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

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: Out of 2948 cases identified from FAERS, 365 cases with irAEs were analyzed. The largest number of cases were reported for pembrolizumab (n=307), followed by atezolizumab (n = 91), avelumab (n = 41), and nivolumab (n =37). Pembrolizumab was found to have safety signals for all irAEs considered together (PRR: 1.8 (1.52, 2.14), ROR: 2.07 (1.69, 2.55), IC: 0.36 (0.29, 0.44)). A safety signal was also found for rash (PRR: 2.11 (1.17, 3.8), ROR: 2.14 (1.18, 3.9), IC: 0.44 (0.17, 0.71)). Safety signals for atezolizumab included hyperthyroidism and nephritis, while hypothyroidism was identified as a concern for avelumab.

Conclusion: Immune-related adverse events are found to be associated with immune checkpoint inhibitor therapy in bladder cancer. Pembrolizumab appears to have the highest risk, though this may be due to its early approval (2014). Appropriate treatment guidelines must be developed to address the management of irAEs associated with ICI therapy in bladder cancer.

# 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 pneumonitis, 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

The FAERS dashboard was searched by product to obtain cases related to the use of ICIs in bladder cancer. This data was then filtered to retain only irAE cases. Other adverse events and duplicate cases were removed. Following this, the demographic and drug characteristics were summarized.

To assess whether an ICI has a safety signal associated with a particular irAE, three metrics were used: 1. Proportional reporting ratio (PRR): This approach compares the proportion of reports for a specific adverse event with a drug of interest to the proportion of the same event reported for all other drugs.

1. Reporting odds ratio (ROR): This metric is obtained by comparing the ratio of a drug’s adverse event reports to all other reports for that drug against the same ratio across all drugs.
2. Information component (IC): For this metric, the observed vs. expected reporting of a drug-adverse event combination is compared.

A random forest model was fit to distinguish between serious and non-serious cases on the basis of age, sex, and ICI.

## 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 was downloaded as an Excel file. First, the column were renamed so as to make them easier to use in code. Then, products with concomitant drugs were removed, so as to focus only on cases associated with ICIs. Then, cases which also had other drugs as the suspect active ingredients were removed. This was followed by retaining only the irAEs. A list of common irAEs was used. This list is available in the supplementary material. Any reactions which had the same age, weight, FDA received date, country of occurrence, suspected active ingredient, and reported reaction were considered duplicates and were removed. Following this, the reactions were coded according to the MedDRA Preferred Terms (PTs), and classified according to the System Organ Class (SOC). The age values were converted to numeric and the countries were re-classified as US, outside US, and not specified. The code for the analysis would involve loading the file, removing duplicates, assessing missing data, and deciding whether to remove it. 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

Firstly, descriptive statistics were used to describe the demographic and other characteristics. This was followed by creating some descriptive figures. The PRR, ROR and IC (along with their 95% CI) were then calculated to assess the drug signal. A random forest model was built using age, sex, and ICI, to distinguish between serious and non-serious cases.

# 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%).

Most of the reaction were reported by healthcare professionals. Since FAERS is a US-based dashboard, many reactions were reported from the US.

