Use of Sensitivity Analysis to Address Potential Missing Data and Selection Bias from Linked Genomics Datasets in a Real-World Study of Patients Receiving Immune-Checkpoint Inhibitors for Metastatic Melanoma

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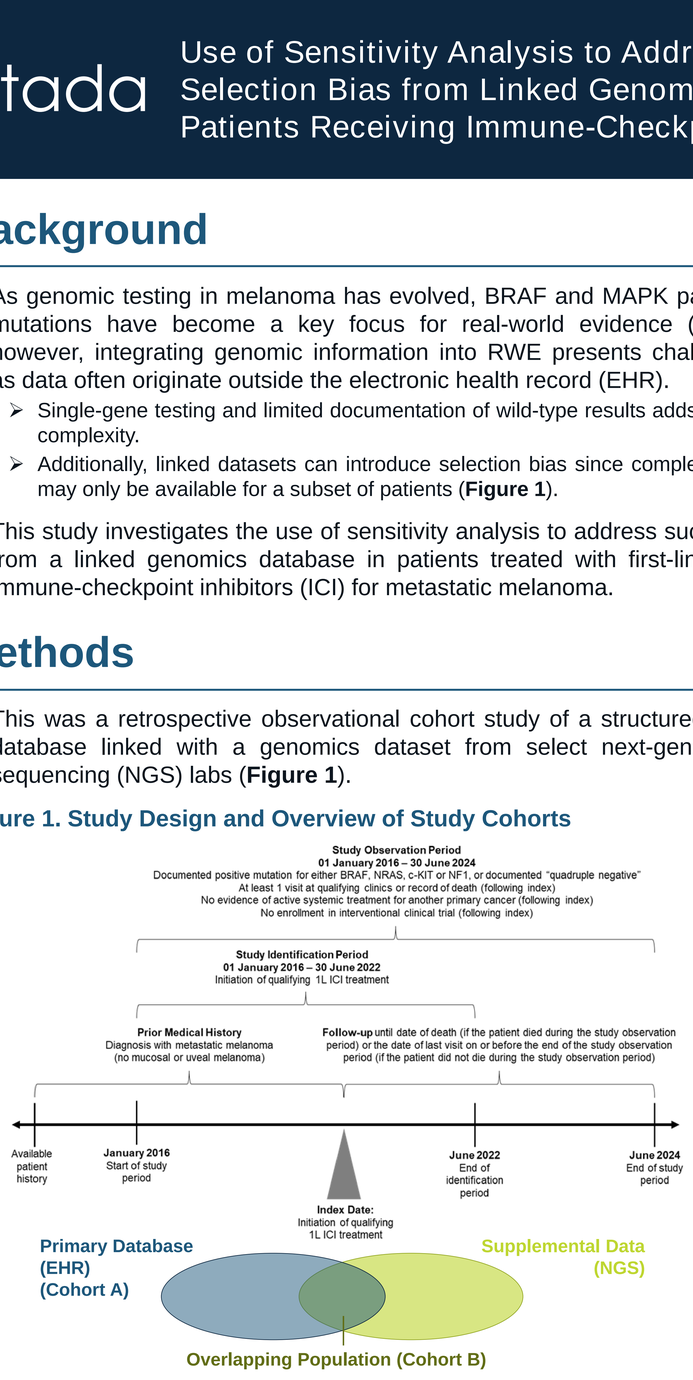
Background

- As genomic testing in melanoma has evolved, BRAF and MAPK pathway mutations have become a key focus for real-world evidence (RWE); however, integrating genomic information into RWE presents challenges as data often originate outside the electronic health record (EHR).
  - Single-gene testing and limited documentation of wild-type results adds further complexity.
  - Additionally, linked datasets can introduce selection bias since complete data may only be available for a subset of patients (**Figure 1**).
- This study investigates the use of sensitivity analysis to address such bias from a linked genomics database in patients treated with first-line (1L) immune-checkpoint inhibitors (ICI) for metastatic melanoma.

Methods

- This was a retrospective observational cohort study of a structured EHR database linked with a genomics dataset from select next-generation sequencing (NGS) labs (**Figure 1**).

