

# COLUMBUS-AD: phase III study of adjuvant encorafenib + binimetinib in resected stage IIB/IIC BRAF V600-mutated melanoma

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Stage IIB/IIC melanoma has a high risk of recurrence after surgical resection. While, for decades, surgery was the only option for high-risk stage II disease in most countries, adjuvant therapies now exist. Anti-programmed cell death protein 1 (PD-1) antibodies significantly improve recurrence-free survival versus placebo in patients with fully resected stage IIB/IIC melanoma. Combined BRAF MEK inhibitor therapy showed benefits in high-risk stage III and advanced disease; however, its role in patients with fully resected stage *BRAF*-mutated IIB/IIC melanoma is still unknown. Here we describe the rationale and design of the ongoing randomized, placebo-controlled COLUMBUS-AD trial, the first study of a BRAF-MEK inhibitor combination therapy (encorafenib + binimetinib) in patients with *BRAF* V600-mutated stage IIB/IIC melanoma.

**Plain language summary – COLUMBUS-AD: a clinical study of a targeted anticancer treatment for stage IIB/IIC BRAF-mutated melanoma:** Melanoma is a type of skin cancer. Although most stage II melanomas (cancer affecting the first two layers of skin) can be cured with surgery, the risk of the cancer returning and spreading to other areas of the body is high in some patients with stage IIB/IIC melanoma. Furthermore, once the melanoma has spread, it is much more difficult to treat successfully and remove all the cancer cells from the body. Some melanomas have a DNA alteration (or mutation) in what is known as the *BRAF* gene. This mutation can be identified by testing a sample of the tumor tissue removed during a biopsy or surgery. Testing for *BRAF* mutations at diagnosis can help ensure that patients receive the most appropriate treatment for their cancer. In some countries, surgery is the only option for patients with stage II melanoma, while in other countries, patients may be offered additional (adjuvant) anticancer treatment with immunotherapy (agents that work with the immune system to kill cancer cells). While immunotherapy can reduce the risk of melanoma recurrence, persistent, long-term toxicities are common and the use of this treatment in all stage IIB/IIC melanoma patients is not always possible. Here, we describe the rationale and design of an ongoing clinical trial (COLUMBUS-AD), which will be the first study (to our knowledge) to investigate the efficacy and safety of a treatment that specifically targets cancers with *BRAF* mutations (i.e., the BRAF-MEK inhibitor combination of the drugs encorafenib and binimetinib) in patients with *BRAF*-mutated stage IIB/IIC melanoma.

**Clinical Trial Registration:** NCT05270044 (ClinicalTrials.gov)

**Tweetable abstract:** The COLUMBUS-AD trial will examine the efficacy and safety of targeted therapy with encorafenib + binimetinib in patients with resected stage IIB/IIC BRAF-mutated melanoma #melanoma #studydesign #COLUMBUS-AD.

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Cutaneous melanoma is the most deadly form of skin cancer because of its high propensity to metastasize [1]. Unlike many other cancers, the incidence of melanoma has been increasing in most countries over the last few decades [1–4]. About 50% of cutaneous melanomas harbor v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) mutations, most commonly V600E (~70–90% of *BRAF* mutated melanomas) or V600K (~10–20%) mutations [5–7]. The presence of a *BRAF* mutation is associated with higher rates of loco-regional recurrence in patients with stage II & III melanoma [8,9].

While most early-stage cutaneous melanomas (Stage I–IIA) can be cured with surgical excision alone, patients with American Joint Committee on Cancer (AJCC) stage IIB or IIC disease (2–4 mm Breslow tumor thickness with ulceration or >4 mm tumor thickness with or without ulceration; without sentinel lymph node involvement), who represent approximately 50% of patients with stage II disease, have a high risk of recurrence after surgical resection [3,10].

