Immune-Related Adverse Events (irAEs) in NSCLC Patients Treated with Programmed Cell Death-1 (PD-1) Inhibitors – An Analysis Using the Data from FDA Adverse Event Reporting System (FAERS)

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BACKGROUND

PD-1 inhibitors have emerged as a frontline treatment for several types of cancer based on their ability to support the immune system in attacking and shrinking tumors. However, PD-1 inhibitor therapies are also known to be associated with immune-related adverse events (irAEs).

In this study we examined the magnitude of irAE risk associated with PD-1 inhibitors by organ system. In addition, we estimated the occurrence of serious outcomes of these irAEs in patients treated with either PD-1 or non PD-1 inhibitor therapies.

OBJECTIVES

The objectives of the study are to estimate:

- Prevalence of irAEs among NSCLC patients treated with PD-1 inhibitors and non PD-1 inhibitors
- Risk of developing irAEs associated with PD-1 inhibitors therapy by organ system
- Risk of serious outcomes in PD-1 inhibitors and non PD-1 inhibitors therapy

DATABASE AND ANALYSIS APPROACH

- The study was based on the FAERS database for the period from January 2015 to December 2020. NSCLC patients were identified using NLP algorithm, accounting for a total of 85,261 adverse events (AEs) reports. Duplicate reports were deleted in accordance with FDA guidelines and the most recent case number for the analysis was considered irrespective of the therapies. Only those adverse events where the drug was reported as the primary suspect were analyzed (N=46,878).
- Of the various AEs involved in the shortlisted reports, only those that accounted for at least 1% of the reports were included in the analysis. These AEs were examined to check if they were immune related or otherwise. The irAEs were further classified based on the different organ systems including endocrine, cardio-vascular, gastro-intestinal & digestive, musculo-skeletal, nervous system and skin.
- Reports involving specific PD-1 inhibitors (nivolumab, pembrolizumab and cemiplimab) were identified using text string searches for each drug of their generic names, brand names, and abbreviations. The remaining drugs were identified as non PD-1 inhibitors. Descriptive analyses were used to summarize characteristics of adverse event reports treated with 1) any therapies, and 2) only treated with PD-1 inhibitors. Frequency distributions of irAEs and health outcomes for each organ system were reported.
- The disproportionality analyses with reporting odds ratios (ROR) were estimated to quantify the event signals in the FAERS database. The ROR estimates the odds of irAEs in those exposed to PD-1 inhibitors divided by the odds of irAEs in those not exposed to PD-1 inhibitors (i.e. all other drugs in the database). A significant disproportionality, or in other words a possible signal, was defined as the lower bound of the 95% confidence interval (95% CI) exceeding 1. This algorithm was used for the analysis of irAEs in any and each organ system.
- Health outcomes for irAE events were presented as three major groups: death, disability and other serious outcomes (i.e. life-threatening, hospitalization and other outcomes). All statistical analyses were conducted using SAS 9.4.

RESULTS

Study population

A total of 46,878 adverse events were considered for the analysis. Of these, 15,035 (32.1%) adverse events were reported related to PD-1 inhibitors and 31,843 (67.9%) adverse events were reported related to non PD-1 inhibitors.

Characteristics of study population

- Among 46,878 AE reports, males accounted for 50.9% of the AEs and females 37.6% of the AEs. The gender information was not available for 11.5% of reports. There was no substantial difference in mean age of males and females (66.2 years and 64.6 years respectively).
- Among 1,817 irAEs, 1,315 irAEs were reported related to PD-1 inhibitors. Of these, males reported two times higher irAEs than females (65.9% vs. 27.8%) among patients on PD-1 inhibitor therapy. The mean age of males and females were reported as 68.2 years and 67.1 years respectively.
- More than 99.2% of adverse event reports were submitted by manufacturers (either as expediated or periodic reports).

