.

Despite the observed incidence rates being similar across treatment groups, the EAIRs for several AEs were lower for the encorafenib plus binimetinib group relative to the other treatment groups, providing compelling data in support of the tolerability of the combination.

Although pyrexia has emerged as a common, often recurrent, treatment-limiting effect associated with dabrafenib plus trametinib therapy [3,4,15–17], it occurred in 18% of patients treated with encorafenib plus binimetinib in the COLUMBUS study versus 16% of patients treated with encorafenib and 30% of patients treated with vemurafenib. In previously reported phase 3 melanoma study, pyrexia related to vemurafenib was reported in 21% of patients [18]. Furthermore, pyrexia with encorafenib plus binimetinib in the current analysis was typically limited to a single episode (only 10/192 [5%] experienced more than one episode) and rarely led to dose interruption or adjustment (4%) or discontinuation (<1%). Pyrexia associated with encorafenib plus binimetinib therapy in the COLUMBUS study occurred later during the course of treatment (median time to first onset, 85 days [12.1 weeks] versus 4.3 weeks with dabrafenib plus trametinib therapy) [4], and serious pyrexia events in the COLUMBUS study lacked association with hypotension, chills/rigors, dehydration, renal failure or syncope [19] (24% of patients treated with dabrafenib plus trametinib in phase I/II studies experienced concomitant chills, night sweats, influenza-like illness, hypotension, cytokine-release syndrome and/or systemic inflammatory response syndrome without a documented increase in body temperature) [17]. Most grade III pyrexia events were managed with treatment interruption; antibiotics, antipyretics and steroids were occasionally administered (n = 4, 5 and 1, respectively) [19]. In dabrafenib plus trametinib trials, pyrexia was the most common reason for dose interruption (30–32% of patients), reduction (13–14% of patients) and discontinuation (2–3% of patients, [3,4].

The incidence of photosensitivity with encorafenib plus binimetinib (5%) was lower than that reported with vemurafenib plus cobimetinib (28–48%) [5,6,8]. It was typically mild (predominantly grade I or II) and rarely interfered with the course of therapy (1 patient required dose interruption, and no patient discontinued therapy).

Unlike photosensitivity associated with vemurafenib plus cobimetinib, which is frequently recurrent and long lasting [8], most patients who experienced photosensitivity with encorafenib plus binimetinib experienced a single event. The improvement in photosensitivity AEs seen in patients treated with encorafenib plus binimetinib may be due to the ultraviolet A-absorbing nature of vemurafenib which is distinct relative to encorafenib [14]. The pharmacokinetic profile of encorafenib indicates prolonged binding to the target molecule, thereby providing greater BRAF inhibition and increased potency and specificity, which may also contribute to the observed differences. These factors may result in better tolerability, including reduced occurrence of photosensitivity [20].

Serous retinopathy was mainly asymptomatic or of low severity and reversible. Detection was predominantly through regular, specialised eye examination, which, unlike prior similar trials, was protocol mandated for all patients in the encorafenib plus binimetinib group. Our findings are consistent with previously published reports of MEKi-associated retinopathy, in which symptoms are often mild and transient, and retinal changes are typically reversible [21–24]. Most patients who develop serous retinopathy do not require pharmacologic intervention; however, topical non-steroidal anti-inflammatory or carbonic anhydrase inhibitors may be useful agents for select patients seeking symptomatic relief [22]. Observed MEKi-related toxic effects, including serous retinopathy, were largely in line with other BRAFi/MEKi combination actively monitored trials [10].

LVD was uncommon among patients who received encorafenib plus binimetinib therapy (8%) and was typically of mild or moderate severity (grade I, 2%; grade II, 4%; grade III, 2%). In this group, LVD was typically managed by dose interruption and/or reduction and was generally reversible without treatment discontinuation. In clinical studies, approximately, 4–8% of patients experienced decreased ejection fraction with dabrafenib plus trametinib therapy, leading to discontinuation in 1%–3% of patients [3,16]. This has been primarily attributed to the trametinib component [25].

Gastrointestinal events such as nausea, diarrhoea, vomiting, abdominal pain and constipation can occur when treated with with encorafenib plus binimetinib. Most events were of grade I or II. The average time to nausea or diarrhoea was within the first month, and vomiting was within the first two months of starting treatment. Among patients who received encorafenib plus binimetinib, nausea and vomiting were the most common adverse reactions leading to dose interruptions. Additional guidance on dose modifications due to specific AEs associated with encorafenib or binimetinib can be found in approved product labeling.

