NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-World Treatment Patterns and Clinical Outcomes of BRAF V600-Mutant Metastatic Melanoma Patients Treated at Academic Oncology Centers in the United States
Protocol number	C4221039
Protocol version identifier	2.0
Date	29-August-2025
EU Post Authorization Study (PAS) register number	EUPAS1000000307
Active substance	Encorafenib (L01EC03) plus Binimetinib (L01EE03)
Medicinal product	Braftovi® plus Mektovi®
Research question and objectives	The overarching aim of this study is to describe the real-world characteristics, treatment patterns, and clinical outcomes of patients with BRAF V600-mutant metastatic melanoma (MM) presenting for care at academic oncology centers in the United States. **Primary Objectives** 1. Describe the real-world treatment patterns (i.e., MM treatments, treatment interruptions, reasons for treatment interruptions, treatment discontinuations, reasons for treatment discontinuations, treatment switch, time to treatment discontinuation [TTD], time to treatment switch [TTS], time to next treatment or death [TTNTD]) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences (as determined with clinical input) 2. Describe the baseline demographic and clinical characteristics of patients with BRAF V600-mutant MM,

	overall and for specific treatment regimens, classes, or sequences **Exploratory Objectives** 1. Describe the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences 2. Compare the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM treated with specific treatment regimens, classes, or sequences
Country(ies) of study	United States
Authors	Redacted

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
BMI	Body mass index
BRAF	B-raf proto-oncogene
CI	Confidence interval
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMR	Electronic medical record
HR	Hazard ratio
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IL-2	Interleukin-2
IO	Immunotherapy
IQR	Interquartile range
IRB	Institutional review board
Kg	Kilogram
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LOT	Line of therapy

MEK	Mitogen-activated protein kinase
Redacted	[redacted]
MM	Metastatic melanoma
NI	Non-interventional
NR	Non-response
NSAID	Nonsteroidal anti-inflammatory drug
OS	Overall survival
PD	Progessive disease
PFS	Progression-free survival
RCT	Randomized clinical trial
RECIST	Response Evaluation Criteria in Solid Tumors
RPDR	Research patient data registry
SAP	Statistical analysis plan
STD DEV	Standard deviation
SOC	Standard of care
T-VEC	Talimogene laherparepvec
TT	Targeted therapy
TTD	Time to treatment discontinuation
TTNTD	Time to next treatment or death
TTS	Time to treatment switch
US	United States
1L	First-line

2L	Second-line
3L	Third-line

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
Principal Investigators			
Redacted			
Other Project Participants			
Redacted			

4. ABSTRACT

Title	Real-World Treatment Patterns and Clinical Outcomes of BRAF V600-Mutant Metastatic Melanoma Patients Treated at Academic Oncology Centers in the United States Version 2.0 August 29, 2025 Author: Redacted
Rationale and Background	Encorafenib + binimetinib, a targeted therapy (TT) regimen, was approved by the United States (US) Food and Drug Administration (FDA) in 2018 for treatment of B-raf proto-oncogene (BRAF) V600-mutant metastatic melanoma (MM). Current standard of care (SOC) for this population is to position immunotherapy (IO)-based regimens in first-line (1L) followed by TT regimens in 2L, given recent literature suggesting better outcomes with this treatment sequencing strategy. Nevertheless, many patients progress on 1L IO therapy and experience high-grade toxicity. Given the evolving clinical practice recommendations for BRAF V600-mutant MM, a comprehensive overview of the real-world patient characteristics, treatment patterns, and clinical outcomes of patients with BRAF V600-mutant MM is needed to shed light on present unmet needs and the potential value of encorafenib + binimetinib for addressing this need.
Research Question and Objectives	The overarching aim of this study is to describe the real-world characteristics, treatment patterns, and clinical outcomes of patients with BRAF V600-mutant MM presenting for care at academic oncology centers in the US from January 1, 2018 to June 30, 2024 (or the most recent date of data availability). **Primary Objectives** 1. Describe the real-world treatment patterns (i.e., MM treatments, treatment interruptions, reasons for treatment interruptions, treatment discontinuations, reasons for treatment discontinuations, treatment switch, time to treatment discontinuation [TTD], time to treatment switch [TTS], time to next treatment or death [TTNTD]) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences (as determined with clinical input)

	2. Describe the baseline demographic and clinical characteristics of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences **Exploratory Objectives** 1. Describe the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences 2. Compare the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM treated with specific treatment regimens, classes, or sequences
Study Design	A retrospective non-interventional (NI) longitudinal cohort design
Population	This study will be conducted in patients with BRAF V600-mutant MM receiving treatment with SOC regimens of interest at academic oncology centers contributing to the Redacted Research Patient Data Registry (RPDR) from January 1, 2018 to June30, 2024 (or most recent date of data availability).
Variables	The exposure is not applicable. Outcomes include treatment patterns (i.e., treatment regimens, number of LOTs received, treatment interruptions, reasons for treatment interruptions, treatment switch, TTS, TTNTD, treatment discontinuation, TTD, reasons for treatment discontinuation, treatment sequences), and clinical outcomes (i.e., PFS, and OS). Key covariates include demographics (i.e., age at index, sex, race), clinical characteristics (e.g., BMI, disease stage at MM diagnosis), comorbidities (e.g., myocardial infarction, diabetes, autoimmune disorders), prior treatments (i.e., radiation, surgery, adjuvant therapy, neoadjuvant therapy, local therapy), and medications (i.e., antibiotics, corticosteroids, opioids, NSAIDs, acid reducing agents)
Data Sources	De-identified Redacted RPDR electronic medical record (EMR) data and abstracted chart review data
Study Size	The planned sample size for the present study is 390 patients. As all statistical analyses for the primary objectives are descriptive in nature and no hypotheses are being tested, no formal sample size computations will be performed.

Data analysis	Continuous variables will be described using means, standard deviations, medians, and interquartile ranges. Categorical variables will be described using frequencies with proportions. Time-to-event outcomes will be described using the Kaplan-Meier method. In exploratory comparative analyses, PFS and OS will be compared between patients with BRAF V600-mutant MM treated with specific treatment regimens, classes, or sequences using univariable and multivariable Cox proportional hazards models.
Milestones	1. Redacted IRB submission and approval: 26 April 2024 2. Development of case report form (CRF): 31 May 2024 3. Development of electronic case report form (eCRF): 28 June 2024 4. Initiation of first pilot test: 4 December 2024 5. Completion of first pilot test: 10 December 2024 6. Initiation of second pilot test: 1 May 2025 7. Completion of second pilot test: 26 June 2025 8. Initiation of data collection: 1 October 2025 9. Completion of data collection: 30 January 2026 10. Completion of final analyses: 30 April 2026 11. Final study report: 30 June 2026