Table 1. Characteristics of immune-related adverse events (irAEs) among NSCLC patients FDA Adverse Event Reporting System 2015–2020

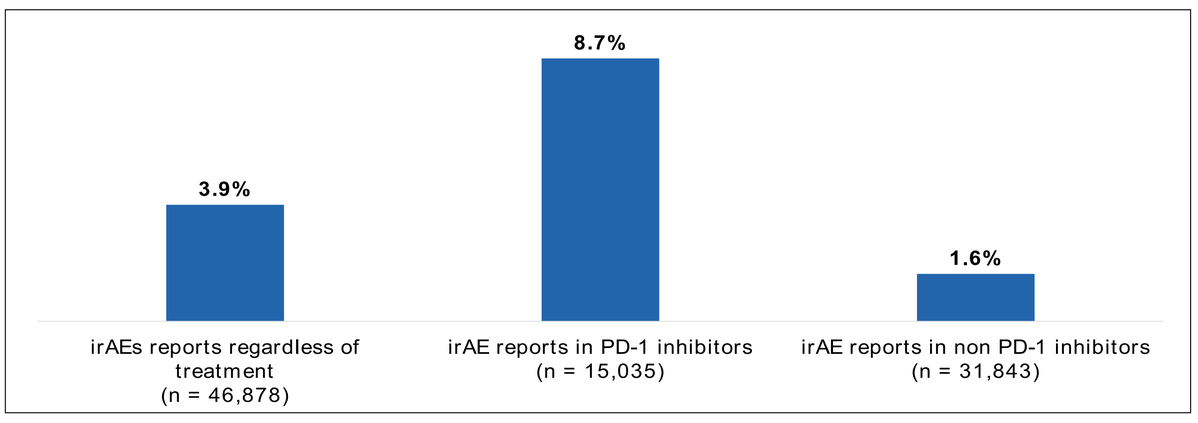
Characteristics	Number of reports (n, %)		
	Any AE reports (N=46,878)	Overall irAEs reports (N=1,817)	irAEs in PD-1 inhibitors (N=1,315)
Patient sex			
Female	17,605 (37.6%)	537 (29.6%)	365 (27.8%)
Male	23,883 (50.9%)	1,164 (64.1%)	867 (65.9%)
Not specified	5,390 (11.5%)	116 (6.4%)	83 (6.3%)
Summary statistics of patient age			
Female average ± SD	64.6 ± 11.92	65.9 ± 11.88	67.1 ± 11.52
Male average ± SD	66.2 ± 10.53	67.7 ± 9.72	68.2 ± 9.53
Patient age group (year)			
<65	14,682 (31.3%)	557 (30.7%)	382 (29.0%)
65-74	13,061 (27.9%)	652 (35.9%)	473 (36.0%)
75+	7,534 (16.1%)	379 (20.9%)	298 (22.7%)
Not specified	11,601 (24.7%)	229 (12.6%)	162 (12.3%)
Report type			
Direct	398 (0.8%)	18 (1.0%)	15 (1.1%)
Expediated	42,236 (90.1%)	1,742 (95.9%)	1,259 (95.7%)
Periodic	4,244 (9.1%)	57 (3.1%)	41 (3.1%)

irAE reports in patients treated with PD-1 inhibitors and non PD-1 inhibitors

Of all reports included in the study, 3.9% were seen to be irAEs. Of the reports related to PD-1 inhibitors, 8.7% were irAEs, compared to 1.6% of reports related to non PD-1 inhibitors. The occurrence of irAEs in PD-1 inhibitors was thus five times higher than in non PD-1 inhibitors.