Stage IIB/IIC melanoma patients have high rates of recurrence, including distant metastasis [10–12], as well as a poorer prognosis than patients with stage IIIA melanoma ( $\leq 2.0$  mm tumor thickness with 1–3 clinically occult tumor-involved lymph nodes), for which adjuvant treatment options are currently available. Analysis of the AJCC 8th edition patient database showed that 18% of stage IIB and 25% of stage IIC patients die from melanoma within 10 years of diagnosis [10]. Available data suggest that the 10-year cumulative recurrence rate in stage IIB/IIC melanoma patients may be at least twice as high as the 10-year melanoma-specific mortality rates reported in the analysis of the AJCC 8th edition database [13–16]. As well as being associated with significant mortality, melanoma recurrence poses a significant therapeutic challenge and adversely affects patients' quality of life (QoL) and emotional well-being [17].

Identification and characterization of *BRAF* mutations has led to the development of several highly specific, targeted therapies that have significantly changed the therapeutic landscape of *BRAF*-mutated melanoma. Overall, remarkable progress has been made in the treatment of locally advanced/metastatic and resected stage III melanoma due to the development of immune checkpoint inhibitors (ICI; ipilimumab, nivolumab, and pembrolizumab) and the BRAF- mitogen-activated protein kinase (MEK) inhibitor combinations encorafenib + binimetinib, vemurafenib + cobimetinib, and dabrafenib + trametinib [18]. These treatments are now considered standard of care for patients with stage III or IV melanoma, in whom they have greatly improved a historically poor prognosis [19,20].

More recently, pembrolizumab has been shown to prevent disease relapse in stage IIB and IIC melanoma patients. Interim findings from the placebo-controlled KEYNOTE-716 trial (NCT03553836) revealed that, at a median follow-up of 27.4 months, adjuvant therapy with the anti-programmed cell death protein 1 (PD-1) checkpoint inhibitor pembrolizumab prolonged recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) in patients with fully resected stage IIB/IIC melanoma (hazard ratio [HR] 0.64; 95% CI 0.50–0.84 and HR 0.64; 95% CI 0.47–0.88, respectively) [12]. Interim findings from the placebo-controlled CheckMate 76K trial have also shown clinically meaningful benefits with nivolumab (another anti-PD-1 agent) when administered as adjuvant therapy in 760 patients with resected stage IIB/IIC melanoma [21]. Consequently, the current standard of care for patients with stage IIB/IIC melanoma in most countries, not considering the specificity of BRAF mutation, is wide local excision and sentinel lymph node biopsy (SLNB) followed by adjuvant immunotherapy, when available [12,19]. However, to our knowledge, no published studies have specifically assessed the efficacy and safety of immunotherapy in patients with stage IIB/IIC *BRAF*-mutated melanoma.

## Introduction to the COLUMBUS-AD study

Here, we describe the design and rationale of the randomized, placebo-controlled, triple-blind, multicenter Phase III COLUMBUS-AD study (ClinicalTrials.gov identifier: NCT05270044; Registered 8 March 2022), which is

currently evaluating adjuvant encorafenib + binimetinib compared with placebo in patients with fully resected stage IIB/IIC *BRAF* V600E/K-mutated melanoma.

## Background & rationale

Approximately 20% of melanomas are stage II at diagnosis, and half of these are high-risk stage IIB/IIC tumors [3]. Whether patients with fully resected stage IIB/IIC *BRAF* V600E/K-mutated melanoma will benefit from adjuvant BRAF-MEK inhibitor targeted therapy is currently still an unanswered question.