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	August 29 2025	Substantial	Section 6	The study milestones were updated.	As a result of administrative delays with Redacted, the study timelines have been delayed.
			Section 8	The secondary objective was removed.	Based on feedback received from Redacted and the nurse abstractors during the pilot test, these revisions were implemented to mitigate abstractor burden. The secondary objective to describe clinician-assessed tumor response was determined to be very complex to abstract, with multiple terms used to denote response (e.g., response, stable disease, mixed response, complete response, partial response, progressive disease).
			Section 9	The number of eligible patients for chart abstraction was reduced from 500 to 390.	The reduction in the eligible sample size was due to data limitations identified following the initial screening of 592 patients using NLP. Of those, only 390 met the criteria for both metastatic status and a BRAF V600 mutation.
				The baseline period was expanded from 6 months to 12 months following the index date.	This expansion was intended to reduce the impact of further sample size loss due to patients having a confirmed metastatic melanoma diagnosis earlier than 6 months prior to the initiation of 1L treatment, who meet all other eligibility criteria.
				The study exclusion criteria were updated to exclude patients who enrolled in a clinical trial during the observation period.	This exclusion criteria is intended to avoid bias in downstream comparative analyses. Clinical trial enrollment status is not available in the structured data, therefore we are not able to identify patients who enrolled in a clinical trial prior reviewing their charts. Additionally, the date of clinical trial enrollment is also not available, so we are unable to censor patients at enrollment date.
				The following baseline characteristic variables were removed: BRAF mutation subtype, tumor size, select sites of metastases (i.e., skin, lung, bone, intestine).	These variables were excluded to mitigate abstractor burden.

6. MILESTONES

Milestone	Planned Date
Redacted IRB submission and approval	26 April 2024
Development of case report form (CRF)	31 May 2024
Development of electronic case report form (eCRF)	28 June 2024
Initiation of first pilot test	4 December 2024
Completion of first pilot test	10 December 2024
Initiation of second pilot test	1 May 2025
Completion of second pilot test	26 June 2025
Initiation of data collection	1 October 2025
Completion of data collection	30 January 2026
Completion of final analyses	30 April 2026
Final study report	30 June 2026

7. RATIONALE AND BACKGROUND

Melanoma is the fifth most common cancer and the leading cause of cancer-related mortality in the United States (US). In 2023, there were an estimated 97,610 incident melanoma cases in the US. Approximately 78% of patients with melanoma present with localized disease, 10% with regional spread to lymph nodes, and 5% with metastatic melanoma (MM). While the 5-year relative survival rate for melanoma is 93.5%, the prognosis for MM is poor, with a 5-year relative survival rate of 34% and median overall survival (OS) ranging from 8.7 to 17.9 months.[1-3]

Approximately 40-60% of patients with MM present with B-raf proto-oncogene (BRAF) V600 mutations.[4, 5] BRAF V600 mutations hyperactivate the BRAF protein and cause dysregulation of the mitogen-activated protein kinase (MEK) pathway, promoting uncontrolled cellular proliferation.[6, 7] In the past decade, the treatment landscape for BRAF V600-mutant MM has been revolutionized by the advent of targeted therapy (TT) regimens that inhibit the mutated BRAF protein within the MEK signaling pathway and immunotherapy (IO)-based regimens that promote antitumor activity.[8-13] The approval of these therapies has led to a dramatic increase in the 5-year OS rate for BRAF V600-mutant MM, from <5% to 50%. Monotherapy or a combination of TT or IO-based regimens recommended for the treatment of BRAF V600-mutant MM fall mainly into three categories:[13]

(a) ***Combination BRAF/MEK inhibitors (i.e., TT regimens):*** encorafenib + binimetinib, dabrafenib + trametinib, vemurafenib + cobimetinib

(b) ***Monotherapy or combination PD(L)-1 checkpoint inhibitor (i.e., IO regimens):*** nivolumab, nivolumab + ipilimumab, nivolumab + relatlimab, pembrolizumab, pembrolizumab + ipilimumab

(c) ***Combination BRAF/MEK inhibitors and PD(L)-1 checkpoint inhibitor (i.e., combination TT+IO regimens):*** cobimetinib + vemurafenib + atezolizumab, dabrafenib + trametinib + pembrolizumab.

Encorafenib + binimetinib, a combination BRAF/MEK inhibitors, was approved by the US Food and Drug Administration on June 27, 2018 for treatment of unresectable BRAF V600E/K-mutant melanoma or BRAF V600E/K-mutant MM.[14, 15] Approval of encorafenib + binimetinib was based on findings from COLUMBUS, a phase 3 randomized clinical trial (RCT), wherein encorafenib + binimetinib demonstrated superior progression-free survival (PFS) compared with vemurafenib alone (median PFS: 14.9 months vs 7.3 months; hazard ratio [HR]: 0.54, $p<0.0001$).[16] Although the standard of care (SOC) for BRAF V600-mutant MM consists of first-line (1L) treatment with IO or TT regimens,[13, 17] recent clinical trials investigating the optimal treatment sequence in BRAF V600-mutant MM have demonstrated an OS benefit for treatment with IO followed by TT, which has led to IO therapy being positioned as the preferred 1L regimen for this population.[13, 18, 19] Nevertheless, several questions remain unanswered. First, given the appreciable proportion of patients who

progress on 1L IO regimens, a comprehensive understanding of the efficacy of IO and TT regimens in second-line (2L)+ settings for BRAF V600-mutant MM is critical. Second, as approximately 40% of patients with BRAF V600-mutant MM treated with 1L IO regimens will have refractory disease and more than 50% of patients treated with some IO regimens (i.e., nivolumab + ipilimumab) will experience high-grade toxicity, additional research on factors associated with resistance to 1L IO regimens and the benefits of 1L TT regimens for this resistant subgroup is needed to shed light on pathways for improving prognosis in this population.[20]

Given the evolving clinical practice recommendations for BRAF V600-mutant MM, a comprehensive understanding of the real-world patient characteristics, treatment patterns, and clinical outcomes of patients with BRAF V600-mutant MM is needed to elucidate on present unmet needs and the potential value of encorafenib + binimetinib for addressing this need. This real-world study will describe and compare the treatment patterns and clinical outcomes of patients with BRAF V600-mutant MM receiving SOC regimens at academic oncology centers in the US.

8. RESEARCH QUESTION AND OBJECTIVES

The overarching aim of this study is to describe the real-world characteristics, treatment patterns, and clinical outcomes of patients with BRAF V600-mutant MM presenting for care at academic oncology centers in the US from January 1, 2018 to June 30, 2024 (or the most recent date of data availability).

