REVIEW

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Development of encorafenib for BRAF-mutated advanced melanoma

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Purpose of review
To describe the pharmacological properties, preclinical and clinical data of the novel V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF)-inhibitor encorafenib (LGX818) and to compare these with established BRAF-inhibitors in the treatment of locally advanced or metastatic melanoma.

Recent findings
Encorafenib has shown improved efficacy in the treatment of metastatic melanoma in comparison with vemurafenib. Combination with the MEK inhibitor (MEKi) binimetinib allows for higher dose intensities of encorafenib further improving response rates (RRs).

Summary
Combination therapy with BRAF and MEKi has evolved as a standard of care in the treatment of locally advanced or metastatic $BRAF^{V600}$-mutated melanoma. Despite compelling initial RRs, development of treatment resistance eventually leads to tumor progression in the majority of BRAF/MEK-inhibitor treated patients. Moreover, treatment-related adverse events are frequent, resulting in a substantial proportion of dose modifications and/or treatment discontinuations. The second-generation BRAF inhibitor encorafenib has been developed aiming at improved efficacy and tolerability through modifications in pharmacological properties. Clinical phase 3 data show improved progression-free survival both for encorafenib monotherapy and combination therapy with binimetinib compared with vemurafenib. Overall survival data and regulatory approval of this novel substance are eagerly awaited.

Keywords
binimetinib, BRAF-inhibitor, encorafenib, LGX818, melanoma

INTRODUCTION

The V-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) inhibitors (BRAFi) vemurafenib and dabrafenib have been used in everyday clinical practice for the treatment of metastatic melanoma in (dermato-)oncologic centers worldwide for more than 5 years. Following initial regulatory approval of vemurafenib and dabrafenib monotherapy in 2011 and 2013, respectively [1,2], combination therapy with BRAF and Mitogen-Activated Protein (MAP) Kinase/Extracellular Signal-Regulated Kinase (ERK) kinase (MEK) inhibitors (MEKi) subsequently replaced BRAFi monotherapy as a first-line therapeutic option in patients with BRAF-mutated melanoma. Currently approved combination regimens (either dabrafenib and trametinib or vemurafenib and cobimetinib) achieve objective response rates (RRs) of 68–70% as compared with approximately 50% with BRAFi monotherapy [3,4]. Median progression-free survival (PFS) ranges between 11 and 12 months with combination therapy, whereas median overall survival (OS) has been reported at 22–26 months. A pooled analysis of 563 patients treated with dabrafenib and trametinib showed that after 3 years of follow-up, 23% of patients remained progression-free. Typical adverse events associated with BRAFi and MEKi occur regularly with both combination regimens. Although efficacy is nearly identical, a recently published indirect comparative study showed that combination treatment with vemurafenib and cobimetinib is associated with a higher

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Curr Opin Oncol 2018, 30:125–133

DOI:10.1097/CCO.0000000000000426

KEY POINTS

- Combination therapy with BRAF and MEKi (either vemurafenib and cobimetinib or dabrafenib and trametinib) is the most established first-line treatment option besides immunotherapy in $BRAF^{V600}$-mutated melanoma.
- Encorafenib (LGX818), a second-generation BRAF inhibitor, is characterized by distinct pharmacological properties, in particular a substantially prolonged dissociation half-life of more than 30 h.
- Pharmacological modifications may lead to increased on-target effects (efficacy) and decreased off-target effects (adverse events) with encorafenib.
- The phase III COLUMBUS trial showed superior efficacy data of encorafenib over vemurafenib monotherapy. Combination of encorafenib with the MEKi binimetinib allowed for increased doses of encorafenib and further increased efficacy in terms of RR and progression-free survival.

frequency of treatment-related adverse events than treatment with dabrafenib and trametinib [5].

Efficacy and safety data of these two combination regimens point toward two major difficulties clinicians face when treating melanoma patients with BRAFi/MEKi combinations. First, despite excellent initial RRs, treatment resistance and progression develops in almost 80% of patients within the first 3 years of therapy [6▪]. Second, treatment-related adverse events occur frequently, leading to dose interruptions or modifications in approximately half and treatment discontinuation in about 15% of all patients [5], which in turn may lead to earlier resistance development and limit efficacy. These problems support the need for second-generation BRAFi with modified pharmacological properties that may improve efficacy and tolerability. The present review will focus on encorafenib (formerly LGX818), the most intensively studied second-generation BRAFi in advanced melanoma to date.

