NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	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
Protocol number	C4221035
Protocol version identifier	1.0
Date	24 February 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) in the Phase 3 COLUMBUS clinical trial versus in real-world data (RWD) from Flatiron Health. This study will help contextualize real-world clinical effectiveness of ENCO+BINI and assess the suitability of pooling clinical trial and RWD on ENCO+BINI from these two sources for use in future real-world studies.
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	first-line
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
ECOG	European Cooperative Oncology Group
EHR	electronic health record
ENCO+BINI	Encorafenib + Binimetinib
ESMO	European Society of Medical Oncology
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-CM	International Classification of Diseases 9th Revision Clinical Modification
ICD-10-CM	International Classification of Diseases 10th Revision Clinical Modification
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
MAPK	mitogen-activated protein kinase

MICE	multivariate 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
SAS	Statistical Analysis Software
SSDI	Social Security Death Index
TT	targeted therapy
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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

None.

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	23 January 2023
Development of study protocol/statistical analysis plan	24 February 2023
Completion of statistical analyses	21 April 2023
Abstract submission to European Society of Medical Oncology (ESMO) 2023	10 May 2023
Final study report	02 June 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) 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]

These is increasing interest in using real-world data (RWD) to evaluate effectiveness of encorafenib plus binimetinib (ENCO+BINI). One important use of the emerging RWD for ENCO+BINI is to assess how clinical effectiveness in real-world practice compares to efficacy observed in clinical trials. Clinical trial data (CTD) and real-world data on ENCO+BINI may also be pooled to provide a larger sample size for future evidence generation studies, provided outcomes are sufficiently consistent between CTD and RWD settings.

However, use of RWD presents important challenges.[11] In general, differences in baseline characteristics between patients enrolled in clinical trials and patients receiving treatment in RWD settings can result in bias. While this concern can be mitigated with adequate statistical adjustment, missing data in RWD sources on key confounders of outcomes may also hamper ability to adjust for such baseline differences. Suitability of RWD for specific uses therefore needs to be assessed on a case-by-case basis considering details of the RWD data source and outcomes of interest.

In this study, we will compare overall survival (OS) between patients receiving ENCO+BINI in the Phase 3 COLUMBUS trial versus in the Flatiron Health Electronic Health Records (EHR) database. Baseline profiles of patients will also be compared across these settings to characterize differences in patients receiving ENCO+BINI and adjustments will be made for differences in baseline factors associated with OS. Missingness for key baseline characteristics will be addressed using a multiple imputation approach that has been validated for Flatiron Health EHR data in metastatic melanoma.[12] This study will help contextualize real-world clinical effectiveness of ENCO+BINI, and assess the

suitability of pooling CTD and RWD on ENCO+BINI from these 2 sources for use in future RWE studies.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective

To compare OS between patients with metastatic BRAFV600-mutant melanoma initiating ENCO+BINI in the COLUMBUS Phase 3 trial versus Flatiron Health real-world practice data.

Exploratory Objective

To compare progression-free survival (PFS) between patients with metastatic melanoma initiating ENCO+BINI in the COLUMBUS Phase 3 trial versus Flatiron Health real-world practice data.

This objective is designated as exploratory in this study as, unlike for OS, differences in assessment of PFS between trial and 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 data exploration to characterize number and frequency of assessments of PFS available in RWD vs in CTD, and discussion of comparability of the assessment of disease progression in RWD vs CTD.

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 in the COLUMBUS clinical trial versus real-world practice data extracted from the Flatiron Health EHR database. Comparisons will be adjusted for differences in baseline characteristics across ENCO+BINI patients in these settings, and account for missing data on adjustment factors in the Flatiron Health EHR database. PFS will also be investigated as an exploratory endpoint, subject to comparability of outcome assessment between these 2 settings.

8.2. Setting

Patients with BRAFV600-mutant metastatic melanoma initiating treatment with ENCO+BINI will be included from the COLUMBUS clinical trial and from RWD extracted from the Flatiron Health EHR database.

8.2.1. Inclusion criteria

Inclusion criteria are provided separately for the 2 data sources below. 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

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, and
- With available data on mortality

Pfizer has contracted with Flatiron for a custom data extract containing information on patients with advanced melanoma. 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 2 data sources.