8.1. Primary Objectives

1. Describe the real-world treatment patterns (i.e., MM treatments, treatment interruptions, reasons for treatment interruptions, treatment discontinuations, reasons for treatment discontinuations, treatment switch, time to treatment discontinuation [TTD], time to treatment switch [TTS], time to next treatment or death [TTNTD]) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences (as determined with clinical input)

2. Describe the baseline demographic and clinical characteristics of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences

8.2. Exploratory Objectives

1. Describe the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM, overall and for specific treatment regimens, classes, or sequences

2. Compare the clinical outcomes (i.e., PFS, OS) of patients with BRAF V600-mutant MM treated with specific treatment regimens, classes, or sequences

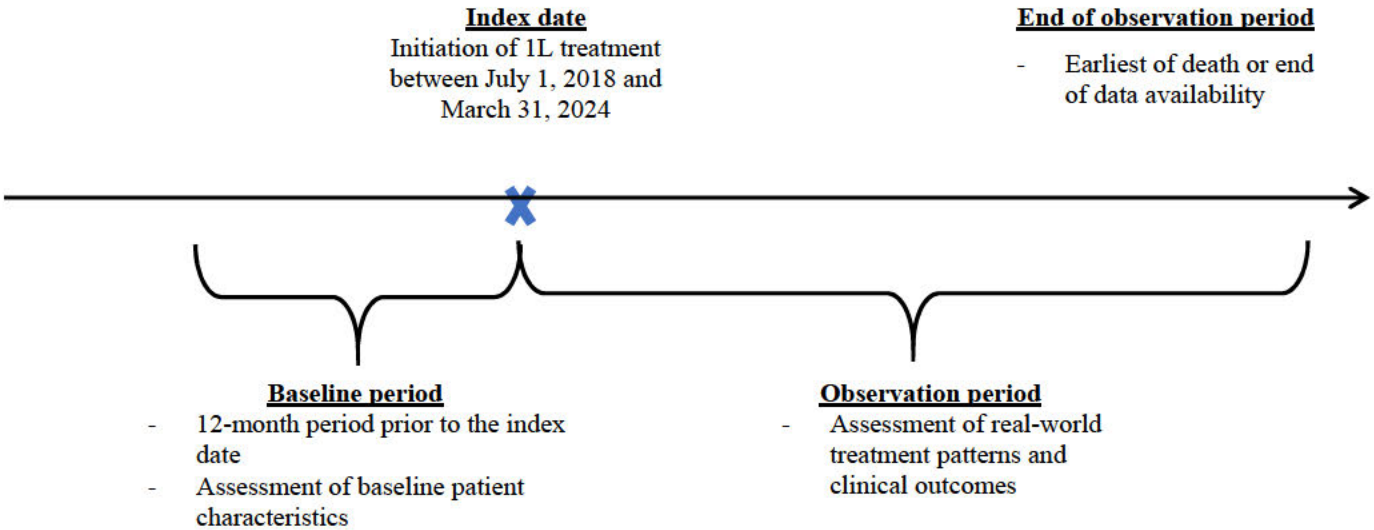
9. RESEARCH METHODS

9.1. Study Design

A non-interventional (NI) longitudinal cohort design will be employed for this study. Individual-level data collected retrospectively from academic oncology centers contributing to the Redacted Research Patient Data Registry (RPDR; **see Section 9.4**) will be used to address all study objectives.

The ***study period*** will be from January 1, 2018 to June 30, 2024 (or the most recent date of data availability at the time of data delivery). The ***index date*** will be defined as the date of initiation with 1L treatment regimens for BRAF V600-mutant MM between July 1, 2018 and March 31 2024, to align with the June 27, 2018 FDA approval date of encorafenib + binimetinib for the treatment of unresectable BRAF V600E/K-mutant melanoma or BRAF V600E/K-mutant MM and maximize the inclusion of patients treated with encorafenib + binimetinib.[14, 15]. This index date range was also chosen such that all patients have an index date occurring at least 3 months before data cutoff (e.g., on or before March 31, 2024), to enable a comprehensive evaluation of study endpoints, and a 6-month baseline period. Patients' baseline demographic and clinical characteristics will be assessed based on all available data in the 12 months prior to or on the index date (i.e., ***baseline period***). If multiple records for baseline characteristics are available within this 12-month period, the record(s) closest to the index date will be used. The ***observation period*** will be defined as the period following the index date to the earliest of patient death or end of data availability. Treatment patterns and clinical outcomes will be assessed during the observation period. The study design scheme is illustrated in **Figure 1**.

Figure 1 Study design scheme



9.2. Setting

This study will be conducted in patients with BRAF V600-mutant MM receiving treatment with SOC regimens of interest at academic oncology centers contributing to the Redacted RPDR from January 1, 2018 to June 30, 2024 (or most recent date of data availability).

9.2.1. Inclusion Criteria

The inclusion criteria described below for the study population are contingent on data availability.

1. Initiation of 1L therapy with the following regimens between July 1, 2018 and March 31 2024:

    a. TT regimen
        i. Encorafenib + binimetinib
        ii. Dabrafenib + trametinib
        iii. Vemurafenib + cobimetinib
    b. IO regimen
        i. Pembrolizumab
        ii. Nivolumab
        iii. Ipilimumab + nivolumab
        iv. Nivolumab + relatlimab
        v. Pembrolizumab + ipilimumab
    c. Combination TT + IO regimen
        i. Dabrafenib + trametinib + pembrolizumab
        ii. Cobimetinib + vemurafenib + atezolizumab

2. Confirmed diagnosis of unresectable stage III or stage IV melanoma during the baseline period (See **Annex 2 Figure 1** for more details on the approach used to identify unresectable stage III patients as defined by clinical input)

3. Record of a BRAF V600E or V600K mutation during the baseline period

4. At least 18 years of age on the index date

9.2.2. Exclusion Criteria

The exclusion criteria described below for the study population are contingent on data availability.

1. Received treatment for another malignancy during the baseline period

2. Presence of chronic active or active hepatitis B or hepatitis C infection during the baseline period

3. Enrolled in a clinical trial during the observation period

9.3. Variables

9.3.1. Treatment Cohorts

Treatment cohorts (i.e., specific treatment regimens, classes, or sequences) to evaluate in the present study will be identified based on findings from the assessment of treatment patterns (as described in **Section 9.3.2)** and clinical input.

PFS and OS will be described for the overall study population, and if sample size permits, described and compared between treatment cohorts identified from the assessment of treatment patterns.

A key cohort of interest is patients with severe disease who first receive induction therapy with a TT regimen and subsequently receive an IO regimen. If sample size permits, treatment patterns and clinical outcomes will be described and compared in this cohort and in key prognostic subgroups within this cohort (e.g., patients with liver metastasis, high lactate dehydrogenase [LDH] levels).

9.3.2. Treatment Patterns

Treatment patterns will be assessed during the observation period. Treatments of interest for this study will be based on regimens recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology for Melanoma: Cutaneous V3.2023 for BRAF V600-mutant MM and clinical input,[13] and include the following:

- TT regimen
    - Encorafenib + binimetinib
    - Dabrafenib + trametinib
    - Vemurafenib + cobimetinib
- IO regimen
    - Nivolumab
    - Nivolumab + ipilimumab
    - Nivolumab + relatlimab
    - Pembrolizumab

  - Pembrolizumab + ipilimumab

- Combination TT+IO regimen
  - Dabrafenib + trametinib + pembrolizumab
  - Cobimetinib + vemurafenib + atezolizumab

The distribution of treatments and treatment patterns (as described in **Table 1**) will be summarized at the therapeutic class level and agent level (if data permits) for up to three LOT (i.e., 1L, 2L, 3L).