RESULTS

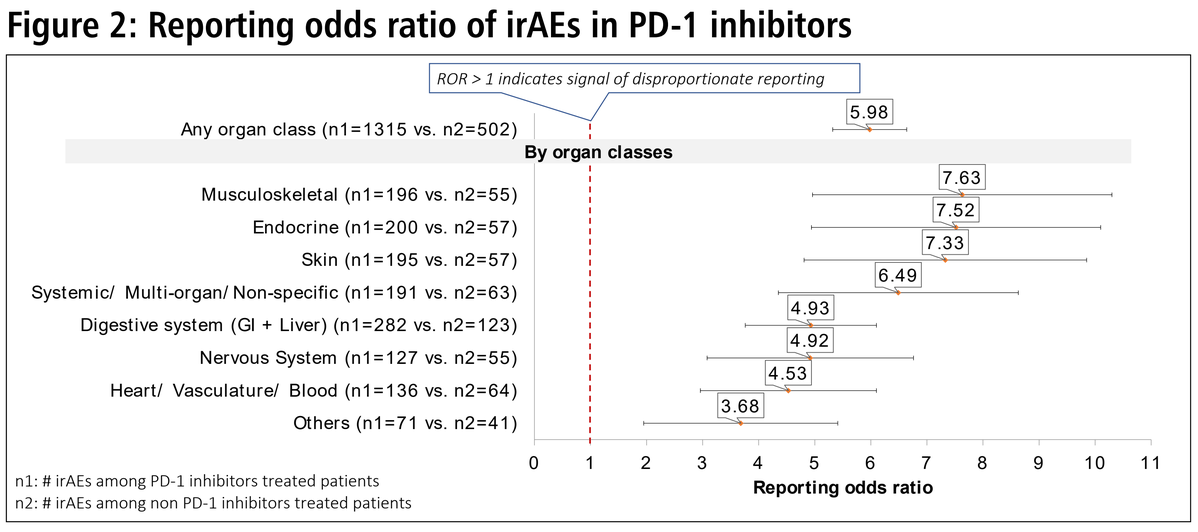
Figure 1: irAE reports in patients treated with PD-1 inhibitors and non PD-1 inhibitors



Reporting odds ratio of irAEs in PD-1 inhibitors

- The likelihood of developing any irAEs in any organ system and in each organ system were studied using reporting odds ratio (ROR) with 95% confidence intervals.
- The risk of developing irAEs in any organ system was 5.98 with 95% CI of 5.39-6.64 in PD-1 inhibitors compared to non PD-1 inhibitors.
- The associated risk of irAEs is the highest in musculoskeletal systems (ROR: 7.63 CI: 5.65-10.30), followed by endocrine system (ROR: 7.52 CI: 5.60-10.10) and skin (ROR: 7.33 CI:5.45-9.85).
- The associated risk of irAEs is relatively lower in cardiovascular/blood related systems (ROR: 4.53 CI: 3.36-6.10) and other organ systems – eye, ear, kidney and lungs collectively (ROR: 3.68 CI: 2.50-5.41).

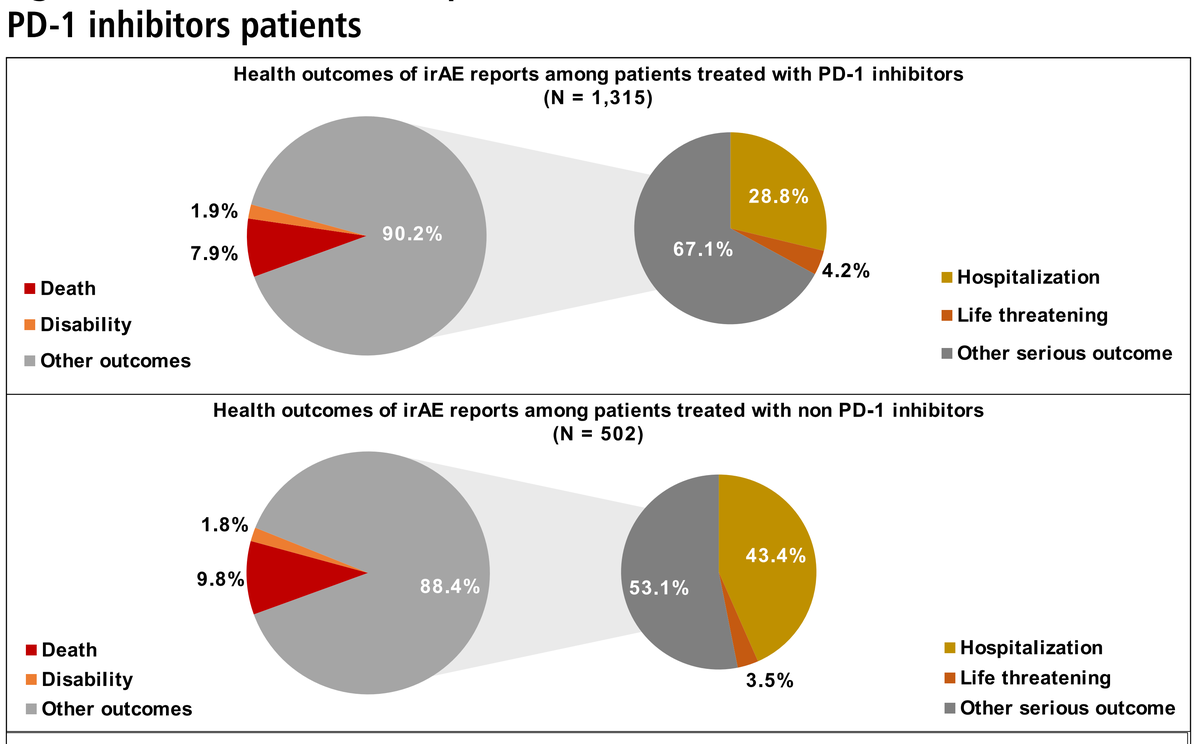
Figure 2: Reporting odds ratio of irAEs in PD-1 inhibitors



