Protocol #: C4221028

OCEANMIST - Comparative effectiveness of different targeted therapies for BRAF-mutated unresectable/metastatic melanoma in the United States

SUMMARY OF CHANGES IN AMENDED NON-INTERVENTIONAL STUDY PROTOCOL

This amended protocol describes a revised approach for assessment of comparative effectiveness of encorafenib plus binimetinib relative to other targeted therapies for BRAF-mutated unresectable/metastatic melanoma. Analyses conducted based on the originally submitted protocol for study C4221028 were limited to descriptive and unadjusted analyses of real-world data from Flatiron Health, as the sample size of the identified encorafenib plus binimetinib study cohort was judged to be too small for conduct of adjusted comparative effectiveness analyses. Based on the findings of a recently completed study (*Protocol #C4221035: Overall survival (OS) in patients with metastatic BRAFV600-mutant melanoma treated with encorafenib plus binimetinib in the COLUMBUS trial versus in real-world practice data*), which showed consistent OS outcomes between the COLUMBUS trial Flatiron Health after accounting for differences in patient profiles, in this amended protocol, to enrich the sample size for the encorafenib plus binimetinib combination cohort, data will be pooled across Flatiron and COLUMBUS, and compared versus real-world data for other targeted therapies as described further below.

Key elements of the revised approach are summarized below:

1. **Pooling of data for encorafenib + binimetinib patients across the phase 3 COLUMBUS trial and the Flatiron Health real-world database**: The pooling of data for encorafenib + binimetinib patients across these two sources is justified by the results of study C4221035, which showed, that after harmonizing key patient selection criteria, adjusting for differences in baseline characteristics, and imputing missing data on baseline characteristics, OS for metastatic BRAFV600-mutant melanoma patients was similar across the COLUMBUS trial and real-world practice data from the Flatiron Health database (HR = 1.03, 95% CI: 0.53, 1.54; p=0.90). Given this empirical consistency in OS outcomes, pooling patients across these settings can be justified and allows for a larger sample size for assessment of comparative effectiveness of encorafenib + binimetinib versus other targeted therapies.

2. **Application of key patient selection criteria consistent with the COLUMBUS trial for all treatment groups:** To ensure included patient populations are comparable across settings, key patient selection criteria applied from the COLUMBUS trial will also be applied to all treatment groups drawn from the Flatiron real-world database. These include the following: age ≥18 years at initiation of targeted therapy, metastatic BRAF V600E/K mutated melanoma without central nervous system metastases, untreated or with prior first-line immunotherapy, and ECOG performance status of 0 or 1.

3. **Imputation of missing data on baseline characteristics**: To allow for more comprehensive adjustment for confounding due to differences in baseline characteristics between treatment groups, multiple imputation will be conducted to account for missing data in baseline characteristics.

The approach outlined here largely follows the approach described in *Protocol #C4221035*, with minor updates to the selection criteria, adjustment factors and statistical methods following discussions with a clinical expert in melanoma and further review of the clinical trial and real-world data.

Classification of Change as Substantial and Non-Substantial and Rationale

This is a Substantial Protocol Amendment for the reasons described above.

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	OCEANMIST - Comparative effectiveness of different targeted therapies for BRAF-mutated unresectable/metastatic melanoma in the United States
Protocol number	C4221028
Protocol version identifier	2.0
Date	19 JUL 2023
Active substance	Encorafenib plus Binimetinib
Medicinal product	Braftovi ® plus Mektovi®
Research question and objectives	The study objective is to describe and compare OS in patients with metastatic BRAFV600-mutant melanoma treated with encorafenib plus binimetinib (ENCO+BINI) versus other targeted therapies.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
AE	Adverse event
AJCC	American Joint Committee on Cancer
BMI	Body mass index
BRAF	v-Raf murine sarcoma viral oncogene homolog B protein
CI	Confidence interval
CTD	Clinical trial data
DAB+TRAM	Dabrafenib + Trametinib
ECOG	European Cooperative Oncology Group
EHR	Electronic health record
ENCO+BINI	Encorafenib + Binimetinib
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GRACE	Good Research for Comparative Effectiveness
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICD-9	International Classification of Diseases 9th Revision
ICD-10	International Classification of Diseases 10th Revision
IEC	Independent Ethics Committee
IO	Immunotherapy
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LOT	Line of therapy

MEK	Mitogen-activated protein kinase (MAPK) kinase
MICE	Multiple imputation by chained equations
NDI	National Death Index
NI	Non-interventional
OS	Overall survival
PFS	Progression free survival
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real-world data
SMR	Society of Melanoma Research
TT	Targeted therapy
US	United States
VEM+COBI	Vemurafenib + Cobimetinib

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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4. AMENDMENTS AND UPDATES

Significant updates have been made to the data source and analytical approach compared to the original OCEANMIST protocol submission. Below, we provide a high-level overview of the key differences with additional details described in Sections 5-8 and Section 12 below.