Table 1 Treatment Patterns

Variable	Data Source (see Section 9.4)	Operational Definition
Treatment regimens	Structured electronic medical record (EMR); Chart review	TT, IO, or combination TT + IO regimens (as described in **Section 9.3.2)** received at each LOT will be described.
Number of LOTs received	Structured EMR; Chart review	Number of patients with 1L treatment, 2L treatment, and 3L treatment during the observation period.
Treatment interruption	Chart review	Proportion of patients with treatment interruptions by LOT, as documented in patients' charts with corresponding date(s) of treatment interruptions.
Reasons for treatment interruption	Chart review	Reasons for treatment interruption as documented in patients' charts.
Treatment switch	Structured EMR; Chart review	Proportion of patients with treatment switch to subsequent treatment regimen by LOT.
TTS	Structured EMR; Chart review	Time from index date to date of switch to subsequent treatment regimen Patients who do not switch will be censored at the date of last follow-up.

TTNTD	Structured EMR; Chart review	Time from index date to earliest of switch to subsequent treatment regimen or death. Patients who do not switch or who die will be censored at the date of last follow-up.
Treatment discontinuation	Chart review	Proportion of patients with treatment discontinuation by LOT, as documented in patients' charts with corresponding date(s) of treatment discontinuations.
TTD	Chart review	Time from index date to date of treatment discontinuation for any reason, including death, as documented in patients' charts. Patients who do not discontinue treatment or die during the observation period will be censored at the date of last follow-up.
Reasons for treatment discontinuation	Chart review	Reasons for treatment discontinuation as documented in patients' charts.
Treatment sequences	Structured EMR; Chart review	Proportion of patients receiving specific treatment sequences (to be determined by distributions observed in the data and clinical input; e.g., 1L ipilimumab ± nivolumab followed by 2L encorafenib ± binimetinib).

9.3.3. Baseline Characteristics

Demographic and clinical characteristics will be summarized on the index date or during the baseline period, as applicable for the overall sample of adult patients with BRAF V600-mutant MM and for treatment cohorts identified from the assessment of treatment patterns. If multiple assessments for a variable are available within the baseline period, the last completed assessment closest to or on the index date will be used. For laboratory assessments, if multiple results are reported on the same day, an average will be taken. Demographic and clinical characteristics of interest are summarized below in **Table 2**, and are contingent on clinical input and their availability in Redacted RPDR data.

Table 2 Baseline Characteristics

Variable	Data Source (see Section 9.4)	Operational Definition/Categories

Age at index	Structured EMR	Patient age in years at the index date (i.e., initiation of 1L therapy)
Race	Structured EMR	Asian, Black or African American, White, Other, Unknown/Missing
Sex	Structured EMR	Male, Female
Body mass index (BMI)	Structured EMR	Body weight (in kilogram [kg]) divided by squared height (in m^2)
Year of index	Structured EMR	Calendar year of index date
Year of MM diagnosis	Chart review	Calendar year of diagnosis with MM as documented in patients' charts
Time from MM diagnosis to 1L treatment initiation	Chart review	Time from MM diagnosis date (as documented in patients' charts) to index date
Disease stage at MM diagnosis	Chart review	Unresectable stage IIIB, unresectable stage IIIC, unresectable stage IIID, stage IV, as documented in patients' charts
Brain or liver metastasis	Chart review	Brain or liver metastasis as documented in patients' charts
LDH level	Structured EMR	Evaluated in units per liter (U/L)
Eastern Cooperative Oncology Group Performance Status (ECOG PS)	Chart review	Value of 0, 1, or 2+ Unknown/Missing. ECOG PS as documented in patients' charts
Comorbidities	Structured EMR	Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Autoimmune diseases[21] (including Churg Strauss, giant cell arthritis, inflammatory bowel disease [ulcerative colitis, Crohn's disease], multiple sclerosis, myasthenia gravis, polymyalgia rheumatic, psoriasis, psoriatic arthritis, rheumatic arthritis,

		sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus, thyroiditis, and vitiligo), Peptic ulcer disease, Liver disease, Diabetes, Hemiplegia, Renal disease, History of any malignancy, Hypertension, Quan-Charlson Comorbidity Index (see **Annex 2 Table 2** for International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] codes used to identify comorbidities)
Prior treatment with radiation therapy	Structured EMR	Binary variable (value of 0 or 1) will be assigned based on receipt of radiation therapy (see **Annex 2 Table 5** for procedure codes used to identify radiation therapy)
Surgery	Structured EMR	Surgery for MM including wide excision, lymphadenectomy, sentinel lymph node biopsy, and Mohs surgery (see **Annex 2 Table 5** for procedure codes used to identify surgery)
Neoadjuvant therapy	Structured EMR	Neoadjuvant therapy prior to receiving surgery for MM (Nivolumab, Pembrolizumab, Dabrafenib + Trametinib, Ipilimumab, Ipilimumab + Nivolumab, Nivolumab + Relatlimab) Based on clinical input, neoadjuvant therapy will be defined as MM therapies received in the 8 weeks prior to surgery for MM.
Adjuvant therapy	Structured EMR	Adjuvant therapy following surgery for MM (Nivolumab, Pembrolizumab, Dabrafenib + Trametinib, Ipilimumab, Ipilimumab + Nivolumab, Nivolumab + Relatlimab) Based on clinical input and published literature, adjuvant therapy will be defined as MM therapies initiated within 13 weeks following MM surgery[22-23]

Local therapy	Structured EMR	Local immunotherapy regimen (i.e., Talimogene Laherparepvec [T-VEC], Interleukin-2 [IL-2], Imiquimod)
Antibiotics	Structured EMR	Amoxicillin, Amoxicillin and Clavulanate, Ofloxacin, Doxycycline, Vancomycin, Clarithromycin, Piperacillin and Tazobactam, Cefazolin, Vancomycin, Ertapenem, Levofloxacin
Corticosteroids	Structured EMR	Dexamethasone, Prednisone
Opioids	Structured EMR	Tramadol, Hydromorphone, Methadone, Morphine, Oxycodone, Hydrocodone, Oxymorphone, Fentanyl, Tapentadol
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Structured EMR	ASA, Acetylsalicylic acid (aspirin), cyclooxygenase (COX)-2 inhibitors, non-ASA/nonselective COX inhibitor NSAIDs, beta blockers
Acid-reducing agents	Structured EMR	Antacids, histamine-2 blockers, proton pump inhibitors

9.3.4. Clinical Outcomes

PFS, and OS will be assessed during the observation period. PFS and OS will be described for the overall study population, and if sample size permits, described and compared between treatment cohorts identified from the assessment of treatment patterns.

