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)

Pooja Gokhale, PharmD

**Authors**

* Pooja Gokhale, PharmD (ORCID: 0000-0002-7505-7007)

**Author affiliations**

1. Department of Clinical and Administrative Pharmacy, College of Pharmacy, University of Georgia, Athens, GA, USA.

Corresponding author: poojaGokhale@uga.edu

# 1. Summary/Abstract

*Background: Bladder cancer is the ninth most common type of cancer worldwide. Treatment options include surgery, chemotherapy and immunotherapy. Immune checkpoint inhibitors (ICIs) are a class of immunotherapeutic agents recommended for the treatment of bladder cancer. ICIs have been associated with certain immune-related adverse events (irAEs)*

*Methods: Reports in the FAERS dashbaord through December 2024 were analyzed for irAEs to four ICIs recommended in bladder cancer - atezolizumab, avelumab, nivolumab, and pembrolizumab. Standardized queries were used to identify cases of rash, pruritus, hypothyroidism, hyperthyroidism, colitis, hepatitis, and nephritis. Descriptive and disproportionality analyses were performed to detect safety signals.*

*Results: To be added in Part 4*

# 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 2948 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 365 cases. The details are available in the processing code file.*

*The processing was done according to* [*Figure 1*](#fig-processing1)*.*

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| Figure 1: Study Flowchart |

## 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 employs Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Information Component (IC). Further details will be added in Part 4..*

# 4. Results

## 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   |  | Attribute | Atezolizumab | Avelumab | Nivolumab | Pembrolizumab | | --- | --- | --- | --- | --- | --- | | 1 | Attribute | Atezolizumab | Avelumab | Nivolumab | Pembrolizumab | | 1.1 | Age, mean years ± SD | 64.5 ± 13.2 | 72.2 ± 7.3 | 68.5 ± 13.2 | 66.6 ± 19.7 | | 2 | Male | 41 | 25 | 18 | 175 | | 3 | Female | 16 | 6 | 5 | 49 | | 4 | Not Specified (Sex) | 12 | 2 | 8 | 8 | | 5 | Serious | 57 | 30 | 25 | 193 | | 6 | Non-Serious (Reaction) | 12 | 3 | 6 | 39 | | 7 | Died | 5 | 5 | 2 | 30 | | 8 | Hospitalized | 28 | 9 | 7 | 78 | | 9 | Disabled | 1 | 0 | 0 | 2 | | 10 | Life Threatening | 0 | 1 | 0 | 7 | | 11 | Non-Serious (Outcome) | 12 | 3 | 6 | 39 | | 12 | Other Outcomes | 23 | 15 | 16 | 76 | | 13 | Healthcare Professional | 64 | 31 | 25 | 194 | | 14 | Consumer | 5 | 2 | 6 | 38 | | 15 | US | 28 | 4 | 25 | 100 | | 16 | Outside US | 22 | 19 | 6 | 129 | | 17 | Not Specified (Country) | 19 | 10 | 0 | 3 | |

## 4.2 Basic statistical analysis

[*Table 2*](#tbl-summarytable1) *shows the number of reactions by organ system and the ICI.*

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| Table 2: Table 2: Reactions by organ system and drug   |  | Reaction | Atezolizumab | Avelumab | Nivolumab | Pembrolizumab | | --- | --- | --- | --- | --- | --- | | 1 | Reaction | Atezolizumab | Avelumab | Nivolumab | Pembrolizumab | | 1.1 | Cardiovascular | 4 (1.1%) | 5 (1.4%) | 1 (0.3%) | 17 (4.7%) | | 2 | Endocrinological | 13 (3.6%) | 6 (1.6%) | 5 (1.4%) | 42 (11.5%) | | 3 | Gastrointestinal | 16 (4.4%) | 6 (1.6%) | 6 (1.6%) | 41 (11.2%) | | 4 | Neurological | 6 (1.6%) | 1 (0.3%) | 3 (0.8%) | 25 (6.8%) | | 5 | Other | 13 (3.6%) | 12 (3.3%) | 9 (2.5%) | 79 (21.6%) | | 6 | Renal | 9 (2.5%) | 3 (0.8%) | 4 (1.1%) | 14 (3.8%) | | 7 | Respiratory | 3 (0.8%) | 1 (0.3%) | 3 (0.8%) | 11 (3%) | | 8 | Skin | 27 (7.4%) | 7 (1.9%) | 6 (1.6%) | 78 (21.4%) | |