Eligibility criteria applied to the Flatiron custom data extracted received by Pfizer included:

- Diagnosis of melanoma (International Classification of Diseases 9th or 10th Revision Clinical Modification - ICD-9-CM: 172.X; ICD-10-CM: C43.x) and secondary malignancy or metastasis (ICD-9-CM: 196.x, 197.x, 198.x; ICD-10-CM: C77.x, C78.x, C79.x).
- Confirmed BRAF V600E/V600K activating mutation reported in the data based on laboratory or genetic analysis results.
- At least 1 order or administration of ENCO+BINI treatment after the diagnosis of metastatic melanoma and within the available data cut period (01 January 2011 to 01 January 2022)
- Order or administration of ENCO+BINI treatment at least 3 months prior to the data cutoff date (e.g., 01 October 2022)

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 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); the date of the first such order or administration of ENCO+BINI will be taken as the **index date.**
- At least 18 years of age at the index date
- Treatment-naive or had previous 1L IO at index date, based on review of medication orders or administration prior to the index date.
- ECOG status of 0 or 1 at the index date

- With available data on mortality

8.2.2. Exclusion criteria

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

- Patients without information on mortality
- 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 or concurrent uveal or mucosal melanoma, basal cell or squamous cell carcinoma (as per trial inclusion criteria); this exclusion will also be applied to RWD patients
- 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 in the COLUMBUS trial data and Flatiron Health EHR data

Variable	Role	Data source(s)	Operational definition
ENCO+BINI Cohort (Columbus or Flatiron)	Exposure	Columbus trial data; Flatiron EHR	Binary variable indicating whether ENCO+BINI patients are derived from the Columbus trial data vs. Flatiron EHR population
OS	Primary Outcome	Columbus trial data, Flatiron EHR	In 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, 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 EHR	In 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, 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 end of the study period (e.g., 01 January 2022), whichever occurs first
Age at index	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Patient age; defined at the time of study randomization for Columbus trial data and treatment initiation for Flatiron EHR
Sex	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Male, Female, Intersex, and Unknown/Missing
Race	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Asian, Black, White, Other/Multirace, and Unknown/Missing
Ethnicity	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Hispanic/Latino, Non-Hispanic/Latino, and 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 Columbus trial data and Flatiron EHR
Disease stage at diagnosis	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	IIIB, IIIC, IVM1a, IVM1b, or IVM1c; defined at metastatic melanoma diagnosis for both Columbus trial data and 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 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 diagnosis to treatment initiation	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Duration (in months) from metastatic melanoma diagnosis to the initiation of ENCO+BINI treatment
Year of ENCO+BINI Treatment	Baseline Characteristic	Columbus trial data; Flatiron EHR	Calendar year when ENCO+BINI treatment was initiated
Prior Systemic Therapy	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	Binary variable indicating whether patients previously received systemic therapy (e.g., prior surgery, radiotherapy, immunotherapy, or chemotherapy) before ENCO+BINI
Prior Surgery	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	A binary variable indicating whether patients previously used surgery to reduce/remove tumors as a form of treatment
Prior Radiotherapy	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	A binary variable indicating whether patients underwent radiotherapy among those receiving prior systemic therapy

Prior Immunotherapy	Baseline Characteristic / Potential Confounder	Columbus trial data; Flatiron EHR	A binary variable indicating whether patients underwent immunotherapy among those receiving prior systemic therapy

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 ENCO+BINI. A cohort of ENCO+BINI 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 ENCO+BINI groups from both data sources. 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. The **baseline period** will be defined as a time window ranging before and potentially shortly after (e.g., ~3 months prior to ~1 month after) the index date. Different durations of the time window will be considered to maximize data availability on baseline characteristics; specific durations will be selected based on data availability and guided by clinical input.

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 ENCO+BINI cohorts in Columbus trial versus in Flatiron RWD

OS will be summarized for ENCO+BINI cohorts in the Columbus trial and Flatiron RWD. In the Columbus trial, OS will be defined as the time from the date of randomization to the date of death due to any cause; if death was not observed, patients will be censored at the date of last contact or the data analysis cutoff date whichever occurs first. In Flatiron RWD, OS 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.