The operational definition for each clinical outcome is described in **Table 3**

Table 3 Clinical Outcomes

Variable	Data Source (see Section 9.4)	Operational Definition
PFS	Structured EMR; Chart review	Clinician-assessed progressive disease (as documented in patients' charts) will be defined using the following approaches outlined in Rauwerdink et al. 2020[24] and RECIST criteria respectively:

		• Non-response (NR): defined as progressive metastatic lesions without any sites of tumor regression, **OR;** • Progressive disease (PD) per RECIST v1.1 criteria: defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression). Rauwerdink et al. 2020 assessed the correlation between clinician-assessed tumor response categories (i.e., R, MR, and NR) and categories defined by RECIST criteria. Results from this assessment suggested high concordance between these clinician-assessed tumor response categories and RECIST criteria. Among patients categorized as "NR", 93% had progressive disease per RECIST criteria. These findings suggest a high degree of concordance between clinician-assessed response (as defined in the present study) and RECIST criteria, which may provide some support for the reliability of study findings.[24] PFS will be defined as the time from index date to the earliest evidence of NR or PD (as documented in patients' charts) or death due to any cause. Patients without a PFS event will be censored at the earliest date of switch to a subsequent therapy or their last confirmed activity date in Redacted RPDR data. Redacted's mortality data is primarily sourced from the Social Security Death Index (SSDI), and SSDI mortality data for the most recent three

		years are not available in the database. Beyond data from the SSDI, additional information on death is available in the EMR data if the death occurred in an [Redacted] facility/hospital; deaths reported to [Redacted] by a next of kin can be abstracted from patient charts. As such, mortality may be underreported. Nevertheless, vital status is recorded in the database and may be used along with dates of clinical visits for patients with MM, which are expected to occur every 3 – 6 months per guideline recommendations for the first 2 years after diagnosis and every 3 – 12 months for the next 3 years,[13] and clinical input to inform the approach for evaluating PFS.
OS	Structured EMR; Chart review	Mortality events will be evaluated based on records with a date of death. OS will be defined as time from the index date to death due to any cause. Patients who do not die during the observation period will be censored at the last confirmed activity date in [Redacted] RPDR. As [Redacted]'s mortality data may be unreported, vital status may be used along with dates of clinical visits for patients with MM[13] and clinical input to inform the approach for evaluating OS.

9.3.5. Other Variables

The duration of follow-up time will also be summarized. The operational definition is described in **Table 4.**

Table 4 Other Variables

Variable	Data Source (see Section 9.4)	Operational Definition
Follow-up time	Structured EMR	Duration (in months) between the index date and end of the observation

9.4. Data Sources

Longitudinal data from the Redacted RPDR database will be used to address all study objectives. Redacted RPDR aggregates de-identified hospital inpatient and outpatient clinical data from electronic health records (2000-present; EPIC post-2015, legacy electronic medical record [EMR] systems pre-2015) from 9 major hospitals affiliated with the Redacted [redacted] The RPDR gathers data from hospital systems and stores it in a single clinical data registry, or data warehouse, to allow for clinical research and ensure the security of patient information. The hospital systems use a formal drug reconciliation protocol to ensure that drugs are correctly documented in the EMR at the time of hospital discharge. The database stores de-identified clinical information for more than 6.5 million patients and over 2 billion records. There were ~1.5 million active patients in 2019, and ~3.6 million "loyalty cohort" patients (i.e., those with a Redacted primary care provider). The average length of follow-up in the database is ~7 years.

The database contains structured data elements from EMR (e.g., demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology). Other data elements not available in the structured data (e.g., disease stage, BRAF mutation status, site(s) of metastasis, tumor size, ECOG PS, treatment discontinuation, reasons for treatment discontinuation, treatment interruptions, reasons for treatment interruptions, disease progression, clinician-assessed tumor response, and deaths reported to Redacted by a next of kin) can be extracted via chart review. This study will use both structured EMR data and chart review data (in structured format), and all data used in this study will be de-identified.

9.4.1. Structured EMR Data

Structured data elements from the Redacted RPDR include demographics, providers, visits, diagnoses, medications, procedures, laboratories, microbiology, and reports (e.g., discharge, operative, and radiology). In addition, the Notes Repository is composed of notes and reports for EPIC Ambulatory Notes, LMR Ambulatory Notes, Discharge Reports, EPIC Progress Notes, etc. Structured data on mortality are available for (1) patients whose death information had been linked to SSDI at least three years before the data cutoff (i.e., mortality information sourced from SSDI is not available for the most recent three years of data) and (2) patients whose death occurred in an Redacted facility/hospital (i.e., in-facility death). Data are updated every 1-2 months. The limitations of the data source (including the completeness of mortality data) are described in **Section 9.9.**

9.4.2. Chart Review Data

Certain data elements of interest (e.g., disease stage, BRAF mutation status, site(s) of metastasis, tumor size, ECOG PS, treatment discontinuation, reasons for treatment

discontinuation, treatment interruptions, reasons for treatment interruptions, disease progression, clinician-assessed tumor response, and deaths reported to Redacted by a next of kin) are not available within the structured RPDR and require abstraction from patients' medical charts. Abstraction of these data elements, which will be linked with structured data elements as described in **Section 9.6**, will be conducted by Redacted personnel. Chart abstraction is planned for 390 eligible patients who will comprise the study population for analyses.

The chart abstraction process will be conducted in a stepwise fashion as follows:

1) Development of natural language processing (NLP) algorithm

a) NLP will be used to identify the population of interest based on eligibility criteria described in **Section 9.2** to be efficient in the chart abstraction process. The inclusion criteria for this study, notably, a confirmed diagnosis of stage IIIB, IIIC, or IV melanoma and a record of a BRAF V600E or V600K mutation, require patient chart review. Initial sample counts based on Redacted identified approximately 18,000 patients with MM from 1st Jan 2018 to 30th June 2022. The NLP algorithm will be utilized to identify an initial pool of patients of interest with these criteria without the need to perform a chart review of approximately 18,000 charts.

b) Redacted will work with study investigators to develop an NLP algorithm with an acceptable error rate, which will then be applied to the Redacted RPDR to identify an initial candidate pool of BRAF V600-mutant MM patients for chart abstraction.

c) Search terms used in the NLP algorithm may include:

   i) Patients with melanoma: 'cutaneous melanoma', or 'melanoma'

   ii) Among i), patients with unresectable Stage III or Stage IV melanoma: 'metastatic', 'unresectable', 'unresectable Stage 3', 'unresectable Stage III', 'Stage IV' or 'Stage 4'

   iii) Among ii), patients with BRAF V600: 'BRAF V600', 'BRAF V600E', or 'BRAF V600K'

d) To minimize false positives and enhance the specificity of the NLP algorithm, the algorithm will also include exclusionary search phrases, and patients with clinical notes including terms that are in close proximity to these exclusionary phrases will be excluded. Exclusionary phrases may include:

   i) "Patient does NOT have metastasis.", "Patient does NOT have BRAF V600 mutation.", "Melanoma with negative genetic test result", "BRAF wild-type", "BRAF WT"

e) The NLP algorithm will be revised and finalized in collaboration with Pfizer and Dr. Boland, a clinical expert in MM, and quality testing during two rounds of algorithm revision to ensure that the algorithm yields an acceptable error rate.