Data Source Updates

- In this study, data for encorafenib plus binimetinib patients will be pooled from the phase 3 COLUMBUS trial and the Flatiron Health real-world database to maximize sample size. In contrast, the original study design, only used encorafenib plus binimetinib data from Flatiron Health. This pooling is justified based on the empirical consistency in OS outcomes across COLUMBUS and Flatiron Health after harmonizing key patient selection criteria, adjusting for differences in baseline characteristics, and imputing missing data on baseline characteristics (HR = 1.03, 95% CI: 0.53, 1.54; p=0.90), described in study C4221035.

Analytical Approach Updates

- To ensure identification of patient populations in Flatiron that are comparable to patients in the COLUMBUS trial, key patient selection criteria related to age, ECOG performance score, history of brain metastasis and prior use of immunotherapy and targeted therapies from the COLUMBUS trial will be applied to all treatment groups in Flatiron Health.

- To ensure that representation of each targeted therapy from the real-world data was as comprehensive as possible and that patients were followed from treatment initiation consistent with the COLUMBUS trial, patients included in each treatment cohort will be required to have index dates (i.e., treatment initiation dates) that were on or after the dates of FDA approval of that targeted therapy in metastatic melanoma (specifically, 09 January 2014 for DAB+TRAM, 10 November 2015 for VEM+COBI and 27 June 2018 for ENCO+BINI). This is in contrast to the original approach, which defined the follow-up period for all cohorts as beginning from 20 November 2015. This could have led to the exclusion of some patients initiating DAB+TRAM before approval, and could potentially inadvertently include off-label usage of ENCO+BINI.

- For the real-world cohorts, patient baseline characteristics will be obtained from visits ≤3 months prior to the index date, with data from visits closest in time to the index date being used as available. In contrast, in the original protocol, to maximize availability of baseline characteristics, the 'baseline' period was allowed to include visits up to 6 months prior to treatment initiation. The decision to use a stricter definition of baseline here was based on clinical input that certain baseline characteristics of interest (e.g., ECOG PS) are best assessed closest to the index date, despite potential for increased missingness. To address missingness, imputation of baseline characteristics was conducted as described below.

- Key clinical characteristics like ECOG and LDH were missing at baseline for 40-60% of patients in the original study cohort, which would have hampered ability to adjust for potential confounding due to these factors. To address missingness, we will impute data using multiple imputation by chained equations prior to conducting adjusted analyses. Imputation models will be based on baseline characteristics that would be considered in adjusted models for OS.

- Inverse probability of treatment weighting without any imputation was proposed in the original study design to account for baseline differences. Instead, we will use multivariable Cox proportional hazards models fit to each of the imputed dataset and combined results across all imputations. This approach is preferred as it allows us to assess how included covariates are associated with OS in our final models, in addition to estimating differences between the treatments of interest.

- Comparisons of OS and PFS were stratified by first-line and second-line of therapy in the original study design. Analyses conducted in this revised protocol will not be stratified by line of therapy to allow for a larger sample size to compare OS and PFS across targeted therapy treatment cohorts. A line of therapy variable will be included in Cox proportional hazard models, which can facilitate future analyses of comparative effectiveness by line of therapy if required.

5. MILESTONES

Milestone	Planned date
Amendment to study protocol	19 May 2023
Completion of statistical analyses	7 June 2023
Abstract submission to Society for Melanoma Research (SMR) 2023 Congress	21 June 2023
Final study report	21 July 2023

6. RATIONALE AND BACKGROUND

Melanoma, caused when malignant cancer cells form in melanocytes, is the fifth most common cancer in the United States (US) and the deadliest form of skin cancer.[1] Incidence of melanoma has been increasing over recent decades, with the overall incidence rate of 229.1 cases per million person based on recent estimates. Based on American Cancer Society estimates, there were an estimated 99,780 new cases of melanoma and ~7,650 deaths from melanoma in the US in 2022.[1-3]

Approximately 9% of melanoma patients are diagnosed with regional spread to lymph nodes and 4% are diagnosed with metastatic disease.[1] Compared to patients with localized melanoma, patients with metastatic melanoma have poorer prognosis and worse outcomes, which can be further worsened by the presence of v-Raf murine sarcoma viral oncogene homolog B protein (BRAF) mutations.[4] The BRAF protein plays an important role in normal cell growth, proliferation, differentiation, and survival.[5] The presence of BRAF V600 mutations, found in ~40–60% of melanoma cases, can lead to sustained mitogen-activated protein kinase (MAPK) kinase (MEK) pathway signaling, resulting in tumor growth and progression.[6]

Recommended treatment options for metastatic melanoma include immunotherapy (IO), which attempts to stimulate host responses to effectuate tumor destruction, and targeted therapies (TT), which inhibit molecular pathways to prevent tumor growth and maintenance.[7] The discovery of targeted therapy as a treatment for melanoma has emerged as a milestone development in oncological research.[8] In 2018, the US Food and Drug Administration (FDA) approved the use of encorafenib (BRAFTOVI®) in combination with binimetinib (MEKTOVI®) for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation (as detected by an FDA-approved test) based on the pivotal phase 3 COLUMBUS trial.[9, 10] This accompanied existing BRAF-/MEK-inhibitor therapies including dabrafenib plus trametinib (FDA approval 09 January 2014) and vemurafenib plus cobimetinib (FDA approval 10 November 2015).