[*Figure 2*](#fig-result) *shows the number of reactions by drug, along with the seriousness of the reaction.*

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| Figure 2: Bar chart of outcome of immune checkpoint inhibitors |

[*Figure 3*](#fig-result1) *shows the bar chart by type of organ system involved in the reaction.*

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| Figure 3: Bar chart of types of reactions |

## 4.3 Full analysis

*The following tables show the results from the disproportionality analysis.*

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| Table 3: Table 1: Atezolizumab Reactions by Organ System   |  | Reaction | Atezolizumab PRR (95% CI) | Atezolizumab ROR (95% CI) | Atezolizumab IC (95% CI) | | --- | --- | --- | --- | --- | | 1 | Reaction | Atezolizumab PRR (95% CI) | Atezolizumab ROR (95% CI) | Atezolizumab IC (95% CI) | | 1.1 | All irAEs | 0.69 (0.56, 0.85) | 0.64 (0.5, 0.82) | -0.42 (-0.66, -0.17) | | 2 | Rash | 0.73 (0.37, 1.45) | 0.73 (0.36, 1.46) | -0.35 (-1.14, 0.44) | | 3 | Pruritus | 1.59 (0.79, 3.2) | 1.61 (0.79, 3.26) | 0.47 (-0.18, 1.12) | | 4 | Hypothyroidism | 0.21 (0.03, 1.58) | 0.21 (0.03, 1.58) | -1.93 (-4.67, 0.8) | | 5 | Hyperthyroidism | 3.51 (1.07, 11.45) | 3.53 (1.07, 11.61) | 1.1 (0.33, 1.87) | | 6 | Colitis | 0.49 (0.14, 1.65) | 0.48 (0.14, 1.65) | -0.84 (-2.34, 0.67) | | 7 | Hepatitis | 2.92 (0.73, 11.65) | 2.94 (0.73, 11.77) | 0.97 (-0.02, 1.97) | | 8 | Nephritis | 3.65 (0.98, 13.56) | 3.68 (0.98, 13.73) | 1.12 (0.29, 1.96) | |

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| Table 4: Table 2: Avelumab Reactions by Organ System   |  | Reaction | Avelumab PRR (95% CI) | Avelumab ROR (95% CI) | Avelumab IC (95% CI) | | --- | --- | --- | --- | --- | | 1 | Reaction | Avelumab PRR (95% CI) | Avelumab ROR (95% CI) | Avelumab IC (95% CI) | | 1.1 | All irAEs | 0.79 (0.59, 1.06) | 0.75 (0.53, 1.07) | -0.31 (-0.7, 0.08) | | 2 | Rash | 0.54 (0.17, 1.71) | 0.53 (0.16, 1.71) | -0.83 (-2.4, 0.75) | | 3 | Pruritus | 0.81 (0.25, 2.64) | 0.81 (0.25, 2.67) | -0.27 (-1.82, 1.28) | | 4 | Hypothyroidism | 3.05 (0.98, 9.51) | 3.08 (0.97, 9.75) | 1.32 (0.12, 2.52) | | 5 | Hyperthyroidism | 0.84 (0.11, 6.52) | 0.84 (0.11, 6.57) | -0.23 (-2.92, 2.46) | | 6 | Colitis | 0.42 (0.06, 3.11) | 0.42 (0.06, 3.12) | -1.16 (-3.92, 1.59) | | 7 | Hepatitis | 1.2 (0.15, 9.7) | 1.2 (0.15, 9.78) | 0.23 (-2.41, 2.87) | | 8 | Nephritis | 1.05 (0.13, 8.35) | 1.05 (0.13, 8.42) | 0.06 (-2.6, 2.72) | |