2) Patient Selection

a) From this initial pool, patients will be randomly selected for chart abstraction and evaluated for study eligibility by applying the inclusion and exclusion criteria described in **Section 9.2** as documented in the patient chart.

3) Drafting and programming of case report form (CRF)

a) AG will draft a Word-based CRF and work with Pfizer and Redacted to revise and finalize the CRF.

b) AG will subsequently program an Excel-based electronic CRF (eCRF) for chart abstraction. The eCRF will also be used to automatically compile the abstracted chart review data into a structured format for analyses.

c) To ensure the clarity of the eCRF, a pilot test will be carried out on 5 randomly selected cases. During pilot testing, data abstractors will be invited to comment on the questions they do not fully understand, request clarifications, and provide suggestions on improving the questions. AG may further refine the questions based on the feedback received. AG will also review de-identified structured chart review data collected during the pilot test to ensure that the quality of the data meets expectations and there is no unanticipated ambiguity or difficulty in capturing diverse real-world data in the chart abstraction form.

d) If necessary, AG will work to resolve any potential issues prior to finalizing the eCRF.

4) Chart Abstraction

a) Subsequently, the data abstraction process for the remaining charts will be conducted on an ongoing basis by Redacted. De-identified abstracted chart review data will be uploaded to Redacted's Data Enclave portal, a virtual desktop with access to Redacted RPDR, weekly, and the quality of the de-identified chart review data will be monitored throughout the data collection process by AG.

b) Study eligibility will be confirmed upon chart abstraction by applying the inclusion and exclusion criteria described in **Section 9.2** as documented in the patient chart.

c) Chart abstraction will be conducted for the 390 eligible patients who have a confirmed diagnosis of MM, harbor a BRAF V600 mutation, and meet all other eligibility criteria using the eCRF.

9.4.3. Analytic Data

The final analytic dataset will consist of linked Redacted RPDR EMR data and abstracted chart review data (in structured format), with no patient identifiable information.

Analysis Group (AG) will access the final analytic dataset through Redacted's Data Enclave portal. See **Section 9.6** for more details on data management.

9.5. Study Size

The planned sample size for the present study is 390 patients. As all statistical analyses for the primary objectives are descriptive in nature and no hypotheses are being tested, no formal sample size computations will be performed.

9.6. Data Management

AG will access all data through Redacted's Data Enclave portal. Assigned users from AG will have remote access to Redacted desktops through the Data Enclave portal. The Data Enclave portal access period will be for 1 year starting from when AG gets access to the portal and starts reviewing batches of abstracted chart review data. Pfizer will not have access to any data from this study.

Chart abstraction will be conducted in batches, with AG reviewing each batch of abstracted data through access to the Data Enclave portal.

Data linkage between the Redacted RPDR EMR data and abstracted chart review data will occur at the two time points previously described in **Section 9.4.3** AG will clean and prepare the final analytic dataset, which consist of data collected from both the Redacted RPDR EMR and chart abstraction.

9.7. Data Analysis

Analyses will be conducted using SAS version 9.4 and/or R. All analyses will be quality controlled as described in **Section 9.8**.

The extent of missing data will be summarized for baseline characteristics, treatment patterns, and clinical outcomes, overall and for relevant subgroups. Baseline characteristics, treatment patterns, and clinical outcomes will be evaluated in the subset of patients with complete information on these variables. No imputation will be conducted for missing data.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Primary Analysis

9.7.1.1. Description of Treatment Patterns

Treatment patterns described in **Section 9.3.2** will be summarized during the observation period in the overall population and for treatment cohorts identified from the assessment of treatment patterns. The distribution of treatments will be summarized at the therapeutic class level and agent level by LOT for up to 3L. Number of LOTs will be summarized using frequencies and proportions. Treatment sequences (i.e., the movement of treatments from 1L to 2L to 3L) will be summarized at the class level and agent level (if data permits) and visualized using a treatment flow diagram (i.e., Sankey diagram). Reasons for treatment interruption and reasons for treatment discontinuation will be summarized using frequencies (with proportions). Time-to-event treatment patterns (TTD, TTS, TTNTD) will be summarized using Kaplan-Meier (KM) analyses. Event rates, median times and 95% confidence intervals (CI), censoring rates, and numbers at risk will be presented along with KM curves. The proportion of patients with treatment discontinuations, treatment interruptions, and treatment switches will be summarized using frequencies and proportions.

9.7.1.2. Description of Baseline Characteristics

Baseline demographic and clinical characteristics outlined in **Section 9.3.3** will be summarized for the overall population and for treatment cohorts identified from the assessment of treatment patterns using means (standard deviations [STD DEV]) and medians (interquartile ranges [IQR]) for continuous variables, and frequencies (with proportions) for categorical variables.

9.7.1.3. Description of Other Variables

The duration of follow-up time described in **Section 9.3.5** will be summarized in the overall population and for treatment cohorts identified from the assessment of treatment patterns using means (STD DEV) and medians (IQR).

9.7.2. Exploratory Analysis

9.7.2.1. Description of PFS and OS

OS and PFS will be summarized during the observation period in the overall population and for treatment cohorts identified from the assessment of treatment patterns. OS and PFS will be summarized using KM analyses. Event rates, median times and 95% CIs, censoring rates, and numbers at risk will be presented for OS and PFS, along with KM curves.

9.7.2.2. Comparison of PFS and OS

OS and PFS will be compared between treatment cohorts of interest identified from the assessment of treatment patterns using univariable and multivariable Cox proportional hazards models. Multivariable Cox models will be adjusted for key confounders identified with clinical input. The proportional hazards assumption will be tested for each Cox model using tests of Schoenfeld residuals.[25] For each model, hazard ratios and 95% CIs will be reported.

9.8. 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.

9.9. Limitations of the Research Methods

Several limitations should be considered when interpreting results from this real-world study:

- This analysis relies on diagnosis and procedure codes associated with medical records to determine a diagnosis of BRAF V600-mutant MM, clinical characteristics, procedures, and certain clinical outcomes. These codes are subject to misspecification and may lead to the mischaracterization of patients with BRAF V600-mutant MM, based on the medical record available in the EMR.
- Medication prescription data indicate the date on which a drug was prescribed to a patient but do not provide information on drug dispensing, medication fill status (i.e., whether prescriptions were filled/refilled on time), or medication adherence and compliance (i.e., whether medication was taken and as prescribed). This may lead to the misclassification of treatment patterns.
- Information necessary to determine tumor response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, as used in the COLUMBUS trial,[11, 16] are not routinely available or uniformly collected in real-world settings. Where available, RECIST criteria will be used alongside clinician-assessed tumor response information, ascertained using the institution-specific methodology (i.e., clinician-assessed tumor response[24]), to inform the assessment of real-world PFS. Real-world assessment of PFS may be subject to bias from variability in tumor assessment interval, tumor assessment modalities, and interpretation of tumor response.