Figure 1. Study Design and Overview of Study Cohorts



- The target population included patients with metastatic melanoma initiating 1L ICIs who had documentation of at least one mutation of interest (BRAF, NRAS, NF-1, c-KIT) or confirmed quadruple-negative status (**Cohort A**).
- A sensitivity analysis was conducted among a subset of patients with NGS testing for all four mutations of interest (**Cohort B**).
- Patient characteristics were descriptively assessed in each cohort, and overall survival was assessed using Kaplan-Meier analysis.

Results

- Overall, 990 and 291 patients were included in Cohorts A and B with mean (SD) ages of 64 (14) and 67 (12) years, respectively.
- Cohort A included more patients indexed between 2016-2018 (n=340, 34%) relative to Cohort B (n=32, 11%) (**Table 1, bolded**).
- No substantial differences in metastatic sites, body mass index (BMI), ECOG performance status or lactate dehydrogenase (LDH) were observed between cohorts (**Table 1**).

Table 1. Patient characteristics by documentation of mutation testing

Variable	Cohort A (Overall, N=990)	Cohort B (Full Panel, N=291)
Mean (SD) age at baseline, years	63.9 (13.7)	67.3 (12.4)
Age ≥ 65 years, n (%)	513 (52)	177 (61)
Male, n (%)	631 (64)	204 (70)
Race, White, n (%)[a]	852 of N=880 (97)	256 of N=261 (98)
BMI ≥ 25 kg/m^2, n (%)[a,b]	651 of N=955 (68)	187 of N=281 (64)
Index year, 2016-2018, n (%)	**340 (34)**	**32 (11)**
Index year, 2019-2022, n (%)[c]	**650 (66)**	**259 (89)**
ECOG 0-1 at baseline, n (%)[a,b]	402 of N=466 (86)	107 of N=129 (83)
ECOG ≥ 2 at baseline, n (%)[a,b]	64 of N=466 (14)	22 of N=129 (17)
Elevated LDH at baseline, n (%)[a,b,d]	163 of N=474 (34)	51 of N=147 (35)
Lung mets at baseline, n (%)[a]	101 of N=207 (49)	25 of N=63 (40)
Brain mets at baseline, n (%)[a]	60 of N=207 (29)	18 of N=63 (29)
Liver mets at baseline, n (%)[a]	49 of N=207 (24)	14 of N=63 (22)
BRAF mutation, n (%)	**757 (76)**	**129 (44)**
NRAS mutation, n (%)	**122 (12)**	**78 (27)**
NF1 mutation, n (%)	**59 (6)**	**54 (19)**
c-KIT mutation, n (%)	**32 (3)**	**10 (3)**
Quadruple-negative, n (%)	**20 (2)**	**20 (7)**

[a]% are reported among patients with available data. [b]Baseline was assessed within 60 days prior to index. [c]2022 includes January-June. [d]LDH >280 U/L was considered elevated.

- Among patients with concurrent testing for all 4 mutations (Cohort B), nearly half (44%) of patients had a BRAF mutation, 27% had an NRAS mutation, and 19% had an NF-1 mutation (**Table 1, bolded**).
- The most common 1L ICI treatments in Cohorts A, B, respectively were nivolumab+ipilimumab (47%, 52%), pembrolizumab monotherapy (29%, 32%) and nivolumab monotherapy (21%, 15%).
- The median overall survival was 20 months in each cohort (95% CI: 18–25 months, Cohort A; 18–27 months, Cohort B).

Limitations

- The study relied solely on structured EHR data for patient characteristics, therefore several variables were subject to missingness.
- Testing patterns have evolved over time from selective, single-gene testing to broad-panel testing with further understanding of the mutation spectrum in melanoma and availability of more advanced technology such as NGS and targeted therapy.
- Because all patients were required to have at least one gene mutation and incomplete results for other genes were included in Cohort A, there were more patients with BRAF mutations relative to the true prevalence which is better characterized in Cohort B.

Conclusions

Sensitivity analysis revealed that partial linked data better represented the full study period with minimal differences in non-genetic prognostic factors relative to complete case analysis.

Inclusion of such explorations can be an important tool for assessing selection bias in RWE studies and supporting generalizability of results when using linked datasets.

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