COLUMBUS AD

COmbined encorafenib and binimetinib versus pLacebo in fUlly resected stage IIB/C Melanoma with a *BRAF* mUtation:

Phase III Study of Adjuvant Encorafenib Plus Binimetinib Versus Placebo In Fully Resected Stage IIB/C BRAFV600-Mutated Melanoma: COLUMBUS-AD Study Design

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The purpose of the COLUMBUS-AD (NCT05270044) study is to evaluate the efficacy and safety of 12 months of encorafenib in combination with binimetinib in the adjuvant setting of BRAF V600E/K mutant stage IIB/C melanoma versus the current standard of care (surveillance).

Background

Significant progress has been made in the treatment of advanced BRAFV600-mutant melanoma.

Encorafenib in combination with binimetinib is a well-tolerated and effective treatment option, providing sustained progression-free and overall survival benefit in the unresectable or metastatic setting.

The focus has shifted to early-stage disease in order to prevent recurrence. It has been estimated that 18% of stage IIB and 25% of stage IIC patients die due to melanoma within 10 years of diagnosis [Gershenwald et al 2017], indicating an unmet medical need.

Study Design

The COLUMBUS-AD study is an international randomized, placebo-controlled, triple-blind, multicenter Phase III trial evaluating adjuvant encorafenib + binimetinib against placebo in patients with fully resected stage IIB/C *BRAF V600-mutant* melanoma.

Participants with completely resected cutaneous melanoma and documented *BRAF V600E/K* status by central assay will be randomized 1 to 1 to receive either treatment with encorafenib and binimetinib or their two placebos for 12 months.

The randomization will be stratified according to the stage of the disease according to AJCC version 8 between:

- **Stage IIB (i.e., pT3b or pT4a)**
- **Stage IIC (i.e., pT4b)**

The main analysis of RFS will be conducted after approximately 166 RFS events have been observed, which is predicted to occur 4.4 years from the accrual of the first participant. In total, patients will be followed-up for 10 years from randomization.
(Figure 1)

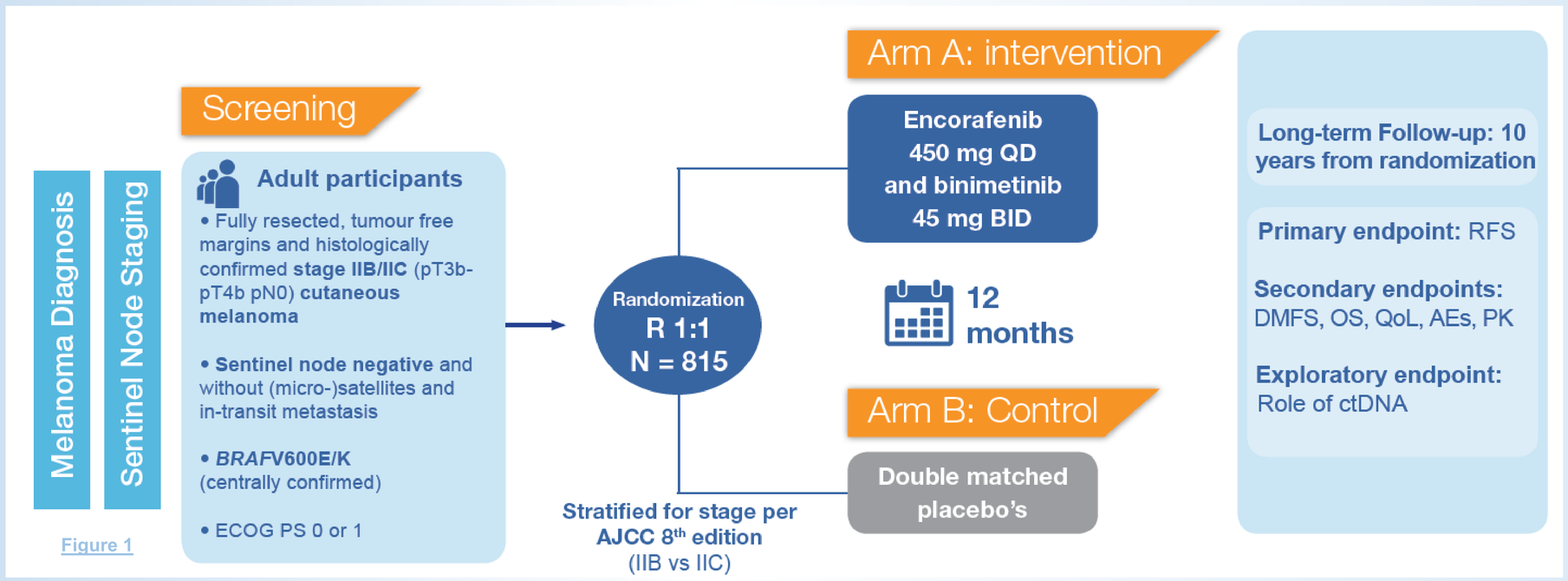

Figure 1

Approximately 815 patients will be enrolled

>170 sites

25 countries

PRIMARY ENDPOINT
Recurrence-free survival (RFS)

SECONDARY ENDPOINTS
Distant metastasis-free survival (DMFS); Overall survival (OS); Safety & tolerability (AEs); Patient-reported health-related Quality of Life (HRQoL); Pharmacokinetic data (PK)

EXPLORATORY ENDPOINTS
Role of circulating tumor DNA (ctDNA)

COLUMBUS-AD is the first study to evaluate a combination of BRAFi/MEKi in high-risk stage II adjuvant melanoma

This study will evaluate whether the combination of encorafenib and binimetinib can decrease the risk for recurrence and improve distant metastasis-free survival and overall survival versus placebo in completely resected IIB/C *BRAFV600E/K*-mutant melanoma

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Inclusion Criteria

Pre-Screening

- **Male or female ≥ 18 years of age**
- **Fully resected, with tumour free margins, and histologically/pathologically confirmed new diagnosis of stage IIB-IIC (pT3b-pT4bN0) cutaneous melanoma**
- **Sentinel node biopsy within 14 weeks from initial diagnosis of melanoma**
- **Sentinel node staged node negative (pN0)**
- **Available tumour sample for central determination of the *BRAF V600E/K* mutation.**

Screening

- **Melanoma confirmed centrally to be *BRAF V600E/K* mutation-positive**
- **Participant still free of disease as evidenced by the required baseline imaging and physical/dermatological assessments performed respectively within 6 weeks and 2 weeks before randomization.**
- **No more than 12 weeks elapsed between full surgical resection (including Sentinel Lymph Node Biopsy) and randomization**
- **Recovered from definitive surgery (e.g., complete wound healing, no uncontrolled wound infections or indwelling)**
- **ECOG performance status of 0 or 1**
- **Adequate hematological, renal, hepatic, cardiac and coagulation functions**
- **Negative serum beta-HCG test**
- **Female patients of childbearing potential and male patients must agree to follow effective contraception method**