PHARMACOLOGY

Encorafenib is an ATP-competitive v-Raf murine sarcoma viral oncogene homolog (RAF) serine and threonine kinase inhibitor selectively exhibiting antiproliferative effects in BRAF V600E-mutated cells. In humans, oral encorafenib is highly bioavailable (around 85%) and rapidly absorbed with a median time to the maximum observed concentration (T_{max}) of approximately 2-h postdose [7▪▪]. The plasma elimination half-life of encorafenib is approximately 6 h. Elimination of encorafenib occurs mainly through metabolism via cytochrome P450 (CYP) enzymes (CYP3A4, CYP2C19 and CYP2D6). In turn, encorafenib acts as a CYP enzyme inducer leading to a consistent decrease in day 15 exposures by 30–60% compared with those at day 1. Approximately 20 different metabolites of encorafenib have been identified and are excreted to equal parts in urine and feces. Approximately only 2 and 5% of the absorbed encorafenib are excreted unchanged in urine and feces, respectively. Food intake delays the absorption of encorafenib, but does not alter overall drug exposure [8]. Hence, encorafenib capsules are allowed to be ingested regardless of food consumption.

In contrast to dabrafenib and trametinib, encorafenib shows a similar half-maximal inhibitory concentration (IC50) for wild-type BRAF, V600E-mutant BRAF and v-Raf murine sarcoma viral oncogene homolog C in cell-free biochemical assays [7▪▪,9]. Dabrafenib and trametinib have a lower IC50 especially for the wild-type BRAF protein which may be relevant with regards to paradoxical MAP kinase (MAPK) pathway activation which will be discussed later on. Also, encorafenib is characterized by a substantially increased dissociation half-life (T1/2-diss) from V600E-mutant BRAF of more than 30 h, as compared with 2 and 0.5 h reported for dabrafenib and vemurafenib, respectively (Fig. 1a and b; slow vs. fast off-rate inhibitor). The long T1/2-diss, which was confirmed in washout experiments in A375 melanoma cells (Fig. 1c) [10], translates into prolonged target suppression and increased potency of encorafenib compared with established BRAFi. Target suppression after BRAFi exposure can be depicted through measurement of MEK phosphorylation as seen in Fig. 1 comparing encorafenib and vemurafenib. Increased potency of encorafenib results in IC50 values of 40 nmol/l or less in the majority of melanoma cell lines, whereas higher concentrations of dabrafenib (<100 nmol/l), and especially vemurafenib (<1 μmol/l) are necessary to inhibit proliferation of most cell lines [7▪▪]. In addition to its high potency, encorafenib is also a very specific RAF inhibitor which has been shown in a panel defining the inhibitory profile of encorafenib against 99 kinases. In addition to both the V600-mutated and wild-type BRAF-protein, encorafenib demonstrated potent inhibition solely against CRAF (IC50 = 8 nmol/l). Only two other kinases were inhibited with IC50 less than 1 μmol/l, namely Glycogen synthase kinase 3 beta and c-Jun N-terminal kinase 2. In contrast, dabrafenib showed activity against seven kinases other than BRAF and CRAF with an IC50 of less than 100 nm in a panel of 270 kinases [11].

In summary, classic pharmacokinetic and pharmacodynamic properties such as T_{max} and elimination half-life reflect the metabolism of the drug in blood and tissue. However, this does not automatically reflect