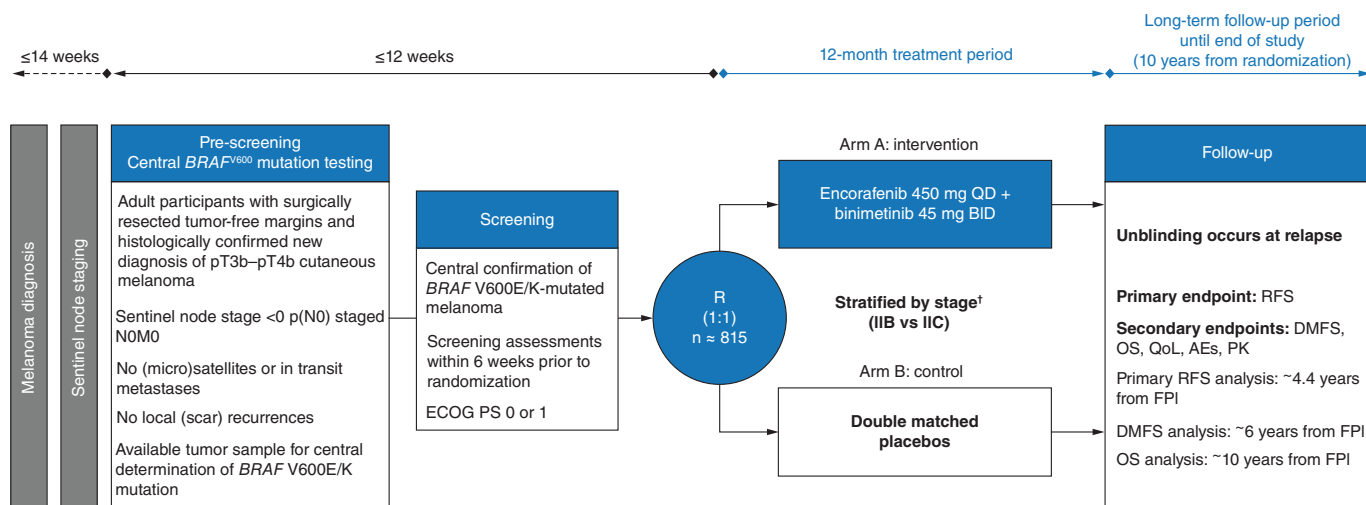
Combination BRAF-MEK inhibitor therapy with either dabrafenib + trametinib, vemurafenib + cobimetinib, or encorafenib + binimetinib is standard of care treatment in patients with advanced *BRAF*-mutated disease [19,21–24]. Dabrafenib + trametinib is the only targeted combination to have been evaluated in the adjuvant setting (in patients with stage III disease) thus far, and has demonstrated clinically meaningful benefits in patients with *BRAF* V600E/K-mutated metastatic melanoma [25,26]. In the 5-year analysis of the COMBI-AD study (NCT01682083), 12 months of adjuvant dabrafenib + trametinib was associated with a significantly prolonged RFS (HR 0.51; 95% CI 0.42–0.61) and DMFS (HR 0.55; 95% CI 0.44–0.70) compared with placebo in patients with resected *BRAF* V600E/K-mutated stage III melanoma [25].

The BRIM8 study (NCT01667419) in patients with resected *BRAF* V600-mutated stage IIC to IIIB or stage IIIC melanoma also found that DMFS was not significantly prolonged with adjuvant vemurafenib monotherapy compared with placebo (HR 0.80; 95% CI 0.54–1.18;  $p = 0.26$ ) [27].

Based on these data, adjuvant dabrafenib + trametinib is the only BRAF-MEK inhibitor combination considered to be relevant for treating patients with stage III *BRAF*-mutated melanoma after complete surgical resection. However, patients with high-risk stage II disease are not eligible for adjuvant BRAF-MEK inhibitor combination therapy [19].