- Redacted RPDR's mortality data is primarily sourced from the SSDI. Due to the lag time with SSDI data, mortality data for the most recent three years are not available in Redacted RPDR. Beyond data from the SSDI, additional information on death is available in the EMR data if the death occurred in an Redacted facility/hospital; deaths reported to Redacted by a next of kin can be abstracted from patient charts. As such, findings from analyses of PFS and OS may be imprecise.
- The data source is limited to academic oncology centers within Massachusetts and may not be demographically representative of the state, as patients in the Redacted system are more likely to be white and have higher socioeconomic status compared with the rest of the Massachusetts patient population.
- As Redacted only includes data on patients receiving care at academic oncology centers within the Redacted RPDR system, study findings may not be generalizable to patients with BRAF V600-mutant MM receiving treatment at community centers across the US.
- As with all analyses of observational data, bias due to residual or unmeasured confounding cannot be ruled out.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

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

10.2. Patient Consent

As this study involves deidentified/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.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

Before accessing and collecting any data through Redacted, an IRB application for exempt research will be submitted to Redacted IRB for review/approval and maintain IRB active status. This retrospective, observational, longitudinal cohort study 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). Because the dataset does not include individually identifiable health information under 45 CFR 164.514, Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirements do not apply.

10.4. 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 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), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, and International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences. [26-30]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The final analytic dataset used in this study consists of linked Redacted RPDR EMR data and abstracted chart review 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 this data source, 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal or in an abstract/presentation at a scientific conference or symposium. Any publication related to the study will be reviewed/approved by Pfizer prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol.

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.

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14. LIST OF TABLES

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ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Figure 1. Approach to Identify Unresectable Disease

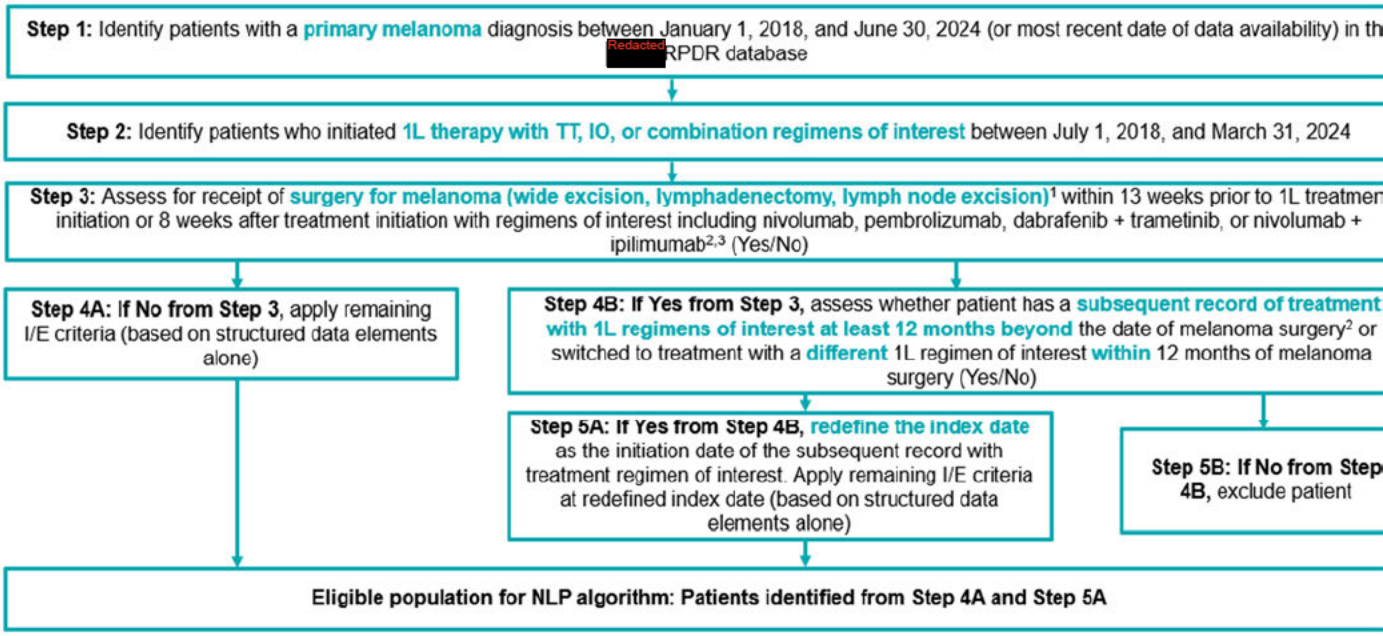

Table 1. ICD-10-CM Diagnosis Codes to Identify Melanoma

Condition	ICD-10-CM Diagnosis Codes
Malignant Melanoma of skin	C43.x

Abbreviations: ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification.

Table 2. ICD-10-CM Diagnosis Codes Used to Identify Comorbidities

Condition	ICD-10-CM Diagnosis Codes
Charlson comorbidity index[1]	
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x–I69.x

Condition	ICD-10-CM Diagnosis Codes
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1
Diabetes with chronic complication	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
HIV/AIDS	B20.x–B22.x, B24.x
Metastatic solid tumor	C77.x–C80.x
Mild liver disease	K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Myocardial infarction	I21.x, I22.x, I25.2
Peptic ulcer disease	K25.x–K28.x
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Renal disease	N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Rheumatic disease	M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
Other comorbidities	
Hypertension	I10.x-I13.x, I15.x-I16.x
Lymphoma	C81.x–C88.x

Abbreviations: AIDS: acquired immune deficiency syndrome; HIV: human immunodeficiency viruses; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification.

Condition	ICD-10-CM Diagnosis Codes

Note:
[1] Comorbidities used in the derivation of the Charlson comorbidity index score are based on Quan H et al. Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries. Am J Epidemiol 2011; 173 (6): 676-682.

Table 3. LOINC Codes Used to Identify Laboratory Measurements

Laboratory measurement	LOINC Codes
LDH	14803-1, 2532-0, 14804-9, 14805-6

Abbreviations: LDH: lactate dehydrogenase; LOINC: logical observation identifiers names and codes**.**

Table 4. Procedure Code Used to Identify Surgeries and Treatments

Procedure	Code type	Codes
Wide excision	CPT	11600 – 11606, 11620 – 11626, 11640 – 11646
Lymphadenectomy	CPT	38700 – 38780
Sentinel lymph node biopsy	CPT	38500, 38510, 38525, 38530
	HCPCS	G8878
Mohs surgery	CPT	17311 – 17315
Radiation therapy	CPT	77401, 77402, 77407, 77412
	HCPCS	G6003 – G6015
Talimogene Laherparepvec	CPT	11900, 11901
	HCPCS	J9325
Interleukin-2	HCPCS	J9015

Abbreviations: CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System.