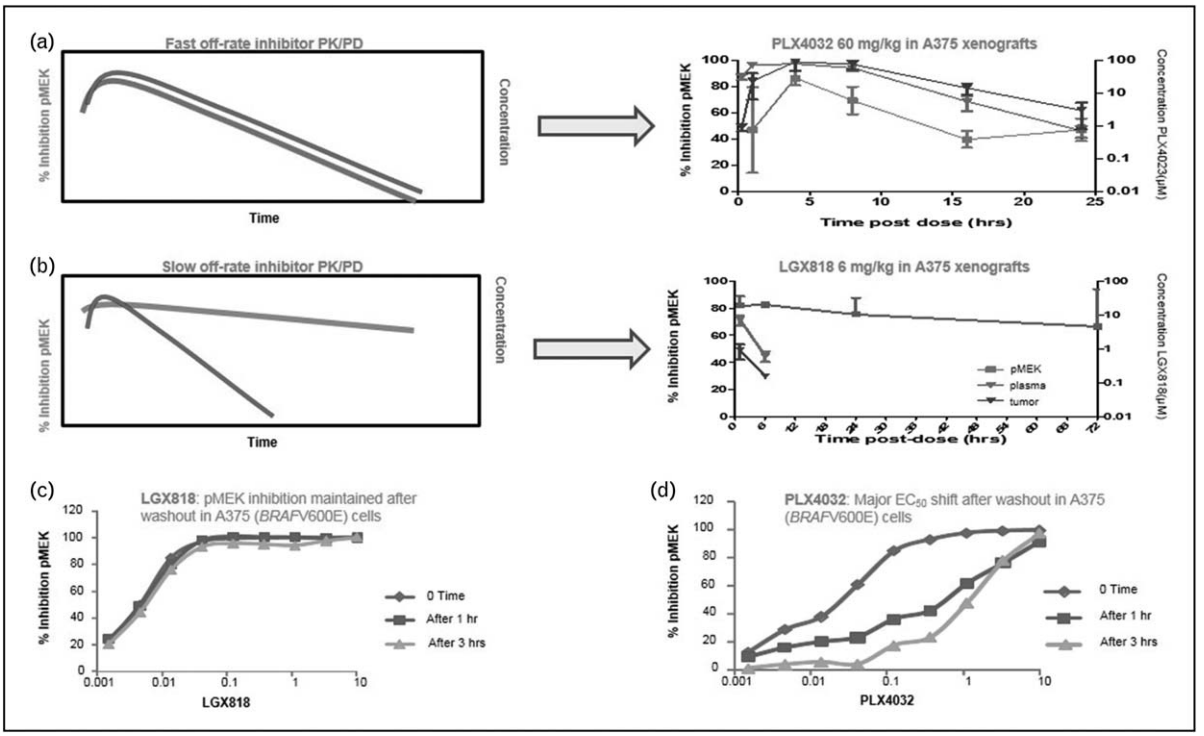

FIGURE 1. Increased dissociation half-life of encorafenib leads to prolonged target-inhibition. Left-sided graphs illustrating the pharmacokinetic and pharmacodynamic differences between fast (a) and slow (b) off-rate inhibitors with short and long dissociation half-lives, respectively. Experiments in A375 (BRAF-mutated) melanoma cell xenografts in mice confirmed classification of PLX4032 (vemurafenib) and LGX818 (encorafenib) into the respective groups (a + b, right-sided graphs). Phosphorylated MEK inhibition was used as a surrogate for target (mutated BRAF protein)-inhibition. Washout experiments in A375 cells showed sustained target-inhibition even at low encorafenib doses (c). In contrast, sustained inhibition was only seen with maximal doses of vemurafenib (d). Adapted with permission [10].

binding to and inhibition of the target molecule(s). The value of drug dissociation properties, represented by the T1/2-diss, is often underestimated. EC50, the half maximum effective concentration integrates information both about association (measured by the IC50) and dissociation (T1/2-diss). In the context of BRAF inhibition, EC50 can be determined by measurement of either phosphorylated MEK or phosphorylated ERK (pERK). Washout experiments in melanoma cells showed that the pERK EC50 of encorafenib only shifted two-fold after washout compared with 14-fold and 23-fold for dabrafenib and vemurafenib, respectively [7▪▪]. The substantially increased T1/2-diss of encorafenib is of clinical importance, as a longer T1/2-diss may potentially translate into an increased efficacy (on-target effect) while reducing toxicity (by avoiding or attenuating off-target effects), thus improving the overall benefit–risk ratio of the substance.