Studies of adjuvant therapies in high-risk stage II disease are evaluating anti-PD1 treatments [12]. Based on these results, the US FDA and European Medicines Agency (EMA) have recently approved pembrolizumab for the adjuvant treatment of adult and pediatric ( $\geq 12$  years of age) patients with stage IIB/IIC melanoma following complete resection [28,29]. According to data from the real-world Dutch Melanoma Treatment Registry, adjuvant ICI treatment of resected stage III/IV melanoma provided similar rates of RFS but was associated with higher rates of premature discontinuation (61.0%) compared with that observed in registration trials of nivolumab (39.2%) and pembrolizumab (44.6%) [30]. While ICIs are associated with a significant risk of severe and long-lasting immune-related toxicities [29,31], the adverse effects of BRAF and MEK inhibitors are mostly moderate and reversible, and the toxicity profile can generally be easily managed with treatment interruption [32–34]. Based on the 1-year RFS of the landmark KEYNOTE-716 study, the absolute benefit of pembrolizumab was 7% (90% with pembrolizumab vs 83% with placebo) [35]. This translates into a number needed to treat (NNT) of 14 to prevent one recurrence and a number needed to harm of 5 when using the 21.2% rate of long-term hormonal replacement therapy required for endocrine treatment-related AE [36]. Essentially, adjuvant pembrolizumab harms patients more frequently than it benefits, although this may still be acceptable if the amount of harm is limited. However, this opens the door to examining adjuvant therapy with BRAF/MEK inhibitors in this population, which might have a better risk-benefit ratio than ICI therapy, as it does not carry the same risk of chronic toxicity. Furthermore, BRAF and MEK inhibitors are administered orally, which may be more convenient than intravenously administered ICI therapy in some patients, albeit with a higher pill burden. Further, no specific adjuvant anti-PD1 therapy results are available for *BRAF*-mutated stage IIB/IIC melanoma. Finally, neoadjuvant immunotherapy has shown promising efficacy in patients with stage III/IV melanoma, including those with recurrent disease [36]; however, those with recurrent melanoma after previous exposure to anti-PD1 therapy are considered to have anti-PD1 resistant disease [37], and thus require alternative treatment options. Therefore, targeted therapy may be a suitable alternative for patients with high-risk resected stage IIB/C disease to keep immunotherapy options available for later treatment. For these reasons, adjuvant targeted therapy as an alternative to ICI therapy may be preferred in patients with *BRAF*-mutated stage IIB/IIC melanoma, particularly those not suitable for or with concerns about toxicity with ICIs.

The encorafenib + binimetinib combination was approved by the FDA and EMA in 2018 for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation [37–41] and subsequently in additional countries. This approval was based on the results of the COLUMBUS study (NCT01909453), which demonstrated a significantly prolonged progression-free survival (PFS) with this combination compared with vemurafenib monotherapy (HR 0.54; 95% CI 0.41–0.71;  $p < 0.0001$ ) in patients with unresected stage IIIB, IIIC or IV melanoma [21,22].



**Figure 1. Study design.**

<sup>†</sup>According to the AJCC Cancer Staging Manual, 8th edition [43].

AE: Adverse event; BID: Twice daily; DMFS: Distant metastasis-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; FPI: First patient in; N0: Negative SLN biopsy; OS: Overall survival; PK: Pharmacokinetics; QD: Once daily; QoL: Quality of life; R: Randomization; RFS: Recurrence-free survival.

While adjuvant therapies with ICIs now exist for high-risk stage II melanoma, no dedicated treatment is currently available for *BRAF*-mutant stage IIB/IIC melanoma. Further, anti-PD1 therapy is still not available in several countries and there are many patients with stage IIB/IIC melanoma who decline adjuvant anti-PD1 treatment for a variety of reasons, including (but not limited to) concern for adverse effects [42]. According to the latest National Comprehensive Cancer Network (NCCN) guidelines [43], after R0 wide excision and negative sentinel lymph node, the treatment options include: clinical trial (for stage II; category IIA recommendation), observation (category IIA recommendation), pembrolizumab (for stage IIB/C; category IIA recommendation) and locoregional radiation therapy (category IIB recommendation). Therefore, enrollment in a placebo-controlled clinical trial would be an acceptable option for such patients. In the COLUMBUS-AD study, the first study of targeted adjuvant therapy in patients with *BRAF* V600-mutated stage IIB/IIC melanoma, we will investigate the efficacy and safety of encorafenib + binimetinib in this setting.

### Study design

The COLUMBUS-AD study (NCT05270044, protocol version 3.0–11 October 2022) is a randomized, triple-blind, placebo-controlled trial being undertaken at 170 sites across 25 different countries (see ClinicalTrials.gov for a full list of participating centers/countries) in collaboration with the European Organisation for the Research and Treatment of Cancer (EORTC) and Pierre Fabre Medicament (the study sponsor).