The differences in AEs discussed previously may be related to the differences in the pharmacokinetic profiles of these therapies. For example, encorafenib demonstrated pharmacokinetic differences compared with other BRAF inhibitors as reported in a phase I study in metastatic *BRAF*-mutant melanomas. In a biochemical assay, encorafenib inhibited *BRAF*V600E kinase activity at similar concentrations as dabrafenib and vemurafenib; but with a considerably longer dissociation half-life. In *BRAF*V600-mutant cell lines, encorafenib was more potent at inhibiting proliferation relative to dabrafenib and vemurafenib. Single-dose pharmacokinetic/pharmacodynamic studies in human melanoma xenograft models (*BRAF*V600E) showed that encorafenib resulted in strong and sustained decreases in pERK even at low doses, consistent with a prolonged dissociation half-life [11].

This detailed analysis of AEs in the COLUMBUS study suggests that encorafenib plus binimetinib is generally well tolerated and has a low discontinuation rate in patients with *BRAF*V600-mutant melanoma, with a distinct safety profile.

Funding

This study was sponsored by Array BioPharma, Inc.

Acknowledgment

The authors would like to thank all the individuals who enrolled in COLUMBUS study as well as their family, caregivers and friends who supported them. These analyses would not be possible without all the hard work and contributions from the dedicated investigators in this trial. The authors would like to thank Laure A. Moutouh-de Parseval for all her contributions to the COLUMBUS study. The authors acknowledge JD Cox, PhD, and Mayville Medical Communications for editorial support.

Conflict of interest statement

Helen J. Gogas received consulting fees from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen and Pierre Fabre and research funding from Bristol-Myers Squibb, Merck Sharp & Dohme and Roche outside the submitted work. Keith T. Flaherty is a member of board of directors of Clovis Oncology*, Strata Oncology*, Vivid Biosciences*, Checkmate Pharmaceuticals; corporate advisory board of X4 Pharmaceuticals*, PIC Therapeutics*; scientific advisory board of Sanofi, Amgen, Asana, Adaptimmune, Fount *, Aeglea, Array BioPharma, Shattuck Labs *, Tolero, Apricity *, Oncoceutics*, Fog Pharma *, Neon, Tvardi * and consultant for Novartis, Genentech, BMS, Merck, Takeda, Verastem, Boston Biomedical, Pierre Fabre, Cell Medica, Debiopharm. *Stock shareholder. Reinhard Dummer has intermittent, project focused

consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi and Catalym outside the submitted work. Paolo A. Ascierto has served in a consulting or advisory role for BMS, Roche-Genentech, MSD, Array, Novartis, Merck Serono, Pierre Fabre, Incyte, Genmab, Newlink Genetics, Medimmune, AstraZeneca, Syndax, Sun Pharma, Sanofi, Idera, Ultimovacs, Sandoz, Immunocore; received research funding from BMS, Roche– Genentech, Array and received travel support from MSD. Ana Arance has received honoraria from, had served in a consulting or advisory role for, or been a member of the speakers bureau for Novartis, Roche, Merck, Merck Sharp & Dohme, and Bristol-Myers Squibb outside the submitted work and has received travel expenses from same companies. Mario Mandala has received personal fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis and Pierre Fabre outside the submitted work. Gabriella Liszkay has received consulting and advisory board fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Amicus, Boehringer-Ingelheim and Novartis outside the submitted work. Claus Garbe has received personal fees and research funding from Novartis and Pierre Fabre during the conduct of the study; personal fees for presentations and consulting or advisory roles from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Philogen and Roche and research funding from Bristol-Myers Squibb and Roche outside the submitted work. Dirk Schadendorf has received personal fees and patient fees from Pierre Fabre during the conduct of the study; has received honoraria and travel expenses from, has a consulting or advisory role with, been a member of the speakers bureau for, and received personal fees from, Amgen, Boehringer Ingelheim, LEO Pharma, Roche, Merck Sharp & Dohme, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Merck - EMD, Pfizer, Philogen and Array BioPharma and has received patient fees from Roche, Merck Sharp & Dohme, Regeneron, Bristol-Myers Squibb, Merck - EMD and Philogen outside the submitted work. Ivana Krajsova is an advisory board member for and has received travel expenses from Bristol-Myers Squibb, Novartis, and Merck Sharp & Dohme during the conduct of the study. Ralf Gutzmer has received research support from Pfizer, Johnson & Johnson, Novartis, Amgen, MerckSerono; honoraria for lectures from Roche, Bristol-Myers Squibb, Novartis, MSD, Almirall-Hermal, Amgen, Merck-Serono, Pierre-Fabre, AstraZeneca, SUN; honoraria for advice from Roche Pharma, Bristol-Myers Squibb, Novartis, MSD, Almirall-Hermal, Amgen, Takeda, Pierre-Fabre, Merck-Serono, 4SC, Incyte, SUN; and support for participation in meetings from Bristol-Myers Squibb, Pierre-Fabre, Merck-Serono, SUN, Roche Pharma. Vanna Chiarion Sileni has received consulting fees from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Incyte, Roche and Pierre Fabre outside the submitted work. Caroline Dutriaux is a member of advisory boards and consulter and investigator in trials for Pierre Fabre.