PARADOXICAL MAP KINASE PATHWAY ACTIVATION AND RELATED ADVERSE EVENTS

Class specific side effects of BRAFi are in part explained by the paradoxical activation of the MAPK pathway in BRAF wild-type cells in various tissues. V600-mutated BRAF typically acts as a constitutively active monomer in the presence of low cellular rat sarcoma viral oncogene homolog (RAS)-guanosine triphosphate (GTP) levels and is specifically inhibited by established BRAFi in its monomer confirmation [12▪▪]. Wild-type BRAF signaling, in contrast, is facilitated by dimerization, either forming homodimers or heterodimers with CRAF. So called αC-OUT BRAFi such as vemurafenib, dabrafenib and also encorafenib are not only incapable of inhibiting dimerized RAF isoforms, which explains why RAF dimerization is a known resistance mechanism to BRAFi therapy [13]; these inhibitors also promote RAF–RAS–GTP interaction and RAF dimerization through allosteric changes in the wild-type BRAF protein, leading to paradoxical MAPK pathway activation especially in cells with preexisting RAS mutations [12▪▪]. Quick dissociation or short T1/2-diss requires frequent and high dosing of the inhibitor and may thus enhance these effects. Along these lines, Adelmann *et al.* [14▪] have recently introduced a 'paradox index' to describe the therapeutic window of different BRAFi. This index was defined as the paradox pERK activation EC80 (concentration leading to an eighty percent pERK

activation) in a RAS-mutated cell line divided by the IC80 against the $BRAF^{V600}$-mutated A375 melanoma cell line. A larger index hence is a surrogate for a better benefit–risk ratio or more positive relation between on-target and off-target effects of a BRAFi. Encorafenib, dabrafenib and vemurafenib achieved an index of 50, 10 and 5.5, respectively. Clinically this is in line with the observation that development of cutaneous squamous cell carcinoma (cSCC) or keratoacanthoma – the adverse event most clearly attributed to paradoxical MAPK pathway activation – appears to be more frequent with vemurafenib (18–19% [1,15,16]) than with dabrafenib (6–10% [2,17,18]) and encorafenib (4% [7▪▪]). Corresponding, also preclinical studies by Stuart *et al.* [10] showed that, in contrast to both vemurafenib and dabrafenib, the potential surrogate of cSCC in the mouse model – gastric hyperplasia – does not even occur at the most efficacious dose of encorafenib, which again points to its wide therapeutic window with lower paradoxical MAPK pathway activation. A recent analysis of 74 melanoma patients treated with encorafenib monotherapy or encorafenib and the MEK-inhibitor binimetinib at our institution [19] could also confirm that hyperproliferative adverse events such as cSCC are less frequent with encorafenib than with other BRAFi. In contrast, our results show that inflammatory adverse events such as palmoplantar hyperkeratosis or dysesthesia seem to occur more frequently particularly with encorafenib monotherapy.

In addition to class effects responsible for adverse events observed with most available BRAFi at similar frequencies, vemurafenib and dabrafenib have been associated with peculiar molecule-specific adverse events. These include photosensitivity with vemurafenib and pyrexia with dabrafenib. Both of these adverse events can substantially impact drug tolerability and patients 'quality of life'. Low rates of photosensitivity and pyrexia reported with encorafenib in monotherapy or

Table 1. Summary of adverse events in encorafenib-containing arms of the phase III COLUMBUS-trial

	Combo450, *n* = 192		**Combo300, *n* = 257**		**Enco300 (parts 1 ± 2, *n* = 276)**	
Median duration of exposure (weeks)	**51**		**52.1**		**31.5**	
Type of AE (%)	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Nausea	41	2	27	2	36	3
Diarrhea	36	3	28	2	12	1
Vomiting	30	2	15	<1	25	4
Fatigue	29	2	22	1	26	1
Arthralgia	26	1	22	1	43	8
Increased CK	23	7	20	5	1	0
Rash[a]	23	1	15	1	43	5
Headache	22	2	12	<1	26	3
Pyrexia	18	4	17	0	16	1
Increased GGT	15	9	14	5	11	4
Myalgia	14	0	14	<1	27	8
Alopecia	14	0	13	0	49	<1
Hyperkeratosis	14	1	10	0	39	3
Dry skin	14	0	8	0	28	0
Transaminases increased	13	6	14	5	5	1
Retinal pigment epithelial detachment	13	2	9	<1	1	0
Palmoplantar keratoderma	9	0	7	<1	24	1
Left ventricular dysfunction	8	2	6	1	3	1
Palmoplantar erythrodys-esthesia syndrome	7	0	4	<1	47	11
Photosensitivity	5	1	2	0	4	0
Secondary nonmelanoma skin neoplasms	4	0	6	1	10	1

AE grades were classified as defined by the National Cancer Institute Common Terminology Criteria. AE, adverse event; CK, creatine kinase; Combo300, encorafenib 300 mg once daily + binimetinib 45 mg twice daily; Combo450, encorafenib 450 mg once daily + binimetinib 45 mg twice daily; Enco300, encorafenib 300 mg once daily monotherapy; GGT, Gamma-glutamyltransferase.