Table 5. List of MM Treatments and Concomitant Medications

Therapeutic class	Agent generic name	Agent brand name
Adjuvant therapy		
Nivolumab	Nivolumab	Opdivo
Nivolumab + Relatlimab	Nivolumab + Relatlimab	Opdualag
Pembrolizumab	Pembrolizumab	Keytruda
Dabrafenib + Trametinib	Dabrafenib Trametinib	Tafinlar Mekinist
Ipilimumab	Ipilimumab	Yervoy
Neoadjuvant therapy		
Nivolumab	Nivolumab	Opdivo
Nivolumab + Relatlimab	Nivolumab + Relatlimab	Opdualag
Pembrolizumab	Pembrolizumab	Keytruda
Dabrafenib + Trametinib	Dabrafenib + Trametinib	Tafinlar + Mekinist
Ipilimumab	Ipilimumab	Yervoy
Vemurafenib	Vemurafenib	Zelboraf
Vemurafenib + cobimetinib	Vemurafenib + cobimetinib	Zelboraf + Cotellic
Local therapy		
Talimogene Laherparepvec	Talimogene laherparepvec	Imlygic
Interleukin-2	Aldesleukin	Proleukin
Imiquimod	Imiquimod	Aldara, Zyclara
Concomitant medications		
Antibiotics		
Amoxicillin	Amoxicillin	Amoxicot, Amoxil, DisperMox, Moxatag, Moxilin, Trimox
Amoxicillin and Clavulanate	Amoxicillin + clavulanate	Amoclan, Augmentin
Ofloxacin	Ofloxacin	Ocuflox
Doxycycline	Doxycycline	Adoxa, Doryx, Monodox, Oracea, Periostat, Vibramycin Calcium, Vibramycin Hyclate, Vibra-Tabs
Vancomycin	Vancomycin	Firvanq, Vancocin HCl Pulvules
Clarithromycin	Clarithromycin	Biaxin
Piperacillin and Tazobactam	Piperacillin + tazobactam	Zosyn
Cefazolin	Cefazolin	Ancef

Ertapenem	Ertapenem	INVanz
Levofloxacin	Levofloxacin	Levaquin
Corticosteroids		
Dexamethasone	Dexamethasone	Baycadron Elixer, Decadron, Dekpak 13, Day Taperpak, Dexamethasone Intensol, DexPak, TaperPak, Zema-Pak
Prednisone	Prednisone	Deltasone, Prednicot, predniSONE Intensol, Rayos, Sterapred, Sterapred DS
Opioids		
Tramadol	Tramadol	ConZip, FusePaq, Synapryn, Qdolo, Rybix ODT, Ryzolt, Ultram, Ultram ER
Hydromorphone	Hydromorphone	Dilaudid, Exalgo, Palladone
Methadone	Methadone	Diskets Dispersible, Dolophine, Methadone, HCl Intensol, Methadose
Morphine	Morphine	Arymo ER, AVINza, Kadian, Kadian ER, Morphabond, MS Contin, Oramorph SR, Roxanol
Oxycodone	Oxycodone	Dazidox, Eth-Oxydose, Oxaydo, OxyCONTIN, Oxydose, Oxyfast, Oxy IR, Roxicodone, Roxybond, Xtampza ER
Hydrocodone	Hydrocodone	Hysingla ER, Vantrela ER, Zohydro ER, Hycodan
Oxymorphone	Oxymorphone	Opana
Fentanyl	Fentanyl	Duragesic, Ionsys
Tapentadol	Tapentadol	Nucynta
NSAIDs		

ASA	Acetylsalicylic acid	Ascriptin, Aspergum, Aspirin, Aspirtab, Bayer, Easprin, Ecotrin, Ecpirin, Entercote, Genacote, Halfprin, Ninoprin, Norwich Aspirin
COX-2 inhibitors	Celecoxib	CeleBREX, Elyxyb
Non-ASA/nonselective COX inhibitor NSAIDs	Naproxen	Aflaxen, Aleve, Anaprox, EC Naprosyn, Naprelan, Naprosyn
	Diclofenac	Cambia, Cataflam, Voltaren, Voltaren-XR, Zipsor, Zorvolex
	Ibuprofen	Addaprin, Advil, A-G Profen, Bufen, Genpril, Haltran, Ibu, Ibu-2, Ibu-200, Ibu-4, Ibu-6, Ibu-8, Ibuprohm, Ibu-Tab, I-Prin, Midol, Motrin, Nuprin, Proprinal, Q-Profen
	Fenoprofen	Nalfon
	Ketoprofen	Orudis, Oruvail
	Oxaprozin	Coxanto, Daypro
	Etodolac	Lodine
	Indomethacin	Indocin, Tivorbex
	Ketorolac	Toradol
	Nabumetone	Relafen
	Sulindac	Clinoril
Beta blockers	Acebutolol	Sectral
	Atenolol	Tenormin
	Betaxolol	Kerlone
	Bisoprolol	Zebeta
	Carvedilol	Coreg
	Labetalol	Normodyne, Trandate
	Metoprolol	Lopressor, Toprol XL
	Nadolol	Corgard
	Nebivolol	Bystolic
	Pindolol	Visken

	Propranolol	Hemangeol, Inderal, InnoPran XL, Propranolol HCl, Intensol
	Timolol	Betimol, Istalol, Timoptic
ARAs		
Antacids	Calcium carbonate	Alka-Mints, Alka-Seltzer, Alkets, Antacid Fast Dissolve, Cal-Gest, Calcium Antacid, Maalox, Mylanta, Pepto-Bismol, Rolaids Extra Strength, Titralac, Tums
	Aluminum hydroxide + magnesium trisilicate	Gaviscon
	Magnesium hydroxide	Milk of Magnesia
	Aluminum Hydroxide + Magnesium Hydroxide + Simethicone	Mylanta, Mygel, DiGel, Gelusil, Rulox
Histamine-2 blockers	Nizatidine	Axid
	Famotidine	Heartburn Relief, Pepcid
	Cimetidine	Tagamet
	Ranitidine	Tritec, Zantac
Proton pump inhibitors	Omeprazole	Prilosec
	Esomeprazole	Nexium
	Lansoprazole	Prevacid
	Rabeprazole	AcipHex
	Pantoprazole	Protonix
	Dexlansoprazole	Dexilant, Kapidex
	Omeprazole + sodium bicarbonate	Zegerid

Abbreviations:
ASA: Acetylsalicylic acid; ARA: Acid-reducing agents; COX: Cyclooxygenase; NSAIDs: Nonsteroidal anti-inflammatory drugs

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