Health outcomes of irAE reports

- Health outcomes of irAEs among those who were treated with PD-1 inhibitors and non PD-1 inhibitors are shown in Figure 3. It is observed that there was a significant difference in outcomes reported in both the therapies.
- The proportion of deaths among patients who were treated with PD-1 inhibitors (7.9%) was lower than the patients who were treated with non PD-1 inhibitors (9.8%). The proportion of hospitalizations was also significantly lower in patients treated with PD-1 inhibitors.

Figure 3: Health outcomes in patients treated with PD-1 inhibitors and non PD-1 inhibitors patients



Note: Percentages are based on non missing values

CONCLUSION

- Our findings are consistent with the existing evidence of higher incidence of irAEs in patients who are concomitantly or sequentially treated with PD-1 inhibitor therapies. This study revealed that among NSCLC patients risk of developing irAEs associated with musculoskeletal system is the highest.
- The proportion of reports with death and hospitalization outcomes were lower in patients treated with PD-1 inhibitors while disability outcome is comparable in patients treated with PD-1 and non PD-1 inhibitors.
- The current study is based on FAERS database, a voluntary reporting system. This might result in reporting bias which includes wide variation in data quality, such as missing data in reports, misclassification of events and outcomes, and misspelling of drug names. We have used multiple methods for coding and analysis of data to minimize the impact of reporting bias. The rate of reporting and lack of information in the FAERS database might lead either to under-reporting or overreporting of adverse events.
- Finally, our findings are for hypothesis generation rather than testing. These findings need to be interpreted cautiously and follow-up studies are required to further explore hypotheses generated by this data.

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Immune-Related Adverse Events (irAEs) in Melanoma Patients Treated with Programmed Cell Death-1 (PD-1) Inhibitors – An Analysis Using the Data from FDA Adverse Event Reporting System (FAERS)

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BACKGROUND

PD-1 inhibitors have emerged as a frontline treatment for several types of cancer based on their ability to support the immune system in attacking and shrinking tumors. However, PD-1 inhibitor therapies are also known to be associated with immune-related adverse events (irAEs).

In this study we examined the magnitude of irAE risk associated with PD-1 inhibitors by organ system. In addition, we estimated the occurrence of serious outcomes of these irAEs in patients treated with either PD-1 or non PD-1 inhibitor therapies.

OBJECTIVES

The objectives of the study are to estimate:

- Prevalence of irAEs among melanoma patients treated with PD-1 inhibitors and non PD-1 inhibitors
- Risk of developing irAEs associated with PD-1 inhibitors therapy by organ system
- Risk of serious outcomes in PD-1 inhibitors and non PD-1 inhibitors therapy