Jan Willem B. de Groot reports receiving personal fees from Roche, Bristol-Myers Squibb, Pierre Fabre, Servier, Novartis and Merck Sharp & Dohme outside the submitted work. Naoya Yamazaki reports receiving research funding from Bristol-Myers Squibb during the conduct of the study; has received personal fees from Bristol-Myers Squibb and has received personal fees and research funding from Ono Pharmaceutical, Merck Sharp & Dohme and Novartis outside the submitted work. Carmen Loquai reports receiving personal fees from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, LEO Pharma and Amgen outside the submitted work. Ashwin Gollerkeri is an Array employee and was a shareholder of Array BioPharma during the conduct of the study. Michael D. Pickard is an Array employee and shareholder of Array BioPharma during the conduct of the study. Caroline Robert is a consultant for Pierre Fabre, Roche, Novartis, Bristol-Myers Squibb, Merck, Array BioPharma, Merck Serono and Amgen outside the submitted work.

References

[1] Colombino M, Capone M, Lissia A, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. J Clin Oncol 2012;30(20):2522–9.

[2] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417(6892):949–54.

[3] Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372(1):30–9.

[4] Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371(20):1877–88.

[5] Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371(20):1867–76.

[6] Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17(9):1248–60.

[7] Bollag G, Hirth P, Tsai J, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature 2010;467(7315):596–9.

[8] Dreno B, Ribas A, Larkin J, et al. Incidence, course, and management of toxicities associated with cobimetinib in combination with vemurafenib in the coBRIM study. Ann Oncol 2017;28(5):1137–44.

[9] Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):603–15.

[10] Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19(10):1315–27.

[11] Delord JP, Robert C, Nyakas M, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF- mutant melanoma. Clin Cancer Res 2017;23(18):5339–48.
[12] Adelmann CH, Ching G, Du L, et al. Comparative profiles of BRAF inhibitors: the paradox index as a predictor of clinical toxicity. Oncotarget 2016;7:30453–60.
[13] Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, pen-label phase 2 study. Lancet Oncol 2013;14:249–56.
[14] Dummer R, Rinderknecht J, Goldinger SM. Ultraviolet A and photosensitivity during vemurafenib therapy. N Engl J Med 2012 Feb 2;366(5):480–1.
[15] Daud A, Tsai K. Management of treatment-related adverse events with agents targeting the MAPK pathway in patients with metastatic melanoma. The Oncologist 2017;22(7):823–33.
[16] Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386(9992):444–51.
[17] Menzies AM, Ashworth MT, Swann S, et al. Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with combined dabrafenib and trametinib in a phase I/II clinical trial. Ann Oncol 2015;26(2):415–21.
[18] Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol 2015 Oct;16(13):1389–98.
[19] Mandala M, Dummer R, Ascierto PA, et al. Characteristics of pyrexia with encorafenib (ENCO) plus binimetinib (BINI) in patients with BRAF-mutant melanoma. In: International congress of the society for melanoma research; october 24-27; 2018 [Manchester, UK].
[20] Trojaniello C, Festino L, Vanella V, Ascierto PA. Encorafenib in combination with binimetinib for unresectable or metastatic melanoma with BRAF mutations. Expert Rev Clin Pharmacol 2019:1–8.
[21] Urner-Bloch U, Urner M, Jaberg-Bentele N, et al. MEK inhibitor-associated retinopathy (MEKAR) in metastatic melanoma: long-term ophthalmic effects. Eur J Cancer 2016;65:130–8.
[22] Urner-Bloch U, Urner M, Stieger P, et al. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol 2014;25(7):1437–41.
[23] van Dijk EH, van Herpen CM, Marinkovic M, et al. Serous retinopathy associated with mitogen-activated protein kinase kinase inhibition (binimetinib) for metastatic cutaneous and uveal melanoma. Ophthalmology 2015;122(9):1907–16.
[24] van Dijk EH, Duits DE, Versluis M, et al. Loss of MAPK pathway activation in post-mitotic retinal cells as mechanism in MEK inhibition-related retinopathy in cancer patients. Medicine (Baltim) 2016;95(18):e3457.
[25] Banks M, Crowell K, Proctor A, Jensen BC. Cardiovascular effects of the MEK inhibitor, trametinib: a case report, literature review, and consideration of mechanism. Cardiovasc Toxicol 2017;17(4):487–93.