[a]The term 'rash' included unspecified, local or generalized, erythematous, macular, papular, maculopapular, dermatitic, follicular, vesicular, psoriasiform and pustular skin eruptions.

Adapted with permission [20▪,21▪].

combination therapy (Table 1) may contribute to an improved safety profile in comparison with established BRAFi.

SENESCENCE VS. APOPTOSIS: ADVANTAGE OR DISADVANTAGE?

Another particular molecular feature of encorafenib is its ability to induce cellular senescence accompanied by autophagy, but not apoptosis, in $BRAF^{V600E}$-mutated melanoma cells [22▪]. Cellular senescence and autophagy have also been described in melanoma cells after vemurafenib treatment, but, in contrast to encorafenib, only in addition to the induction of apoptotic cell death [23,24]. It is currently unclear, how the induction of cellular senescence and autophagy in encorafenib-treated melanoma cells translates clinically in terms of encorafenib efficacy and development of treatment resistance, as both cytoprotective and cytotoxic roles of autophagy have been postulated in cancer therapy [25]. For vemurafenib in particular, autophagy has been proposed as a mechanism of adaptive treatment resistance [24]. Corresponding, combination of BRAF and autophagy inhibition was shown to promote tumor regression in vemurafenib-resistant melanoma xenografts [24]. Borst *et al.* [26▪▪] recently investigated single melanoma cell clones responding to vemurafenib treatment with either cell cycle arrest (senescence) or apoptosis. Differential gene expression analysis revealed a loss of the apoptosis-related gene *BCL2*-Interacting Killer (BIK) in those cell clones undergoing senescence. Moreover, histone deacetylase (HDAC) inhibitor treatment was shown to reverse epigenetic silencing of BIK mRNA expression in these cells, subsequently leading to increased rates of apoptotic cell death. As a potential molecule specificity concerning the induction of senescence and autophagy after treatment with different BRAFi is conceivable, similar experiments with encorafenib are necessary to explore whether combining encorafenib with HDAC or autophagy inhibitors may also lead to increased apoptosis and/or decreased treatment resistance *in vitro*.

DOSE DEPENDENCY IN BRAF INHIBITORS THERAPY: PRECLINICAL AND CLINICAL DATA

Delord *et al.* [7▪▪] recently reported on an extensive phase I dose-escalation and dose-expansion study investigating encorafenib monotherapy in BRAF V600-mutated melanoma. This study also included biochemical assays and preclinical experiments in cell lines and tumor xenografts in mice. Some of the preclinical results have also been described in previous sections of the present review. Mouse xenograft studies by Delord in BRAF V600E-mutated A375 and HMEX1906 models showed that encorafenib effectively inhibits tumor growth at doses as low as 5 mg/kg twice daily (BID). Similar results with vemurafenib and dabrafenib were demonstrated at doses of 60 mg BID and 100 mg once daily. For encorafenib, the authors further showed that increased doses up to 20 mg/kg are necessary to prevent resistance development and achieve extended survival in continuous dosing experiments in xenografted mice. Preclinically, this finding suggests clear dose-dependency of encorafenib efficacy. The clinical part of the same study included a dose-escalation and a dose-expansion cohort consisting of 54 and 35 patients, respectively. About half of the patients in both cohorts had already undergone pretreatment with a BRAF-inhibitor. Encorafenib 450 mg once daily was defined as the maximum tolerated dose (MTD). Due to frequent occurrence of dose limiting toxicities in patients receiving the MTD in the dose-expansion cohort, 300 mg once daily evolved as the recommended phase 2 dose for encorafenib monotherapy. In line with preclinical findings, encorafenib was able to induce tumor regression over a wide dose range. Efficacy analysis yielded an overall RR of 60% in BRAFi-naïve patients in both the dose-escalation cohort (all doses) and the dose-expansion cohort (450 or 300 mg once daily). The RR in BRAFi-pretreated patients was 10 and 22% in these cohorts, respectively. Median time between prior BRAFi therapy and the start of encorafenib was only slightly longer than 5 weeks (38.5 days), which should partially explain the modest RR in BRAFi-pretreated patients. In contrast, Schreuer *et al.* [27▪] recently reported a RR of 32% for the combination of dabrafenib and trametinib in 25 BRAFi (+MEKi)-pretreated patients. However, patients in this cohort had been off BRAFi treatment for a period of at least 12 weeks. The median PFS in treatment-naïve patients in the dose-expansion phase ($n = 18$) reported by the Delord group was 12.4 months (95% confidence interval, 7.4-not reached), which appears to be considerably longer compared to what has been reported previously for BRAFi monotherapy [1,2,7▪▪]. Most frequent drug-related adverse events occurring with encorafenib monotherapy included myalgia, nausea, palmoplantar erythrodysesthesia, arthralgia, alopecia and hyperkeratosis amongst others. As discussed earlier, cSCC was rare (3–4% of patients). Of note, transient Bell's palsy was reported in 8% of patients treated with encorafenib, whereas it has rarely been reported in association with other BRAFi [28].

