Immune-Related Adverse Events (irAEs) associated with Immune Checkpoint Inhibitor (ICI) Therapy in Bladder Cancer: An Analysis of the FDA Adverse Event Reporting System (FAERS)

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# 1. Summary/Abstract

*Write a summary of your project.* *This part has not been completed. The source code has been left as is*

# 2. Introduction

## 2.1 General Background Information

*Bladder cancer is the ninth most common type of cancer, according to a 2022 report published by the International Agency for Research on Cancer1. The American Cancer Society estimates approximately 85,000 new bladder cancer cases, and approximately 17,000 bladder cancer deaths in the United States in 2025.*

*The cancer is more common in males than in females, with a male:female ratio of about 4:12. Risk factors for bladder cancer include smoking and occupational chemical exposures (in particular, aromatic amines and polycyclic aromatic hydrocarbons). Certain dietary factors, impaired microbiome, and pelvic radiotherapy may also increase the risk of bladder cancer3.*

*Treatment of bladder cancer is multifaceted and depends on the type of tumor. Surgical resection, adjuvant and intravesical chemotherapy, Bacillus Calmette–Guérin (BCG) immunotherapy, and systemic chemotherapy are the different treatment options available2.*

*According to the National comprehensive Cancer Network (NCCN) guidelines, immunotherapy with immune checkpoint inhibitors (ICIs) is recommended at various stages of bladder cancer treatment. ICIs such as pembrolizumab, atezolizumab, nivolumab, and avelumab are FDA approved and recommended for the adjuvant and first and second-line treatment of bladder cancer4.*

*ICIs are associated with various adverse effects, particularly with immune-related adverse events (irAEs) such as pnemonitis, hepatitis, colitis, hypothyroidism, dermatitis, and others5.This study aims to analyze real-world adverse event data from the FDA Adverse Event Reporting System associated with ICI therapy in bladder cancer.*

## 2.2 Description of data and data source

*The United States Food and Drug Administration (FDA) maintains a dashboard of adverse event reports in the FDA Adverse Event Reporting System (FAERS)6. FAERS is a publicly available dashboard of safety reports submitted by patients, healthcare professionals, and pharmaceutical companies.*

*Since FAERS consists of self-reported data from multiple sources, there may be duplicates, missing data as well as various errors. The findings of this study should be considered in context of this data limitation.*

## 2.3 Questions/Hypotheses to be addressed

*The study aims to analyze whether irAEs associated with ICIs generate a signal of disproportionate reporting (SDR). The goal is to determine whether irAEs associated with ICIs in baldder cancer are greater than expected, and thus further research and strategies to deal with these adverse events is required.*

# 3. Methods

*Describe your methods. That should describe the data, the cleaning processes, and the analysis approaches. You might want to provide a shorter description here and all the details in the supplement.* *This part has not been completed. The source code has been left as is* *Details have been provided in the data acquisition and statistical analysis parts.*

## 3.1 Data aquisition

*In order to obtain the FAERS data, the ICIs were used to search by product. Pembrolizumab, atezolizumab, avelumab, and nivolumab were the keywords used. Previously, durvalumab, and ipilimumab were also approved for bladder cancer treatment. However, this indication has since then been removed by the manufacturers. As such, these were not considered. Following this, the search was limited to cases of bladder cancer. A total of 1,886 reactions were obtained.*

## 3.2 Data import and cleaning

*The file has been downloaded as an Excel file. The code for the analysis would involve loading the file, removing duplicates, assessing missing data, and deciding whether to remove it.* *This will be followed by filtering the data to retain only irAEs. While this step could be performed within the FAERS dashboard, this is not always a straightforward process. FAERS writes all the reactions associated with an agent in a single column, such that one column may have over 10-15 reactions. As such, this step will be performed here.*

*The FAERS data initially consisted of 2948 reactions associated with ICIs in bladder cancer.*

*Reactions with concomitant suspect products, combination products, and those which were not irAEs were removed. This resulted in a total of 369 cases. The details are available in the processing code file.*