The study protocol has been approved by the Institutional Review Boards (IRB) and/or Independent Ethics Committees (IEC) of the participating centers. The study is being conducted according to the principles of the International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and the Declaration of Helsinki, and written informed consent is being obtained from all participants prior to any study procedures being undertaken.

Eligible patients are randomized 1:1 to receive either active treatment with encorafenib 450 mg once daily (QD) plus binimetinib 45 mg twice daily (BID) or matching placebos (Figure 1). Approximately 71% of patients are expected to have stage IIB disease (defined as pT3b or pT4a), and 29% to have stage IIC disease (defined as pT4b) [43]. Block randomization, *via* an interactive response technology (IRT) system, is stratified by stage (IIB or IIC according to the AJCC Cancer Staging Manual, 8th edition [43]) to ensure comparable representation in each treatment arm.

The encorafenib dose can be reduced to 300 mg (four capsules) or 225 mg (three capsules) QD, and the binimetinib dose to 30 mg BID (two tablets), if needed, to manage toxicity.

Table 1. Eligibility criteria for the COLUMBUS-AD study.

Key inclusion criteria	Key exclusion criteria
<b>Molecular pre-screening</b>	
<ul style="list-style-type: none"> <li>• Signed and dated informed consent, provided before start of pre-screening</li> <li>• Male or female aged <math>\geq 18</math> years</li> <li>• Surgically resected, with tumor-free margins, and histologically/ pathologically confirmed new diagnosis of stage II (pT3b–pT4bN0) cutaneous melanoma<sup>†</sup></li> <li>• Sentinel node staged node negative (pN0)</li> <li>• Sentinel node biopsy within 14 weeks from initial melanoma diagnosis</li> <li>• Available tumor sample for central determination of <i>BRAF</i> V600E/K mutation (FFPE tumor tissue block or <math>\geq 10</math> slides)</li> </ul>	<ul style="list-style-type: none"> <li>• Unknown ulceration status</li> <li>• Uveal and mucosal melanoma</li> <li>• Clinically apparent metastases (N+/M1)</li> <li>• Microsatellites, satellites and/or in-transit metastases</li> <li>• Local (scar) recurrence</li> </ul>
<b>Screening</b>	
<ul style="list-style-type: none"> <li>• Signed and dated informed consent, provided before start of screening</li> <li>• Melanoma confirmed centrally as <i>BRAF</i> V600E/K mutation-positive</li> <li>• Participant is disease free based on baseline imaging and physical assessments performed within 6 weeks and 2 weeks before randomization, respectively</li> <li>• No more than 12 weeks between full surgical resection (including SLNB) and randomization</li> <li>• Recovered from definitive surgery (e.g., complete wound healing, no uncontrolled wound infections, or indwelling drains)</li> <li>• ECOG PS 0 or 1</li> </ul>	<ul style="list-style-type: none"> <li>• History or current evidence of retinal vein occlusion or current risk factors</li> <li>• History of thromboembolic or cerebrovascular events <math>\leq 12</math> week prior to randomization</li> <li>• History of previous or concurrent malignancy within preceding 3 years or any condition with a life expectancy of <math>&lt; 5</math> years</li> <li>• Prior cancer associated with <i>RAS</i> mutation</li> <li>• Hypersensitivity to the study drugs or any of the excipients</li> <li>• Impaired cardiovascular function or clinically significant cardiovascular diseases</li> <li>• Neuromuscular disorders that are associated with creatine kinase above upper limit of normal</li> <li>• Non-infectious pneumonitis and interstitial lung disease</li> <li>• Positive SARS-CoV-2 or variants of SARS-CoV-2 RT-PCR test at screening or suspected to be infected with confirmation pending</li> <li>• Active bacterial, fungal, or viral infection requiring systemic treatment within 2 weeks prior to randomization</li> </ul>
<p><sup>†</sup> According to the AJCC Cancer Staging Manual, 8th edition [44].            ECOG PS: Eastern Cooperative Oncology Group performance status; FFPE: Formalin-fixed paraffin-embedded; RT-PCR: Reverse transcription-polymerase chain reaction; SLNB: Sentinel lymph node biopsy.</p>	