As combination therapy with BRAFi and MEKi has become the predominant strategy targeting

BRAF-mutant advanced melanoma, encorafenib has also been investigated in combination with the MEKi binimetinib. We have recently reviewed the development of binimetinib [29▪] and reported on its role in Neuroblastoma RAS viral oncogene homolog (NRAS)-mutated melanoma elsewhere [30▪]. Based on data showing an additional effect on treatment response duration by combining encorafenib and binimetinib in a BRAF V600E-mutant melanoma mouse model, this combination regimen was first investigated in a phase 1b/2 clinical study including 23 melanoma patients [31]. As seen with other BRAFi/MEKi combinations, addition of a MEKi reduced the occurrence of on-target BRAFi-related – that is cutaneous – adverse events, subsequently allowing for higher dosing of the BRAFi. Hence, the recommended phase 2 doses of encorafenib and binimetinib were defined at 450/600 mg once daily and 45 mg BID, respectively. Preliminary efficacy data were promising with eight of nine patients with BRAFi-naïve melanoma showing an objective response to combination therapy. These results led to the initiation of the phase 3 COLUMBUS trial (Combined LGX818 Used with MEK162 in BRAF Mutant Unresectable Skin Cancer).

Part 1 of the COLUMBUS trial compared encorafenib at a dose of 450 mg once daily and binimetinib 45 mg BID with BRAF-inhibitor monotherapy with either encorafenib 300 mg once daily or vemurafenib 960 mg BID [20▪]. Randomization occurred in a 1 : 1: 1 fashion. The total patient population of 577 patients was further stratified by American Joint Committee on Cancer stage, Eastern Cooperative Oncology Group status, BRAF mutation subtype (V600 E or K) and prior first-line immunotherapy. Only 5% of all patients were pretreated with immunotherapy (either ipilimumab or a pharmacodynamic-1-antibody). The primary endpoint of the study could be reached with median PFS being significantly higher in the combination arm than the two monotherapy arms [14.9 vs. 9.6 vs. 7.3 months (combination vs. encorafenib vs. vemurafenib), hazard ratio 0.54 for combination vs. vemurafenib ($P = 0.001$) and 0.75 for combination vs. encorafenib ($P = 0.051$), Fig. 2]. Confirmed objective RRs by central review were 63, 51 and 40% for combination, encorafenib and vemurafenib (75, 58 and 49% by local review), whereas median duration of response was 16.2., 14.8 and 8.4 months, respectively. The PFS benefit with combination treatment was consistent through most predefined subgroups, especially in comparison with vemurafenib. Notably, this was the first clinical trial to show a significant difference between two different BRAF-inhibitors administered as monotherapy, once again pointing toward a superior potency of encorafenib.