DATABASE AND ANALYSIS APPROACH

- The study was based on the FAERS database for the period from January 2015 to December 2020. Melanoma patients were identified using NLP algorithm, accounting for a total of 100,415 adverse events (AEs) reports. Duplicate reports were deleted in accordance with FDA guidelines and the most recent case number for the analysis was considered irrespective of the therapies. Only those adverse events where the drug was reported as the primary suspect were analyzed (N=29,501).
- Of the various AEs involved in the shortlisted reports, only those that accounted for at least 1% of the reports were included in the analysis. These AEs were examined to check if they were immune related or otherwise. The irAEs were further classified based on the different organ systems including endocrine, cardio-vascular, gastro-intestinal & digestive, musculo-skeletal, nervous system and skin.
- Reports involving specific PD-1 inhibitors (nivolumab, pembrolizumab and cemiplimab) were identified using text string searches for each drug of their generic names, brand names, and abbreviations. The remaining drugs were identified as non PD-1 inhibitors. Descriptive analyses were used to summarize characteristics of adverse event reports treated with 1) any therapies, and 2) only treated with PD-1 inhibitors. Frequency distributions of irAEs and health outcomes for each organ system were reported.
- The disproportionality analyses with reporting odds ratios (ROR) were estimated to quantify the event signals in the FAERS database. The ROR estimates the odds of irAEs in those exposed to PD-1 inhibitors divided by the odds of irAEs in those not exposed to PD-1 inhibitors (i.e. all other drugs in the database). A significant disproportionality, or in other words a possible signal, was defined as the lower bound of the 95% confidence interval (95% CI) exceeding 1. This algorithm was used for the analysis of irAEs in any and each organ system.
- Health outcomes for irAE events were presented as three major groups: life threatening, hospitalization,disability and other serious outcomes (i.e. death and other outcomes). All statistical analyses were conducted using SAS 9.4.

RESULTS

Study population

A total of 29,501 adverse events were considered for the analysis. Of these, 11,464 (38.9%) adverse events were reported related to PD-1 inhibitors and 18,037 (61.1%) adverse events were reported related to non-PD-1 inhibitors.

Characteristics of study population

- Among 29,501 AE reports, males accounted for 50.3% of the AEs and females 36.8% of the AEs. The gender information was not available for 12.9% of reports. There was no substantial difference in mean age of males and females (62.4 years and 59.7 years respectively).
- Among 2,149 irAEs, 1,536 irAEs were reported related to PD-1 inhibitors. Of these, males reported 1.4 times higher irAEs than females (54.1% vs. 39.2%) among patients on PD-1 inhibitor therapy. The mean age of males and females were reported as 65.9 years and 62.8 years respectively.
- Nearly 97% of adverse event reports were submitted by manufacturers (either as expediated or periodic reports).

Table 1. Characteristics of immune-related adverse events (irAEs) among melanoma patients FDA Adverse Event Reporting System 2015–2020

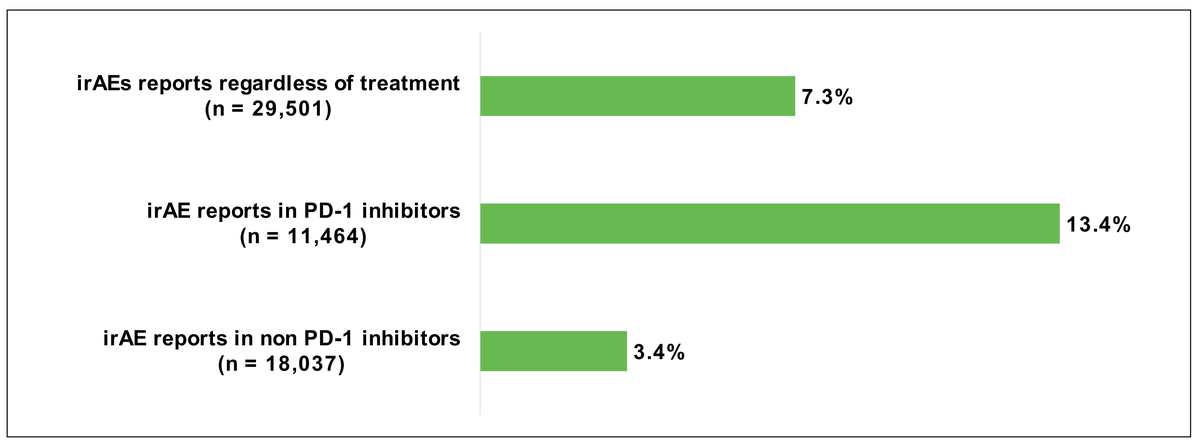
Characteristics	Number of reports (n, %)		
	Any AE reports (N=29,501)	Overall irAEs reports (N=2,149)	irAEs in PD-1 inhibitors (N=1,536)
Patient sex			
Female	10,852 (36.8%)	830 (38.6%)	602 (39.2%)
Male	14,833 (50.3%)	1,148 (53.4%)	831 (54.1%)
Not specified	3,816 (12.9%)	171 (8.0%)	103 (6.7%)
Summary statistics of patient age			
Female average ± SD	59.7±15.07	62.5±14.03	62.8±14.07
Male average ± SD	62.4±14.12	64.5±13.80	65.9±13.16
Patient age group (year)			
<65	10,857 (36.8%)	851 (39.6%)	580 (37.8%)
65-74	5,282 (17.9%)	484 (22.5%)	368 (24.0%)
75+	3,765 (12.8%)	442 (20.6%)	353 (23.0%)
Not specified	9,597 (32.5%)	372 (17.3%)	235 (15.3%)
Report type			
Direct	946 (3.2%)	44 (2.0%)	23 (1.5%)
Expediated	23,793 (80.7%)	2,010 (93.5%)	1,451 (94.5%)
Periodic	4,762 (16.1%)	95 (4.4%)	62 (4.0%)