There is increasing interest in evaluating comparative effectiveness of BRAF-/MEK-inhibitor therapies. In a recent study, we showed that overall survival (OS) for metastatic BRAFV600-mutant melanoma patients was similar across the COLUMBUS trial and real-world practice data from the Flatiron Health database (Hazard Ratio [HR] = 0.94, 95% Confidence Interval [CI]: 0.43, 1.45) after harmonizing key patient selection criteria, adjusting for differences in baseline characteristics, and imputing missing data on baseline characteristics. Given this empirical consistency in OS outcomes, pooling patients across these settings can be justified and allows for a larger sample size for assessment of comparative effectiveness of encorafenib + binimetinib versus other targeted therapies. To that end, this study will expand on this prior work and compare OS between patients receiving encorafenib + binimetinib in the pooled Phase 3 COLUMBUS trial and the Flatiron Health Electronic Health Records (EHR) database versus patients receiving other targeted therapies. Baseline profiles of patients will also be compared to characterize differences in patients receiving different therapies and adjustments will be made for

differences across treatment groups in baseline factors associated with OS. Missingness for key baseline characteristics will be addressed using a validated multiple imputation approach.[12]

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective

To compare OS between patients with metastatic BRAFV600-mutant melanoma initiating encorafenib plus binimetinib (ENCO+BINI) versus dabrafenib plus trametinib (DAB+TRAM) or vemurafenib plus cobimetinib (VEM+COBI)

Exploratory Objective

To compare progression free survival (PFS) between patients with metastatic BRAFV600-mutant melanoma initiating ENCO+BINI versus DAB+TRAM or VEM+COBI

This objective is designated as exploratory as, unlike for OS, differences in assessment of PFS between clinical trial data (CTD) and real-world data (RWD) settings may exist that preclude valid comparisons of this outcome across these settings. Suitability of comparative analyses of PFS will be determined following additional exploration to characterize number and frequency of assessments of PFS, and further analyses of comparability of PFS outcomes across trial and real-world settings.

8. RESEARCH METHODS

8.1. Study design

This is a retrospective cohort study comparing OS outcomes between patients with BRAFV600-mutant metastatic melanoma initiating ENCO+BINI versus DAB+TRAM or VEM+COBI. Comparisons will be adjusted for differences in baseline characteristics across treatment groups, and account for missing data on adjustment factors. PFS will also be investigated as an exploratory endpoint, subject to comparability of PFS outcome assessment between clinical trial and real-world settings.

8.2. Setting

Patients with BRAFV600-mutant metastatic melanoma initiating treatment with ENCO+BINI, DAB+TRAM or VEM+COBI.

8.2.1. Inclusion criteria

Inclusion criteria that will be used to identify patients initiating the targeted therapies of interest are provided separately for the clinical trial and real-world data sources below.

8.2.1.1. COLUMBUS trial

Key inclusion criteria in the COLUMBUS trial were:

- Histologically confirmed diagnosis of locally advanced, unresectable, or metastatic cutaneous melanoma or unknown primary melanoma
- American Joint Committee on Cancer (AJCC) disease stage of IIIB, IIIC, IVM1a, IVM1b, or IVM1c at trial enrolment
- Presence of BRAF V600E or V600K mutation in tumor tissue prior to enrollment
- At least 18 years of age at randomization
- Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 at randomization
- Treatment naive or had progressed on or after previous first-line (1L) immunotherapy at randomization with no prior BRAF- or MEK-inhibitor therapy in the adjuvant setting

Patients from the COLUMBUS trial included in this analysis will be those patients:

- Randomized to ENCO+BINI arm of the trial to receive 450mg once daily encorafenib and 45mg twice daily binimetinib combination therapy

8.2.1.2. Flatiron Health data

Pfizer has contracted with Flatiron for a custom data extract containing information on patients with advanced melanoma. Eligibility criteria applied to the Flatiron custom data received by Pfizer include:

- Diagnosed with melanoma based on International Classification of Disease 9th and 10th Revisions (ICD-9: 172.x; ICD-10: C43x, D03x) and ≥2 visits on different days in the Flatiron database on or after January 1, 2011.
- Clinically confirmed diagnosis of melanoma with pathologic stages III or IV at initial diagnosis or earlier stage disease with a first locoregional or distant recurrence on or after January 1, 2011.
- Age ≥18 years at the time of advanced melanoma diagnosis.
- Evidence of ≥1 BRAF positive test result at any time based on laboratory or genetic analysis results.
- Treatment with ≥1 BRAF-inhibitor (i.e., encorafenib, dabrafenib, vemurafenib) and treatment with ≥1 MEK-inhibitor (i.e., binimetinib, trametinib, cobimetinib) in 1L or 2L line of therapy (LOT), as defined per Flatiron's LOT business rules.