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| Table 1: Descriptive Statistics   | **Attribute** | **Atezolizumab** | **Avelumab** | **Nivolumab** | **Pembrolizumab** | | --- | --- | --- | --- | --- | | Age, mean years ± SD | 64.5 ± 13.2 | 72.2 ± 7.3 | 68.5 ± 13.2 | 66.6 ± 19.7 | | Sex |  |  |  |  | | Male | 41 | 25 | 18 | 175 | | Female | 16 | 6 | 5 | 49 | | Not Specified (Sex) | 12 | 2 | 8 | 8 | | Severity of reaction |  |  |  |  | | Serious | 57 | 30 | 25 | 193 | | Non-Serious (Reaction) | 12 | 3 | 6 | 39 | | Outcomes |  |  |  |  | | Died | 5 | 5 | 2 | 30 | | Hospitalized | 28 | 9 | 7 | 78 | | Disabled | 1 | 0 | 0 | 2 | | Life Threatening | 0 | 1 | 0 | 7 | | Non-Serious (Outcome) | 12 | 3 | 6 | 39 | | Other Outcomes | 23 | 15 | 16 | 76 | | Reporter type |  |  |  |  | | Healthcare Professional | 64 | 31 | 25 | 194 | | Consumer | 5 | 2 | 6 | 38 | | Country |  |  |  |  | | US | 28 | 4 | 25 | 100 | | Outside US | 22 | 19 | 6 | 129 | | 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: Reactions by Organ System and Drug   | **Reaction** | **Atezolizumab** | **Avelumab** | **Nivolumab** | **Pembrolizumab** | | --- | --- | --- | --- | --- | | Cardiovascular | 4 (1.1%) | 5 (1.4%) | 1 (0.3%) | 17 (4.7%) | | Endocrinological | 13 (3.6%) | 6 (1.6%) | 5 (1.4%) | 42 (11.5%) | | Gastrointestinal | 16 (4.4%) | 6 (1.6%) | 6 (1.6%) | 41 (11.2%) | | Neurological | 6 (1.6%) | 1 (0.3%) | 3 (0.8%) | 25 (6.8%) | | Other | 13 (3.6%) | 12 (3.3%) | 9 (2.5%) | 79 (21.6%) | | Renal | 9 (2.5%) | 3 (0.8%) | 4 (1.1%) | 14 (3.8%) | | Respiratory | 3 (0.8%) | 1 (0.3%) | 3 (0.8%) | 11 (3%) | | Skin | 27 (7.4%) | 7 (1.9%) | 6 (1.6%) | 78 (21.4%) | |

Pembrolizumab has the highest number of reactions. The largest percentage of reactions are classified as “Other”. These include reactions which do not belong to the other organ classes, such as myositis.

## 4.3 Full analysis

For the disproportionality analysis, we need 4 different values: a: Number of reports reporting both the drug and the adverse event. b: Number of reports reporting the drug but not the adverse event. c: Number of reports reporting the adverse event but not the drug. d: Number of reports reporting neither the drug nor the adverse event.

For PRR, the formula used is: (a/(a+c)) / (b/(b+d))

For ROR: (a/c)/(b/d)

For IC: log2((a+b+c+d)/(a+c)\*(a+b)/n)

The following tables show the results from the disproportionality analysis.

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| Table 3: Atezolizumab Reactions by Organ System   | **Reaction** | **Atezolizumab PRR (95% CI)** | **Atezolizumab ROR (95% CI)** | **Atezolizumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.69 (0.56, 0.85) | 0.64 (0.5, 0.82) | -0.42 (-0.66, -0.17) | | Rash | 0.73 (0.37, 1.45) | 0.73 (0.36, 1.46) | -0.35 (-1.14, 0.44) | | Pruritus | 1.59 (0.79, 3.2) | 1.61 (0.79, 3.26) | 0.47 (-0.18, 1.12) | | Hypothyroidism | 0.21 (0.03, 1.58) | 0.21 (0.03, 1.58) | -1.93 (-4.67, 0.8) | | Hyperthyroidism | 3.51 (1.07, 11.45) | 3.53 (1.07, 11.61) | 1.1 (0.33, 1.87) | | Colitis | 0.49 (0.14, 1.65) | 0.48 (0.14, 1.65) | -0.84 (-2.34, 0.67) | | Hepatitis | 2.92 (0.73, 11.65) | 2.94 (0.73, 11.77) | 0.97 (-0.02, 1.97) | | 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: Avelumab Reactions by Organ System   | **Reaction** | **Avelumab PRR (95% CI)** | **Avelumab ROR (95% CI)** | **Avelumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.79 (0.59, 1.06) | 0.75 (0.53, 1.07) | -0.31 (-0.7, 0.08) | | Rash | 0.54 (0.17, 1.71) | 0.53 (0.16, 1.71) | -0.83 (-2.4, 0.75) | | Pruritus | 0.81 (0.25, 2.64) | 0.81 (0.25, 2.67) | -0.27 (-1.82, 1.28) | | Hypothyroidism | 3.05 (0.98, 9.51) | 3.08 (0.97, 9.75) | 1.32 (0.12, 2.52) | | Hyperthyroidism | 0.84 (0.11, 6.52) | 0.84 (0.11, 6.57) | -0.23 (-2.92, 2.46) | | Colitis | 0.42 (0.06, 3.11) | 0.42 (0.06, 3.12) | -1.16 (-3.92, 1.59) | | Hepatitis | 1.2 (0.15, 9.7) | 1.2 (0.15, 9.78) | 0.23 (-2.41, 2.87) | | 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: Nivolumab Reactions by Organ System   | **Reaction** | **Nivolumab PRR (95% CI)** | **Nivolumab ROR (95% CI)** | **Nivolumab IC (95% CI)** | | --- | --- | --- | --- | | All irAEs | 0.53 (0.39, 0.73) | 0.47 (0.33, 0.68) | -0.82 (-1.24, -0.39) | | Rash | 0.4 (0.13, 1.29) | 0.4 (0.12, 1.28) | -1.19 (-2.77, 0.39) | | Pruritus | 0.39 (0.09, 1.64) | 0.39 (0.09, 1.64) | -1.22 (-3.15, 0.72) | | Hypothyroidism | 1.58 (0.45, 5.56) | 1.58 (0.44, 5.63) | 0.55 (-0.91, 2) | | Hyperthyroidism | 0.63 (0.08, 4.91) | 0.63 (0.08, 4.93) | -0.59 (-3.28, 2.1) | | Colitis | 1.05 (0.31, 3.55) | 1.05 (0.31, 3.59) | 0.06 (-1.44, 1.57) | | Hepatitis | 0.9 (0.11, 7.3) | 0.9 (0.11, 7.34) | -0.13 (-2.77, 2.51) | | Nephritis | 0 (0, NaN) | 0 (0, NaN) | -Inf (-Inf, NaN) | |