Part 2 of the COLUMBUS trial, most recently reported on in September 2017 [21▪], was designed to independently evaluate the contribution of binimetinib to the efficacy of the encorafenib/binimetinib combination by comparison of encorafenib monotherapy at 300 mg once daily with the combination of encorafenib 300 mg once daily and binimetinib 45 mg BID. The combination cohort included 258 patients, 86 additional patients were randomized in the monotherapy arm, adding up to a total of 280 patients treated with encorafenib 300 mg monotherapy in parts 1 and 2 of the study. Intriguingly, the results of part 2 again point toward the preclinically observed and earlier mentioned dose dependency of encorafenib efficacy. The combination regimen containing the decreased encorafenib dose of 300 mg (combination 300) was able to retain a significant improvement in PFS compared with encorafenib monotherapy (12.9 vs. 9.2 months, hazard ratio 0.77, $P = 0.029$). Yet, the median PFS decreased from 14.9 months with the combination 450 (450-mg encorafenib, 45-mg binimetinib) to 12.9 months with the combination 300 regimen. Concerning safety, the combination 300 regimen was associated with a slightly reduced occurrence of National Cancer Institute Common Terminology Criteria grade 3/4 adverse events (47 vs. 58% with combination 450). However, the proportion of adverse events leading to dose discontinuation (13% with both regimens) or dose interruption/modification (45 vs. 48%) remained relatively unchanged. In both parts of the COLUMBUS study, grade 3/4 adverse events were slightly less frequent with combination therapy than BRAFi monotherapy (58/47% with combination 450/300, 63% with both encorafenib and vemurafenib). Treatment discontinuation due to adverse events was necessary in a similar proportion (13%) of patients in all treatment arms containing encorafenib in mono- or combination therapy. A slightly larger proportion of patients treated with vemurafenib (17%) had to discontinue treatment due to adverse events. Similar to what is known from other combination therapy studies [3,4], typical BRAF-inhibitor-related adverse events such as arthralgia, hyperkeratosis or other dermatologic adverse events occurred less frequently when combining BRAFi and MEKi treatment. In turn, typical MEK-inhibitor-associated toxicities such as increase of blood creatine kinase or ocular toxicities were mainly reported in combination patients. A summary of the most frequent adverse events in the COLUMBUS trial can be found in Table 1.