- Earliest LOT containing a BRAF- and MEK-inhibitor ≥3 months prior to data cutoff (defined as 30 September 2021)

Key inclusion criteria from the COLUMBUS trial will be applied to the Flatiron RWD population to align the populations to the extent possible between the CTD and RWD sources. The sample of patients from the Flatiron Health EHR data for this study will be identified using the following additional criteria applied to the custom data cut received from Flatiron:

- At least 18 years of age at the index date
- Confirmed BRAF V600E or V600K activating mutation reported in the data based on laboratory or genetic analysis results
- Treatment-naive or had previous 1L IO at index date in the therapeutic setting, based on review of medication orders or administration prior to the index date.
- ECOG status of 0 or 1 at the index date

The following criteria will be additionally used to identify patients receiving each of the treatments of interest:

- **ENCO+BINI treatment group:** At least 1 order or administration of ENCO+BINI treatment after the diagnosis of metastatic melanoma and after 27 June 2018 (FDA approval date for ENCO+BINI for use in patients with metastatic melanoma).
- **DAB+TRAM treatment group:** At least 1 order or administration of DAB+TRAM treatment after the diagnosis of metastatic melanoma and after 09 January 2014 (FDA approval date for DAB+TRAM for use in patients with metastatic melanoma).
- **VEM+COBI treatment group:** At least 1 order or administration of VEM+COBI treatment after the diagnosis of metastatic melanoma and after 10 November 2015 (FDA approval date for VEM+COBI for use in patients with metastatic melanoma).

The index date in each treatment group will be the date of treatment initiation.

8.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

- Patients with prior BRAF- or MEK-inhibitor therapy
- Patients with ECOG performance status ≥ 2 (at the time of randomization for patients from COLUMBUS, during the baseline period for patients in Flatiron EHR)
- *Patients with a history of leptomeningeal metastases including brain, spinal cord, or nervous system metastases (based on brain MRI or CT scan with contrast-enhanced brain MRI as the preferred assessment in COLUMBUS and based on the following*

diagnostic codes in Flatiron EHR: ICD-9-CM: 198.3, 198.4 or ICD-10-CM: C79.31, C79.32, C79.40, C79.49) prior to index

- For RWD patients, concurrent enrollment in a clinical trial.

8.3. Variables

Table 1 provides a summary of exposure, outcome, and patient baseline characteristics that will be evaluated within the study.

Table 1. Key exposures, outcomes, and patient baseline characteristics

Variable	Role	Data source(s)	Operational definition/categories
Treatment group (ENCO+BINI, DAB+TRAM, VEM+COBI)	Exposure	COLUMBUS trial data; Flatiron EHR	Indicates whether patients initiated ENCO+BINI, DAB+TRAM or VEM+COBI treatment
OS	Primary Outcome	COLUMBUS trial data, Flatiron	In the COLUMBUS trial data, defined as the time from the date of randomization to the date of death due to any cause; if death is not observed, patients will be censored at the date of last contact or the data analysis cut-off date (e.g., 15 September 2020), whichever occurs first In Flatiron EHR, will be defined as the time from the index date to the date of death; patients without a date of death will be censored at their last known activity date (e.g., the last clinical note date) or the end of the follow-up period, whichever occurs first
PFS	Exploratory Outcome	COLUMBUS trial data, Flatiron her	In the COLUMBUS trial data, defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause, whichever occurred first; if a patient did not have an event at the analysis cut-off date, PFS will be censored at the date of the last adequate tumour assessment In Flatiron EHR, will be defined as the time from the index date to either the date of first disease progression event or death in the absence of progression; patients without disease progression or death will be censored at the last date the patient could have been assessed for progression (e.g., the last clinical note date) or the data analysis cut-off date (e.g., 30 September 2021), whichever occurs first
Age at baseline (years)	Baseline Characteristic / Potential Confounder	COLUMBUS trial data Flatiron EHR	Patient age; defined at the time of study randomization for COLUMBUS trial data and at the time of treatment initiation for Flatiron EHR
Sex	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Male, Female, Intersex, or Unknown/Missing