## 3.3 Statistical analysis

*The first of the analysis will consists of descriptive statistics. Continous variables will be summarized as means, whereas categorical variables will be summarized as counts and percenatges.*

*The second part of the analysis will involve a disproportionality analysis. This analysis uses the following formula to calculate the reported odds ratio (ROR).*

*a = irAES reported with ICIs* *b = irAEs reported with all other drugs* *c = All other AEs reported with ICIs* *d = All other AEs reported with other drugs*

*ROR = a/c / b/d*

*Other details in the analysis will be finalized later.*

# 4. Results

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## 4.1 Exploratory/Descriptive analysis

[Table 1](#tbl-summarytable) *provides the patient characteristics, and summary of reactions by type of immune checkpoint inhibitor, and organ system affected.*

*The mean age reported was 66.94±17.65. A large percentage of the reactions occurred in males (70.2%). This may be because bladder cancer is much more common in males than in females.*

*Over 60% of the reactions were associated with pembrolizumab. A majority of the reactions were serious (83.7%)*

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| Table 1: Table 1: Descriptive Statistics   | Category | Value | | --- | --- | | Age | 66.94 ± 17.65 | | Sex |  | | Female | 76 (20.6%) | | Male | 259 (70.2%) | | Not Specified | 34 (9.2%) | |  |  | | Immune Checkpoint Inhibitors |  | | Atezolizumab | 69 (18.7%) | | Avelumab | 33 (8.9%) | | Nivolumab | 35 (9.5%) | | Pembrolizumab | 232 (62.9%) | |  |  | | Outcome |  | | Non-Serious | 60 (16.3%) | | Serious | 309 (83.7%) | |  |  | | Reporter Type |  | | Consumer | 51 (13.8%) | | Healthcare Professional | 318 (86.2%) | |  |  | | Country |  | | Outside US | 208 (56.4%) | | US | 161 (43.6%) | |  |  | | Reaction Type |  | | Cardiovascular | 27 (7.3%) | | Endocrinological | 66 (17.9%) | | Gastrointestinal | 69 (18.7%) | | Neurological | 35 (9.5%) | | Other | 165 (44.7%) | | Skin | 118 (32%) | |

## 4.2 Basic statistical analysis

[*Figure 1*](#fig-result) *shows the number of reactions by drug, along with the seriousness of the reaction.*

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| Figure 1: Bar chart of outcome of immune checkpoint inhibitors |

[*Figure 2*](#fig-result1) *shows the bar chart by type of organ system involved in the reaction.*

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| Figure 2: Bar chart of types of reactions |

## 4.3 Full analysis

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*Use one or several suitable statistical/machine learning methods to analyze your data and to produce meaningful figures, tables, etc. This might again be code that is best placed in one or several separate R scripts that need to be well documented. You want the code to produce figures and data ready for display as tables, and save those. Then you load them here.*

Example [Table 2](#tbl-resulttable2) shows a summary of a linear model fit.

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| Table 2: Linear model fit table.   | term | estimate | std.error | statistic | p.value | | --- | --- | --- | --- | --- | | (Intercept) | 149.2726967 | 23.3823360 | 6.3839942 | 0.0013962 | | Weight | 0.2623972 | 0.3512436 | 0.7470519 | 0.4886517 | | GenderM | -2.1244913 | 15.5488953 | -0.1366329 | 0.8966520 | | GenderO | -4.7644739 | 19.0114155 | -0.2506112 | 0.8120871 | |

# 5. Discussion

## 5.1 Summary and Interpretation

*Summarize what you did, what you found and what it means.*

## 5.2 Strengths and Limitations

*Discuss what you perceive as strengths and limitations of your analysis.*

## 5.3 Conclusions

*What are the main take-home messages?*

*Include citations in your Rmd file using bibtex, the list of references will automatically be placed at the end*

Note that this cited reference will show up at the end of the document, the reference formatting is determined by the CSL file specified in the YAML header. Many more style files for almost any journal [are available](https://www.zotero.org/styles). You also specify the location of your bibtex reference file in the YAML. You can call your reference file anything you like.

# 6. References

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