Patients, physicians, the sponsor and the EORTC are blinded to the patient's treatment allocation until the first disease recurrence (for patients and physicians) or the date of database lock for the primary end point (for the EORTC headquarters and the sponsor). Treatment will continue for a maximum of 12 months or until disease recurrence (defined as any loco-regional recurrence, distant metastasis, or a new melanoma that has a Breslow thickness of  $> 1$  mm, is ulcerated or requires treatment other than surgery), unacceptable toxicity, withdrawal of consent, initiation of subsequent anticancer therapy, death, or the predefined study end (Figure 1).

Once patients stop taking the study treatment, they enter a follow-up period in which they are monitored for safety, disease status, subsequent treatments and survival for up to 10 years after randomization. The study will end when all patients have had the opportunity of 10 years of follow-up.

### Eligibility criteria

Patients are eligible for inclusion if they have undergone resection of a stage IIB/IIC melanoma with a *BRAF* V600E/K mutation (determined by a molecular characterization of the resected tumor sample in a central pathology laboratory). The study, therefore, includes a pre-screening step in which only patients with a confirmed *BRAF* V600E/K mutation and a negative SLN biopsy (N0) are assessed for other eligibility criteria (Table 1).

Patients must have fully recovered from the surgery, but no more than 12 weeks must have passed since the surgery (including the SLN biopsy) before randomization. Good performance status (Eastern Cooperative Oncology Group [ECOG] performance status 0 or 1) and adequate organ function (hematologic, hepatic, cardiac, coagulation and renal) are also required. Female patients must not be pregnant or breastfeeding and must agree to use protocol-defined contraceptive guidance throughout treatment and at least 30 days afterward. Patients with a history of thromboembolism or retinal vein occlusion, prior cancer associated with a *RAS* mutation, neuromuscular conditions, interstitial lung disease/non-infectious pneumonitis, or an active bacterial, fungal, or viral infection including severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) are ineligible.

### Outcome measures/end points

The primary objective of this study is to determine whether the combination of encorafenib + binimetinib prolongs RFS compared with placebo in patients with resected stage IIB/IIC melanoma with a centrally confirmed *BRAF* V600E/K mutation. The secondary objectives are to compare DMFS, overall survival (OS), health-related QoL

Table 2. Definitions of survival outcomes.

End point	Definition
Recurrence-free survival	Time from randomization until first recurrence (local, regional, or distant metastasis), new melanoma that is ulcerated, thick (Breslow thickness >1 mm) or requires treatment other than surgery, or death from any cause
Distant metastasis-free survival	Time from randomization until first distant metastasis or death from any cause
Overall survival	Time from randomization until death from any cause

(HRQoL), and safety and tolerability between the two treatment arms and to provide additional pharmacokinetic data. A prespecified subgroup analysis will assess the effects of sex and baseline age (<65 vs ≥65 years), AJCC disease stage (IIB vs IIC), Breslow thickness (2.0–4.0 vs >4.0 mm), ulceration status (yes vs no) and *BRAF* mutation (V600E vs V600K) on RFS, DMFS and OS. The exploratory objectives are to evaluate the role of circulating tumor DNA (ctDNA) as a prognostic and predictive biomarker and as a biomarker for the presence of residual disease. Definitions of survival outcomes are shown in Table 2.

### Planned sample size & study period

Based on the estimate that ~45% of patients will have a *BRAF*V600E/K mutation, 2200 patients will be screened to ensure the target sample of 815 patients is enrolled. The study is designed to have 97% power to detect a 45% reduction in the hazard of recurrence or death (i.e., RFS HR of 0.55 with encorafenib + binimetinib vs placebo) at a one-sided significance level of 0.025. It will also have 90% power to detect a 40% reduction in the hazard of distant metastasis or death (DMFS HR of 0.6 with encorafenib + binimetinib vs placebo).