Race	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Asian, Black, White, Other/Multi-Race, or Unknown/Missing
Body mass index (BMI) at index	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Defined as weight (in kg) divided by squared height (in m^2)
ECOG at index	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	0, 1, Unknown/Missing; defined during the baseline period of both the COLUMBUS trial data and Flatiron EHR
BRAF mutation status	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	V600E, V600K, Unknown/Missing
AJCC disease stage at initial melanoma diagnosis	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	0, I, II, III, IV, or Unknown/Missing; defined at initial melanoma diagnosis for COLUMBUS trial data and Flatiron EHR
AJCC disease stage at treatment initiation	Baseline Characteristic	COLUMBUS trial data	IIIB, IIIC, IVM1a, IVM1b, or IVM1c; defined at treatment initiation in the COLUMBUS trial data. Not available in the Flatiron EHR
Lactate dehydrogenase (LDH) at index	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Evaluated in units per liter (U/L) and defined at trial baseline in COLUMBUS trial and during the baseline period in Flatiron EHR
Time from initial melanoma diagnosis to metastatic disease	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Duration (in months) from melanoma diagnosis to the development of metastatic disease
Time from metastatic melanoma diagnosis to treatment initiation	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Duration (in months) from metastatic melanoma diagnosis to the initiation of treatment
Year of treatment initiation	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Calendar year when treatment was initiated
Region	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Europe, North America, Australia, Other, or Missing
Treatment experience in the therapeutic setting	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates whether patients received targeted therapy as first-line treatment (e.g., Treatment naïve) or as second-line treatment after a prior line of immunotherapy treatment (e.g., Prior 1L IO therapy)
Prior systemic therapies in the adjuvant setting	Baseline Characteristic /Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates whether patients previously received systemic therapy (e.g., prior surgery, radiotherapy, immunotherapy, or chemotherapy) before initiating treatment
Prior surgery in the adjuvant setting	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates whether patients previously used surgery to reduce/remove tumors as a form of treatment
Prior radiotherapy in the adjuvant setting	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates whether patients underwent radiotherapy among those receiving prior systemic therapy

Prior IO or chemotherapy in the adjuvant setting	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates whether patients underwent chemotherapy or immunotherapy among those receiving prior systemic therapy
Number of LOTs after TT treatment initiation	Baseline Characteristic / Potential Confounder	COLUMBUS trial data; Flatiron EHR	Indicates the number of LOTs occurring after treatment initiation (0, 1, ≥2, or Missing)
Number of organs involved	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Indicates number of organs involved or sites of metastases at baseline (1, 2, or ≥3), with all patients having at least 1 site given diagnosis of metastatic disease. This data was collected and reported in COLUMBUS. In Flatiron EHR, it will be derived based on counting the number of distinct sites recorded as having metastases based on ICD codes.
Presence of lung metastases	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Indicates whether patients had lung metastases. This data was collected and reported in COLUMBUS. In Flatiron EHR, it will be derived based on having ICD codes reflecting presence of lung or respiratory organ metastases (ICD-9: 197, 197.1; ICD-10: C78.01, C78.02, C78.1, C78.2, C78.30, C78.39).
Presence of liver metastases	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Indicates whether patients had liver metastases. This data was collected and reported in COLUMBUS. In Flatiron EHR, it will be derived based on having ICD codes reflecting presence of liver metastases (ICD-9: 197.7; ICD-10: C78.7)
Presence of other metastases	Baseline Characteristic	COLUMBUS trial data; Flatiron EHR	Indicates whether patients had presence of other metastases (e.g., adrenal glands, bone, digestive tract/system, kidney, lymph nodes, reproductive organs, or unspecified sites). This data was collected and reported in COLUMBUS. In Flatiron EHR, it will be derived based on having ICD codes reflecting presence of other metastases (ICD-9: 196, 196.1, 196.2, 196.3, 196.5, 196.6, 196.8, 196.9, 197.4, 197.5, 197.6, 197.8, 198, 198.5, 198.7, 198.89; ICD-10: C77.0, C77.1, C77.2, C77.3, C77.4, C77.5, C77.8, C77.9, C78.4, C78.5, C78.6, C78.80, C78.89, C79.00, C79.01, C79.02, C79.11, C79.51, C79.52, C79.60, C79.61, C79.62, C79.70, C79.71, C79.72, C79.81, C79.89, C79.9)

8.4. Data sources

COLUMBUS trial

COLUMBUS was a two-part, multicenter, randomized, open-label, Phase 3 clinical trial.[10] Part 1 of the trial investigated the effectiveness and safety of three treatment regimens in patients with locally advanced unresectable or metastatic BRAFV600-mutant metastatic melanoma who were treatment naïve or whose cancer had progressed after 1L IO. In Part 1 of the trial, patients were randomized to one of three treatment arms: 1) 450mg once daily encorafenib and 45mg twice daily binimetinib (n=192), 2) 960mg twice daily vemurafenib (n=191) and 3) 300mg once daily

encorafenib (n=194). Randomization was stratified by AJCC disease stage (IIIB, IIIC, IVM1a, IVM1b, or IVM1c), ECOG performance status (0, 1), and BRAFV600 mutation profile (V600E, V600K). Progression-free survival was the primary endpoint in the trial, while OS was one of the secondary endpoints. Patients were enrolled in Part 1 of the trial between 30 December 2013 through 10 April 2015.