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

A random forest model was built to distinguish between serious and non-serious outcomes using age, sex, and ICI. Inverse weighting was used to deal with the class imbalance. The model was built using cross-validation.

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| Table 7: Random Forest Evaluation Metrics   | **Metric** | **Value** | | --- | --- | | Metric | Value | | Accuracy | 0.2533 | | Precision | 0.1661 | | Recall | 0.8778 | | F1-Score | 0.2791 | | AUC-ROC | 0.541 | |

We see that the accuracy is quite low (~25%). The model is not able to distinguish well between serious and non-serious cases, classifying most non-serious cases as serious. This issue arises due to the class imbalance in the data used to train the model (305 serious cases out of 365). Advanced machine learning methods may be explored to overcome this problem. Some additional methods will be considered in part 5.

# 5. Discussion

## 5.1 Summary and Interpretation

In this study, the safety signals for the most commonly reported irAEs in clinical trials were assessed. Safety signals for pembrolizumab included all irAEs as a whole, as well as a signal for rash. Hyperthyroidism was a concern with atezolizumab, while nephritis may also be an issue. Hypothyroidism could be of concern with avleumab use. No specific signals were found with nivolumab.

## 5.2 Strengths and Limitations

This study used data from the FAERS dashboard, and thus provides real-world evidence regarding the association of irAEs with ICI use in bladder cancer. To my knowledge, this is the first study using FAERS data to assess this association. However, the findings of this study must be considered in context of certain limitations. Firstly, FAERS data has several limitations. The dashboard cannot provide causal information. This is a voluntary system. In the US, only drug manufacturers are mandated to reported adverse events. This means that all events are not reported. Additionally, the reports may have duplicates, or may be incomplete. Efforts have been made in this study to remove the duplicates, but data completeness cannot be ensured. Pembrolizumab was approved in 2014, while avelumab, nivolumab, and atezolizumab were initially approved in 2017, with additonal approvals in later years for other stages of bladder cancer. As such, the larger number of reports associated with pembrolizumab may simple be due to the larger reporting time. A future analysis with additional data may find different results to the one obtained using data until December 2024.

## 5.3 Conclusions

Immune checkpoint inhibitor therapy are associated with immune-related adverse events (particularly rash, hypothyroidism, hyperthyroidism, and nephritis) in bladder cancer. Currently, no established guidelines exist to manage these adverse events. There is a need to develop centralized guidelines and protocols for managing irAEs associated with ICI therapy.

*More details will be added in part 5 to the discussion section.*

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