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| Table 5: Table 3: Nivolumab Reactions by Organ System   |  | Reaction | Nivolumab PRR (95% CI) | Nivolumab ROR (95% CI) | Nivolumab IC (95% CI) | | --- | --- | --- | --- | --- | | 1 | Reaction | Nivolumab PRR (95% CI) | Nivolumab ROR (95% CI) | Nivolumab IC (95% CI) | | 1.1 | All irAEs | 0.53 (0.39, 0.73) | 0.47 (0.33, 0.68) | -0.82 (-1.24, -0.39) | | 2 | Rash | 0.4 (0.13, 1.29) | 0.4 (0.12, 1.28) | -1.19 (-2.77, 0.39) | | 3 | Pruritus | 0.39 (0.09, 1.64) | 0.39 (0.09, 1.64) | -1.22 (-3.15, 0.72) | | 4 | Hypothyroidism | 1.58 (0.45, 5.56) | 1.58 (0.44, 5.63) | 0.55 (-0.91, 2) | | 5 | Hyperthyroidism | 0.63 (0.08, 4.91) | 0.63 (0.08, 4.93) | -0.59 (-3.28, 2.1) | | 6 | Colitis | 1.05 (0.31, 3.55) | 1.05 (0.31, 3.59) | 0.06 (-1.44, 1.57) | | 7 | Hepatitis | 0.9 (0.11, 7.3) | 0.9 (0.11, 7.34) | -0.13 (-2.77, 2.51) | | 8 | Nephritis | 0 (0, NaN) | 0 (0, NaN) | -Inf (-Inf, NaN) | |

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| Table 6: Table 4: Pembrolizumab Reactions by Organ System   |  | Reaction | Pembrolizumab PRR (95% CI) | Pembrolizumab ROR (95% CI) | Pembrolizumab IC (95% CI) | | --- | --- | --- | --- | --- | | 1 | Reaction | Pembrolizumab PRR (95% CI) | Pembrolizumab ROR (95% CI) | Pembrolizumab IC (95% CI) | | 1.1 | All irAEs | 1.8 (1.52, 2.14) | 2.07 (1.69, 2.55) | 0.36 (0.29, 0.44) | | 2 | Rash | 2.11 (1.17, 3.8) | 2.14 (1.18, 3.9) | 0.44 (0.17, 0.71) | | 3 | Pruritus | 0.99 (0.51, 1.94) | 0.99 (0.5, 1.95) | 0 (-0.49, 0.48) | | 4 | Hypothyroidism | 0.87 (0.32, 2.39) | 0.87 (0.31, 2.4) | -0.1 (-0.88, 0.67) | | 5 | Hyperthyroidism | 0.37 (0.1, 1.4) | 0.37 (0.1, 1.4) | -0.88 (-2.27, 0.51) | | 6 | Colitis | 1.99 (0.8, 4.91) | 2 (0.8, 4.97) | 0.41 (-0.02, 0.84) | | 7 | Hepatitis | 0.33 (0.07, 1.64) | 0.33 (0.07, 1.64) | -1 (-2.74, 0.73) | | 8 | Nephritis | 0.5 (0.12, 1.98) | 0.5 (0.12, 1.99) | -0.59 (-1.92, 0.74) | |

*The PRR and ROR when all irAEs are considered is greater than 1 for pembrolizumab (PRR: 1.8 (1.52, 2.14), ROR: 2.07 (1.69, 2.55)). Similary, the IC is greater than 0 (0.36 (0.29, 0.44)). Thus, there is a safety signal associated with pembrolizumab for all irAEs.*

*When considering individual irAEs, pembrolizumab also has a safety signal for rash (PRR: 2.11 (1.17, 3.8), ROR: 2.14 (1.18, 3.9), IC: 0.44 (0.17, 0.71).*

*Atezolizumab has a safety signal for hyperthyroidism (PRR: 3.51 (1.07, 11.45), ROR: 3.53 (1.07, 11.61), IC: 1.1 (0.33, 1.87). There also may be a signal for nephritis (PRR: 3.65 (0.98, 13.56), ROR: 3.68 (0.98, 13.73), IC: 1.12 (0.29, 1.96), though the 95% CI for PRR and ROR is not greater than 1 (though very close to 1).*

*Similarly, avelumab may has a safety signal for hypothyroidism (PRR: 3.05 (0.98, 9.51), ROR: 3.08 (0.97, 9.75), IC: 1.32 (0.12, 2.52)).*

*No significant safety signals were found for nivolumab.*

# 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.

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