The ENCO+BINI arm of Part 1 of the trial will be used in this study (database lock date: 15 September 2020). Part 2 of the trial compared encorafenib 300mg once daily plus binimetinib 45mg twice daily versus encorafenib 300mg once daily alone and will not be considered.

Flatiron Health EHR

The Flatiron Health EHR database is a longitudinal, de-identified real-world database derived from EHRs collected in US cancer clinics. The database covers more than 2.6 million active cancer patients treated at over 800 sites of care across 4 US census regions. Patient-level data includes both structured (diagnosis, demographics, laboratory values, biomarker information, drug orders, visits, etc.) and unstructured (physician notes, radiology, and pathology reports, etc.) sources. Data on death is drawn from structured or unstructured data fields in the EHR, and publicly available sources of mortality including the US Social Security Death Index, and commercial obituary data.[13]

Pfizer has contracted with Flatiron for a custom data extract containing information on patients with advanced melanoma who received treatment with BRAF- or MEK-inhibitor therapies. Patients meeting the eligibility criteria defined for this study will be obtained from this custom data extract as described in Section 8.2 and used in all analyses.

8.5. Study size

The number of patients eligible for the study will be determined in accordance with the sample selection conducted per the criteria described in Section 8.2.

8.6. Data management

Clean, patient-level datasets for COLUMBUS and Flatiron Health data will be generated for use throughout the study. This process will entail basic exploratory checks to ensure data integrity, cleaning and reformatting the raw data as needed, and creating variables for all key study measures. All data will be stored and maintained on a secure encrypted non-cloud-based server and accessed over a secure internal private wide area network. The data will be made accessible only to individuals working on the current study. No attempt will be made to identify individual patients, hospitals, or physicians. Analyses will be conducted using SAS version 9.4 and/or R version 4.1.0 or later.

8.7. Data analysis

8.7.1. Analysis of baseline characteristics

Patient baseline characteristics at or prior to the index visit will be summarized for all treatment groups. Patient characteristics to be summarized will be based on availability in both data sources and clinical input. A list of characteristics expected to be summarized is provided in **Table 1**.

Baseline characteristics will be summarized at the index date if measured at that time. In the Flatiron data, for baseline characteristics that are not measured at the index date, the closest available measure to the index date within a baseline period will be used. Informed by clinical input and considerations of data availability, the **baseline period** will be defined as a 3-month time window prior to and including the index date.

Patient baseline characteristics will be summarized descriptively using mean (with standard deviation) and median (with interquartile range) for continuous variables and count (with proportions) for categorical variables. Missingness for each baseline characteristic (at the index date or within the baseline period) will also be summarized.

8.7.2. Unadjusted comparison of OS between treatment groups

OS will be defined as described in Section 8.3. OS will be summarized for each treatment group (i.e., ENCO+BINI [pooled across COLUMBUS and Flatiron EHR], DAB+TRAM and VEM+COBI). An unadjusted comparison of OS across treatment groups will be conducted using Kaplan-Meier (KM) analyses. OS over time in these treatment groups will be plotted and compared using a log-rank test, with median survival time and survival proportions reported at selected time points (e.g., 6 months, 1 year, 2 years). Hazard ratios for OS comparing ENCO+BINI relative to DAB+TRAM and VEM+COBI will be estimated based on a univariable Cox proportion hazards model. The proportional hazards assumption will be assessed using tests of Schoenfeld residuals.[14]

8.7.3. Imputation of missing data on baseline characteristics

Previous analyses of the Flatiron data have found that there are moderate to large amounts of missing data on baseline characteristics such as ECOG performance score and LDH.[12] As analyses restricted to patients with non-missing data are highly likely to be biased, imputation of missing data on key baseline characteristics is needed to ensure that adjusted analyses of OS between the trial and RWD settings are based on all eligible patients.

In this study, multiple imputation by chained equations (MICE)[15] will be used to impute missing data on baseline characteristics. Briefly, the MICE method imputes data for a missing patient characteristic based on iterative regressions of observed data for that characteristic on observed and imputed values of other baseline characteristics. This process will be repeated for each

characteristic until stable estimates are obtained, and the entire procedure will be repeated so that multiple datasets with imputed values for baseline characteristics are created.