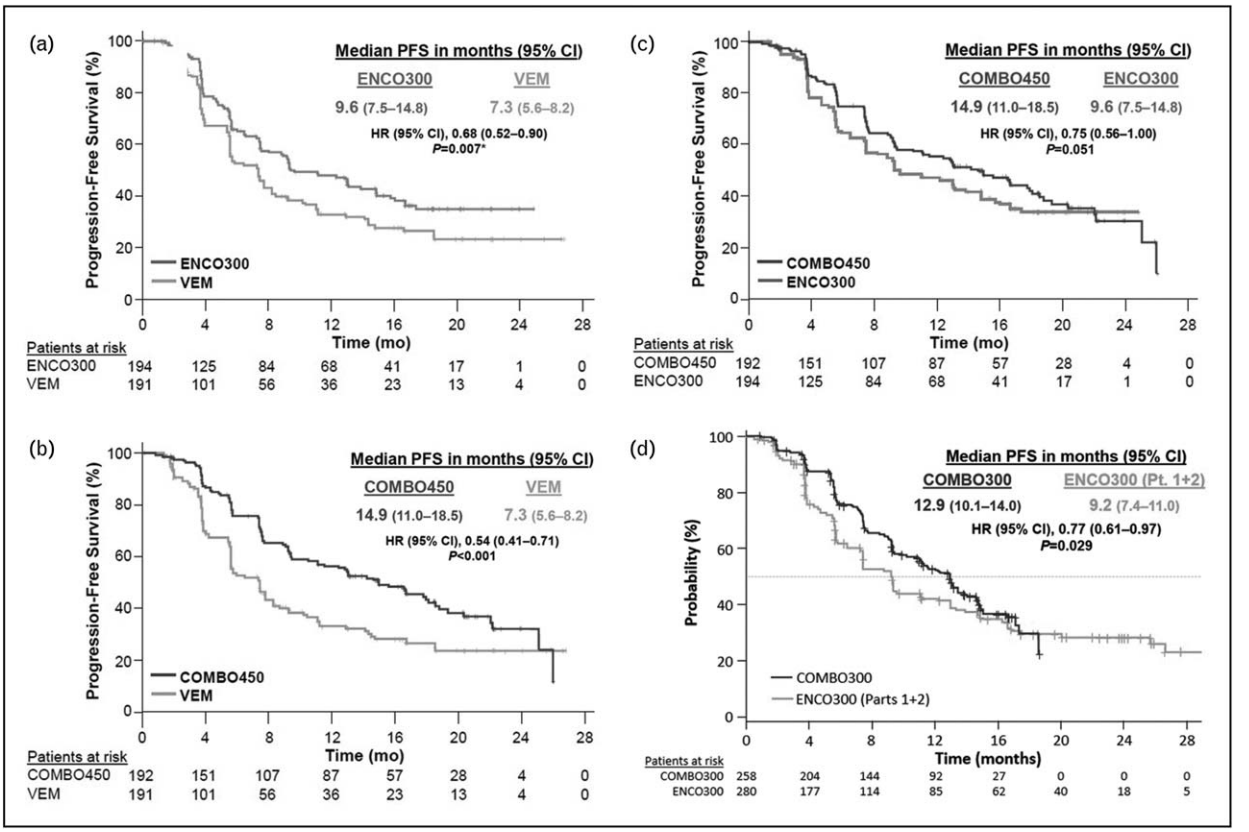

FIGURE 2. Kaplan–Meier estimates of progression-free survival in the four different treatment arms of the phase III COLUMBUS trial. Part 1 of the trial investigated monotherapy with encorafenib 300 mg once daily or vemurafenib 960 mg twice daily and combination therapy with encorafenib 450 mg once daily + binimetinib 45 mg twice daily. Median progression-free survival was significantly longer with encorafenib 300 mg compared with vemurafenib (a) and with encorafenib 450 mg once daily + binimetinib 45 mg twice daily compared with either vemurafenib (b) or encorafenib 300 mg (c). Part 2 of the trial compared progression-free survival between combination therapy with encorafenib 300 mg once daily plus binimetinib 45 mg twice daily and encorafenib 300 mg, again showing superior progression-free survival with combination therapy (d). CI, confidence interval; HR, hazard ratio; *P*, nominal *P* value. Adapted with permission [20▪,21▪].

CONCLUSION AND FUTURE PERSPECTIVES

The BRAFi encorafenib, particularly in combination with the MEK-inhibitor binimetinib, is evolving as a new therapeutic option in BRAF-mutated advanced melanoma. In the light of the promising efficacy data outlined above, including an unprecedented median PFS of 14.9 months with encorafenib/binimetinib combination therapy, OS data of the COLUMBUS trial are eagerly expected by the melanoma community. Owing to its unique design, the COLUMBUS trial is the first phase 3 study demonstrating a clinical dose-dependency of BRAFi efficacy. For other BRAFi, particularly vemurafenib, such an exposure–response relationship has also been suggested, but not clearly proven to date [32]. Further research on this topic is necessary, given the relatively high proportion of dose modifications when treating patients with BRAFi in routine practice, which may impair treatment efficacy. The distinct pharmacological properties of encorafenib are thought to contribute both to improved efficacy (enhanced on-target effect) and better tolerability as a result of less paradoxical MAPK pathway activation combined with a reduction of off-target effects due to high specificity. In conclusion, encorafenib (combined with binimetinib) is expected to emerge as a valuable alternative to established BRAFi/MEKi combinations in the near future. Further clinical studies including encorafenib and binimetinib are already recruiting patients to investigate the potential of sequencing or combining the BRAFi/MEKi combination with immune checkpoint inhibition (SECOMBIT and IMMU-TARGET – ClinicalTrials.gov Identifiers: NCT02631447 and NCT02902042, respectively).

Representing the next step in the development of targeted melanoma therapies, a subsequent generation of BRAFi, so-called paradox breakers, has

been developed [33] and may further improve BRAFi efficacy. As paradoxical MAPK pathway activation does not only account for certain BRAFi-related side effects, but is also a known mechanism of acquired BRAFi treatment resistance [34▪], these molecules, such as PLX8394, do not induce paradoxical ERK phosphorylation in BRAF wild-type cells at all [14▪] and have shown preclinical efficacy in different tumor cell lines resistant to established BRAFi [35▪▪,36▪▪]. A phase 1/2a study assessing the safety, pharmacokinetics and pharmacodynamics of PLX8394 in patients with BRAF-mutated tumors including melanoma is already ongoing (ClinicalTrials.gov Identifier: NCT02428712).

Acknowledgements

None.

Financial support and sponsorship

P.K.'s work is supported by a research fellowship grant from the European Academy of Dermatology and Venerology (EADV).

Conflicts of interest

P.K. has received honoraria for travel support and consulting/advisory roles for Roche, Bristol Myers Squibb (BMS), Merck Sharp & Dome (MSD), Novartis and Amgen outside the submitted work. O.T. is an employee of Pierre Fabre Pharma GmbH, Freiburg, Germany. R.D. has intermittent, project-focused consulting and/or advisory relationships with Novartis, MSD, BMS, Roche, Amgen, Takeda and Pierre Fabre outside the submitted work.

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- ▪ of special interest
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