An unadjusted comparison of OS with ENCO+BINI in the Columbus trial versus in Flatiron RWD will be conducted using Kaplan-Meier (KM) analyses. OS over time in these 2 cohorts 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). A hazard ratio for OS comparing ENCO+BINI in Columbus trial versus in Flatiron RWD 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 in Flatiron RWD

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, multivariate 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 disease stage. Additional variables 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]

Analyses of baseline characteristics in RWD described in Section 8.7.1 will be repeated for each imputed dataset, and then summarized across all imputed datasets.

8.7.4. Adjusted analysis of OS between ENCO+BINI cohorts in Columbus trial versus in Flatiron RWD

Finally, an adjusted comparison of OS between ENCO+BINI cohorts in the Columbus trial and Flatiron RWD 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, body mass index, ECOG performance score, disease stage, LDH, time from diagnosis to metastatic disease, time from metastatic diagnosis to ENCO+BINI initiation and use of prior therapies). Specific adjustment factors listed here may be revised based on expert clinical input.

The adjusted analyses will be conducted using the Columbus trial dataset and each of the RWD datasets with imputed baseline characteristic values in turn. Log-hazard ratios for the difference in OS with ENCO+BINI between the Columbus trial and each imputed dataset will be obtained, and a summary HR 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 summarized for ENCO+BINI cohorts in the Columbus trial and in Flatiron RWD. In CTD, PFS will be 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 cutoff date, PFS will be censored at the date of the last adequate tumor assessment. In RWD, PFS 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 end of the follow-up period, whichever occurs first.

Suitability of comparative analyses of PFS between ENCO+BINI cohorts in the Columbus versus in Flatiron RWD 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 the following:

- 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 ENCO+BINI patients across both settings
- Adjustment can be made for multiple baseline characteristics to mitigate bias due to potential differences in these characteristics across the ENCO+BINI cohorts in the Columbus trial versus the Flatiron RWD
- 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, PPV, NPD 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 observed differences in key baseline characteristics, differences due to factors that were not measured or not available in both Columbus and Flatiron RWD (e.g., sites of metastases and number of metastases) may still contribute to observed differences in OS between settings.
- 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 trial and RWD
- While comparability of OS outcomes for ENCO+BINI cohorts in the Columbus trial and in Flatiron RWD may be demonstrated here, suitability of pooling data across other sources and for analyses of other outcomes will still need to be evaluated on a case-by-case basis

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, 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 European Society of Medical Oncology (ESMO) 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 COLUMBUS trial data and Flatiron Health EHR data	Table summarizing exposure, outcome, and patient baseline characteristics that will be evaluated within the study.
Table 2. Kaplan-Meier analyses comparing OS between ENCO+BINI cohorts in Columbus trial and Flatiron RWD	Table summarizing KM analyses from the CTD and RWD ENCO+BINI cohorts
Table 3. Unadjusted and adjusted hazard ratios comparing OS between ENCO+BINI cohorts in Columbus trial and Flatiron RWD	Table summarizing hazard ratios comparing CTD and RWD ENCO+BINI cohorts

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 for ENCO+BINI cohorts in Columbus trial versus in Flatiron RWD

Appendix Table 1 as illustrated below will be generated both before and after imputation of missing data.

	Columbus trial	Flatiron RWD
	ENCO+BINI	ENCO+BINI
	N =	N =
Demographic Characteristics		
Age (years)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Sex, n (%)		
Female	XX (XX.X)	XX (XX.X)
Male	XX (XX.X)	XX (XX.X)
Missing, n (%)	XX (XX.X)	XX (XX.X)
Race, n (%)		
White/Caucasian	XX (XX.X)	XX (XX.X)
Black/African American	XX (XX.X)	XX (XX.X)
Asian	XX (XX.X)	XX (XX.X)
Native American or Pacific Islander	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
Ethnicity, n (%)		
Hispanic/Latino	XX (XX.X)	XX (XX.X)
Not Hispanic/Latino	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
BMI (kg/m^2)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Missing, n (%)	XX (XX.X)	XX (XX.X)
Year of treatment initiation, n (%)		
2011	XX (XX.X)	XX (XX.X)
2012	XX (XX.X)	XX (XX.X)
2013	XX (XX.X)	XX (XX.X)
2014	XX (XX.X)	XX (XX.X)
2015	XX (XX.X)	XX (XX.X)
2016	XX (XX.X)	XX (XX.X)
2017	XX (XX.X)	XX (XX.X)
2018	XX (XX.X)	XX (XX.X)
2019	XX (XX.X)	XX (XX.X)
2020	XX (XX.X)	XX (XX.X)
2021	XX (XX.X)	XX (XX.X)
2022	XX (XX.X)	XX (XX.X)
Geographic location, n (%)		
North America	XX (XX.X)	XX (XX.X)