Baseline characteristics to be imputed will include ECOG performance score, LDH, and other clinical or demographic characteristics (e.g., race, BMI, etc.). Additional variables (e.g., age, sex, AJCC diagnosis, time from MM diagnosis to treatment initiation, time from initial diagnosis of melanoma to metastatic disease, number of organs at baseline, metastatic sites, treatments in the therapeutic setting, treatments in the adjuvant setting) will be considered for inclusion in the MICE procedure based on their relevance for adjustment and degree of missingness in the study sample. As recommended in the literature, the MICE approach will be used to create multiple datasets (e.g., 100 datasets) with imputed values, which will be used and combined in subsequent analyses.[15]

Missing data on baseline characteristics will be imputed for all treatment groups. Analyses of baseline characteristics described in Section 8.7.1 will be repeated for each imputed dataset, and then summarized across all imputed datasets.

8.7.4. Adjusted comparison of OS between treatment groups

Finally, an adjusted comparison of OS across treatment groups (i.e., ENCO+BINI [pooled across COLUMBUS and Flatiron EHR], DAB+TRAM and VEM+COBI) will be conducted. Hazard ratios will be estimated based on a multivariable Cox proportional hazard model, adjusting for key baseline characteristics known or expected to be related to OS in metastatic melanoma (e.g., age, sex, race, BMI, ECOG, LDH, time from initial melanoma diagnosis to metastatic disease, time from metastatic diagnosis to treatment initiation, treatment experience in the therapeutic setting, prior IO/chemotherapy in the adjuvant setting, prior surgery in the adjuvant setting). Specific adjustment factors listed here may be revised based on expert clinical input.

The adjusted analyses will be conducted in each of the datasets with imputed baseline characteristic values in turn. Log-hazard ratios for OS comparing treatment with ENCO+BINI relative to DAB+TRAM and VEM+COBI each imputed dataset will be obtained, and summary HRs obtained by pooling results across all imputed datasets will be generated using Rubin's rules.[16]

8.7.5. Exploratory analyses of PFS

Analyses assessing PFS will also be explored. PFS will be defined as described in Section 8.3. PFS will be summarized for all treatment groups.

Suitability of comparative analyses of PFS between treatment groups will be determined following additional data exploration to characterize number and frequency of assessments of PFS available in these settings, and discussion of comparability of the assessment of disease progression in RWD vs CTD. If analyses of PFS are deemed suitable based on these evaluations,

unadjusted and adjusted comparisons of PFS will be conducted using the methods described in Sections 8.7.2 and 8.7.4.

8.8. Quality control

Best practice guidelines will be followed to ensure project quality, including structured organization of project materials (e.g., data extracts, statistical software programs, output tables) and standard internal audit process. The audit process both confirms the validity of the analytical approach and ensures that all programs and results are accurate.

8.9. Strengths and limitations of the research methods

The strengths of this study include:

- Key inclusion criteria with respect to diagnosis, disease stage, age, BRAFV600 mutation and ECOG status in the COLUMBUS trial will be applied to the Flatiron RWD to the extent possible to obtain a comparable group of patients across both settings
- Adjustment will be made for multiple baseline characteristics to mitigate bias due to potential differences in these characteristics across the treatment groups
- Concerns about differences in outcome assessment across trial and RWD settings are mitigated for OS given the availability of a real-world mortality endpoint in the Flatiron RWD that has high sensitivity, specificity, positive predictive values, negative predictive values and agreement when compared against the National Death Index (NDI), the gold-standard source for mortality data in the US.[17]

The limitations of this study include the following:

- Application of the COLUMBUS trial inclusion criterion requiring at least 1 measurable lesion based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria will not be implemented due to absence in Flatiron EHR of systematic radiographic imaging to assess tumor response as required by RECIST.
- While adjustment will be made for available baseline characteristics across treatment groups, differences due to factors that were not adjusted for may still contribute to observed differences in OS between settings. For instance, data on number and sites of metastases, while systematically collected in the COLUMBUS trial, can only be derived based on ICD codes in Flatiron EHR. Based on clinical input, data on number and sites of metastases will very likely be underestimated in the Flatiron EHR, and not comparable to the corresponding data from COLUMBUS, precluding adjustment for these variables.

- The analysis conducted here is analogous to an 'intent-to-treat' perspective, and therefore will not account for potential differences in adherence and post-baseline treatments between trial and real-world settings.
- The COLUMBUS trial was a multi-national trial that recruited patients from 160+ sites in 28 countries, and therefore covers a broader range of geographies than the US-based Flatiron RWD; differences in background care across geographies and care settings may contribute to differences in outcomes between the CTD and RWD.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

9.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

9.3. Institutional review board (IRB)/Independent ethics committee (IEC)

This retrospective database analysis does not involve the collection, use, or transmittal of individually identifiable data. As such, the study falls within the definition of exempt research under 45 CFR 46.104(d)(4)(ii) and IRB approval is not required. Because the dataset does not include individually identifiable health information under 45 CFR 164.514, Health Insurance Portability and Accountability Act (HIPAA) requirements do not apply.