The primary efficacy analysis of COLUMBUS-AD is event-driven and will take place when ~166 RFS events have occurred, predicted to take place approximately 4.4 years after the randomization of the first patient. The first patient was enrolled 18 May 2022 and as of March 2023, 51 patients had been enrolled. Patient recruitment is ongoing; the estimated study completion date is in 2035.

### Study procedures

During the 12-month drug-administration period, patients are assessed monthly. To ensure adherence to intervention protocols, patients receive their study medication at each visit and provide blood and urine samples for laboratory safety analysis, blood samples for ctDNA and pharmacokinetics, are assessed for performance status, AEs, and treatment compliance, and undergo a complete physical (including weight and vital signs), dermatologic, cardiac and ophthalmologic examination. Patients also undergo tumor radiographic assessment of the thorax, abdomen, and pelvis at the 6- and 12-month visits and brain MRI as clinically indicated. Patients complete HRQoL questionnaires at 3, 6, 9, 12, 18, 24 and 30 months from randomization.

After the treatment period, in the absence of an RFS event, patients undergo follow-up physical and skin examinations every 3 months for the first 3 years, every 6 months during years 4 and 5, and then annually until the end of the follow-up period. Tumor imaging is performed every 6 months from randomization for the first 3 years and then annually thereafter until the occurrence of distant metastasis or the end of the follow-up period. For patients who complete the follow-up period, the last assessment will occur 10 years after randomization.

The EORTC Headquarters will be responsible for writing the protocol and patient information consent form, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating scientific reports and analyses in cooperation with the Study Coordinator. The retention of participants and completion of follow-up will be performed by the contract research organization. The study sponsor will perform audits to evaluate trial conduct and compliance with the protocol, the sponsor's standard operating procedures, ICH GCP guidelines and the applicable regulatory requirements.

### Data management & statistical analysis

Study-related data will be used according to local data protection law and European Union (EU) General Data Protection Regulation (GDPR 679/2016). Pierre-Fabre Médicament and EORTC are acting as data controllers for this study and will ensure that the processing activities on the personal data in scope of this study are compliant with, but not limited to, the requirements set by GDPR 679/2016, its subsequent amendments, and any additional national laws, recommendations and guidelines, as applicable. Any important protocol modifications will be communicated in accordance with the ICH GCP guidelines.

Data management will be subcontracted to EORTC under the supervision of the sponsor's Data Manager of IRPF Biometry Department. An electronic case report form will be developed for this study and comply with FDA (Guidance for industry: Computerized systems used in clinical investigations 2007) and European regulations (ICH GCP guidelines E6 [R2]), compliant with 21CFR, part 11. The EORTC Data Manager will follow the cleaning of the data over the course of the study. The sponsor's Data Manager will assume storage of the locked clinical database in SAS format on a secured server.

All efficacy analyses will be performed using the full analysis set (FAS; all participants assigned to study intervention) and all safety analyses will be performed using the safety population (all FAS participants who received at least one dose of the study intervention) unless otherwise specified. All statistical testing will be performed at a one-sided significance level of 0.025. CIs will be two-sided with a confidence level of 95%, if not otherwise specified.

For the primary end point, the treatment effect will be described by the estimate of the HR from the Cox model stratified by the stratification factor stage at randomization. The Wald method will be used to construct the two-sided 95% CI of the HR. The same statistical technique will be used to calculate the secondary end point (i.e., DMFS).

Continuous data will be presented using the number of observations, number of missing values, mean, standard deviation, median, lower and upper quartiles, minimum and maximum. The 95% CI will be presented if relevant. Categorical data will be summarized using the number of observations, frequencies, percentages and number of missing values.

No interim analyses with formal stopping rules are planned.

The independent Data Monitoring Committee (iDMC) for EORTC studies is in charge of the independent oversight of this study. The composition of the iDMC is described in the EORTC Policy "Independent Data Monitoring Committees for EORTC studies" (ref. EORTC POL004) and its functioning is ruled by the charter annexed to the Policy.