Europe	XX (XX.X)	XX (XX.X)
Australia	XX (XX.X)	XX (XX.X)
Other	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
Disease-Related Characteristics		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Missing, n (%)	XX (XX.X)	XX (XX.X)
Time from metastatic melanoma diagnosis to treatment initiation (months)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Missing, n (%)	XX (XX.X)	XX (XX.X)
BRAF+ mutation		
V600E	XX (XX.X)	XX (XX.X)
V600K	XX (XX.X)	XX (XX.X)
ECOG performance status, n (%)		
0	XX (XX.X)	XX (XX.X)
1	XX (XX.X)	XX (XX.X)
≥2	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
AJCC stage, n (%)		
Stage IIIB	XX (XX.X)	XX (XX.X)
Stage IIIC	XX (XX.X)	XX (XX.X)
Stage IV	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
LDH (U/L)		
Mean (SD)	XX.X (XX.X)	XX.X (XX.X)
Median (IQR)	XX.X (XX.X, XX.X)	XX.X (XX.X, XX.X)
Missing, n (%)	XX (XX.X)	XX (XX.X)
LDH Level, n (%)		
Low	XX (XX.X)	XX (XX.X)
Normal	XX (XX.X)	XX (XX.X)
High	XX (XX.X)	XX (XX.X)
Missing	XX (XX.X)	XX (XX.X)
Treatment-Related Characteristics		
Prior therapies, n (%)		
Treatment naive	XX (XX.X)	XX (XX.X)
Disease progression after 1L IO	XX (XX.X)	XX (XX.X)
Prior systemic therapies, n (%)		
Any therapy	XX (XX.X)	XX (XX.X)
Medication	XX (XX.X)	XX (XX.X)
Surgery	XX (XX.X)	XX (XX.X)
Radiotherapy	XX (XX.X)	XX (XX.X)

Appendix Table 2: Kaplan-Meier analyses comparing OS between ENCO+BINI cohorts in Columbus trial and Flatiron RWD

	Columbus Trial	Flatiron RWD
	ENCO-BINI	ENCO-BINI
	N =	N =
Summary of deaths, censoring and median survival		
Death, n (%)	XX (XX.X)	XX (XX.X)
Censored, n (%)	XX (XX.X)	XX (XX.X)
Median OS (95% CI)	XX (XX, XX)	XX (XX, XX)
Kaplan-Meier based estimates of % of patients remaining alive at different time points		
6 Months	XX	XX
12 Months	XX	XX
18 Months	XX	XX
24 Months	XX	XX
30 Months	XX	XX
36 Months	XX	XX

Appendix Table 3: Unadjusted and adjusted hazard ratios comparing OS between ENCO+BINI cohorts in Columbus trial and Flatiron RWD

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)
Exposure variable		
ENCO+BINI in Columbus trial (ref. ENCO+BINI in Flatiron RWD)	X.XX (X.XX, X.XX)	X.XX (X.XX, X.XX)
Adjustment factors	-	X.XX (X.XX, X.XX)
Age	-	X.XX (X.XX, X.XX)
Male vs female	-	X.XX (X.XX, X.XX)
Race	-	X.XX (X.XX, X.XX)
BMI		
Disease stage	-	X.XX (X.XX, X.XX)
ECOG	-	X.XX (X.XX, X.XX)
LDH	-	X.XX (X.XX, X.XX)
Time from first diagnosis to metastatic disease…		X.XX (X.XX, X.XX)
Time from metastatic disease to treatment initiation		
Use of prior therapies		X.XX (X.XX, X.XX)