9.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and the Good Research for Comparative Effectiveness (GRACE) Principles.[18-20]

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves electronic health records data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator, Analysis Group, is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Based on the analysis results and discussions with Pfizer, an abstract and/or manuscript may be prepared. If feasible, an abstract will be submitted to the Society for Melanoma Research (SMR) 2023 conference. A study report summarizing the background, objectives, methods, results, and conclusion of the study will be prepared.

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13. LIST OF TABLES

Table	Description
Table 1. Key exposures, outcomes, and patient baseline characteristics in the treatment groups	Table summarizing exposure, outcome, and patient baseline characteristics that will be evaluated within the study.
Table 2. Kaplan-Meier analyses comparing OS between treatment groups	Table summarizing KM analyses from the ENCO+BINI, DAB+TRAM and VEM+COBI treatment groups
Table 3. Unadjusted and adjusted hazard ratios comparing OS between treatment groups	Table summarizing hazard ratios comparing ENCO+BINI to the DAB+TRAM and VEM+COBI treatment groups

14. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.

APPENDIX: TABLE SHELLS

Appendix Table 1: Baseline patient characteristics, by treatment group

	ENCO+BINI	VEM+COBI	DAB+TRAM
	N =	N =	N =
Demographic Characteristics			
Age at baseline (years)			
Mean (SD)			
Median (IQR)			
Sex, n (%)			
Female			
Male			
Missing, n (%)			
Race, n (%)			
White/Caucasian			
Black/African American			
Asian			
Native American or Pacific Islander			
Other			
Missing			
BMI (kg/m^2)			
Mean (SD)			
Median (IQR)			
Missing, n (%)			
Year of treatment initiation, n (%)			
2014			
2015			
2016			
2017			
2018			
2019			
2020			
2021			
Region, n (%)			
North America			
Europe			
Australia			
Other			
Missing			
Disease-Related Characteristics			
Number of organs involved (metastatic sites) at baseline, n (%)			
1			
2			
≥3			
Missing			
Lung metastasis, n (%)			
No			
Yes			

Missing			
Liver metastasis, n (%)			
No			
Yes			
Missing			
Other metastasis, n (%)			
No			
Yes			
Missing			
Time from initial melanoma diagnosis to metastatic disease (months)			
Mean (SD)			
Median (IQR)			
Missing, n (%)			
Time from metastatic melanoma diagnosis to treatment initiation (months)			
Mean (SD)			
Median (IQR)			
Missing, n (%)			
BRAF mutation status, n (%)			
V600E			
V600K			
ECOG performance status, n (%)			
0			
1			
≥2			
Missing			
AJCC stage at initial melanoma diagnosis, n (%)			
0			
I			
II			
III			
IV			
Unknown			
Missing			
AJCC stage at treatment initiation, n (%)			
Stage IIIC			
Stage IV			
Missing			
LDH categories, n (%)			
≤ ULN			
> ULN			
Missing			
Treatment-Related Characteristics			
Treatment experience in the therapeutic setting, n (%)			
Treatment naive			
Prior 1L IO therapy			
Prior systemic therapies in the adjuvant setting, n (%)			
Yes			

No			
Prior IO or chemotherapy in the adjuvant setting, n (%)			
Yes			
No			
Prior surgery in the adjuvant setting, n (%)			
Yes			
No			
Number of LOTs after targeted therapy, n (%)			
0			
1			
≥2			
Missing			

Appendix Table 2: Kaplan-Meier analyses comparing OS between treatment groups

	ENCO+BINI	VEM+COBI	DAB+TRAM
	N =	N =	N =
Summary of deaths, censoring and median survival			
Death, n (%)			
Censored, n (%)			
Median follow-up (95% CI)			
Median OS (95% CI)			
Kaplan-Meier based estimates of % of patients remaining alive at different time points			
6 Months			
12 Months			
18 Months			
24 Months			
30 Months			
36 Months			

Appendix Table 3: Unadjusted and adjusted hazard ratios comparing OS between treatment groups

Results from adjusted models in Appendix Table 3 will be based on multiple imputation via multivariate imputation by chained equations. Expected adjustment factors are listed below; specific functional forms/categorization of adjustment factors will be based on the data.

	Unadjusted model	Adjusted model
	HR (95% CI)	HR (95% CI)
Treatment group		
DAB+TRAM vs. ENCO+BINI (ref)		

VEM+COBI vs. ENCO+BINI (ref)		
Adjustment factors		
Age (years)		
Male vs female		
Asian race vs. White		
Other race vs. White		
Unknown race vs. White		
BMI (kg/m^2)		
ECOG (1 vs. 0)		
LDH (>ULN vs. ≤ULN)		
Treatment naïve vs. prior 1L IO treatment		
Prior IO/chemotherapy (Yes vs. No)		
Prior surgery (Yes vs. No)		
Time from initial melanoma diagnosis to metastatic disease		
Time from metastatic disease to treatment initiation		