### Safety & tolerability

The iDMC is overseeing the study, and will review the cumulative safety data at three prespecified meetings throughout the study. Investigators record all AEs identified by direct observation and through participant interviews (using non-leading questions) at all study visits. This includes all events occurring between randomization and 30 days after the last dose of medication recorded, irrespective of causality. Investigators also report treatment-related serious AEs and new cutaneous/non-cutaneous malignancies (regardless of causality) until the end of the study. The severity of AEs is graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), and the potential relationship of AEs to treatment is being assessed by the investigator.

Based on the known toxicology and AE profiles of encorafenib, procedures are included for the prevention and early detection of: QT prolongation; pregnancy; secondary cutaneous neoplasms (squamous cell carcinoma or new melanoma); non-cutaneous malignancy associated with a *RAS* mutation; and drug-drug interactions with moderate or strong cytochrome P450 (CYP) 3A4 inhibitors. Based on the known AE profile of binimetinib, procedures are included for the prevention or early detection of: left ventricular dysfunction; hemorrhage; hepatotoxicity; pneumonitis/interstitial lung disease; ocular toxicity and creatine kinase elevation/rhabdomyolysis.

### SARS-CoV-2

As part of its ongoing responsibility to patient safety, the iDMC is monitoring the impact of trial participation on a patient's risk of SARS-CoV-2 infection and will take appropriate actions based on continuing benefit-risk assessments in each participating country. If patients cannot visit the site because of local restrictions/policies, the center may use other means (such as home visits or telemedicine) to provide trial participants with ongoing assessments of clinical needs and AEs.

### Conclusion

There is an unmet medical need to assess other treatment options, such as targeted therapy, for their ability to reduce the rate of disease recurrence in patients with resected stage IIB/IIC melanoma, including those with a *BRAF* V600 mutation. The favorable toxicity profile of BRAF-MEK inhibitors, particularly the reversibility of associated AEs, has been demonstrated in numerous clinical trials, as well as their ability to prolong PFS and OS in patients with unresectable or metastatic *BRAF*-mutated melanoma. The COLUMBUS-AD study will address the important questions of whether combination BRAF + MEK inhibitor therapy reduces the risk of any recurrence,

distant metastasis, or death in patients with stage IIB/IIC *BRAF* V600E/K-mutated melanoma. If the results of this study are positive, this may add a therapeutic option to the adjuvant treatment arsenal for patients with stage IIB/IIC melanoma.

#### Executive summary

##### Purpose of COLUMBUS-AD Study

- The COLUMBUS-AD study is the first study to investigate the effects of adjuvant treatment with a BRAF inhibitor + MEK inhibitor (in this case encorafenib + binimetinib) on disease recurrence in patients with resected stage IIB/IIC melanoma and *BRAF* V600E/K mutations, who are a population at high risk of disease recurrence.

##### Design

- COLUMBUS-AD is an international, randomized, placebo-controlled, triple-blind, multicenter phase III study that is comparing adjuvant encorafenib + binimetinib with matching placebo in ~815 patients with fully resected stage IIB/IIC *BRAF* V600E/K-mutated melanoma.
- Patients receive encorafenib + binimetinib or placebo for 12 months and are followed for up to 10 years.

##### Primary & secondary end points

- The primary end point of COLUMBUS-AD is recurrence-free survival, and the secondary end points are distant metastasis-free survival, overall survival, health-related quality of life, safety/tolerability and pharmacokinetic parameters.

##### Key dates

- The first patient was enrolled 18 May 2022 and patient enrolment is ongoing; the primary completion date is expected in Quarter 2 of 2027, and final study completion in 2035.

#### Author contributions

Conceptualization: all authors; writing – review & editing: all authors. All authors approved the final manuscript for submission.

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### Ethical conduct of research

The authors declare that the study protocol has been approved by the Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the participating centers. The study is conducted according to the principles of the ICH Good Clinical Practice, and the Declaration of Helsinki, and written informed consent is obtained from all participants prior to any study procedures being undertaken.

### Data sharing statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study. Contact information for trial sponsor: Isabelle Klauck, [isabelle.klauck@pierre-fabre.com](mailto:isabelle.klauck@pierre-fabre.com).

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