irAE reports in patients treated with PD-1 inhibitors and non PD-1 inhibitors

Of all reports included in the study, 7.3% were seen to be irAEs. Of the reports related to PD-1 inhibitors, 13.4% were irAEs, compared to 3.4% of reports related to non PD-1 inhibitors. The occurrence of irAEs in PD-1 inhibitors was thus four times higher than in non PD-1 inhibitors.

RESULTS

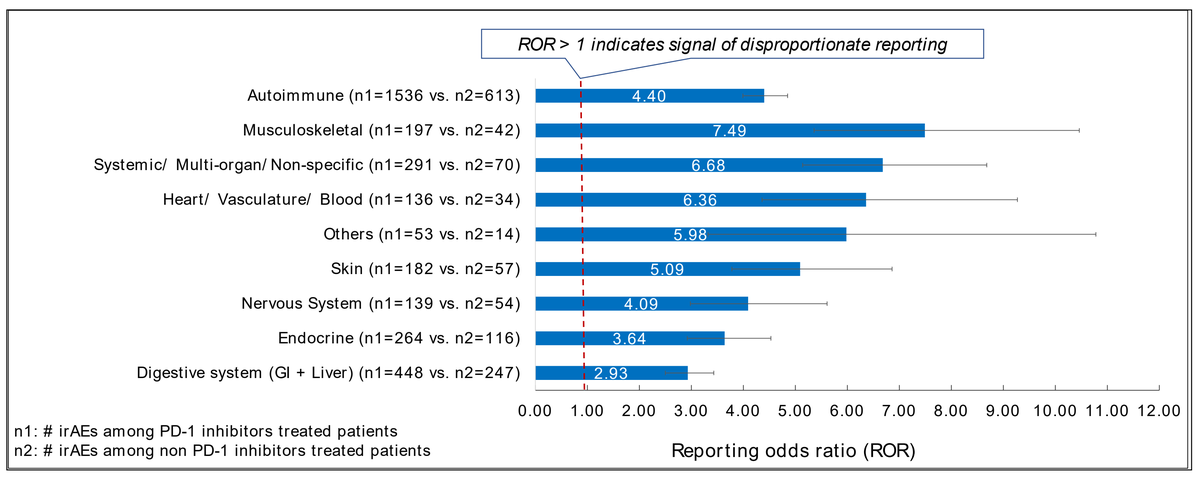
Figure 1: irAE reports in patients treated with PD-1 inhibitors and non PD-1 inhibitors



Reporting odds ratio of irAEs in PD-1 inhibitors

- The likelihood of developing any irAEs in any organ system and in each organ system were studied using reporting odds ratio (ROR) with 95% confidence intervals.
- The risk of developing irAEs in any organ system was 4.40 with 95% CI of 3.99-4.85 in PD-1 inhibitors compared to non PD-1 inhibitors.
- The associated risk of irAEs is the highest in musculoskeletal systems (ROR: 7.49 CI: 5.36-10.46), followed by systemic/multi-organ/non-specific (ROR: 6.68 CI: 5.14-8.68) and heart/vasculature/ blood (ROR: 6.36 CI: 4.36-9.27).
- The associated risk of irAEs is relatively lower in endocrine systems (ROR: 3.64 CI: 2.92-4.53) and digestive system (GI and liver) (ROR: 2.93 CI: 2.50-3.43).

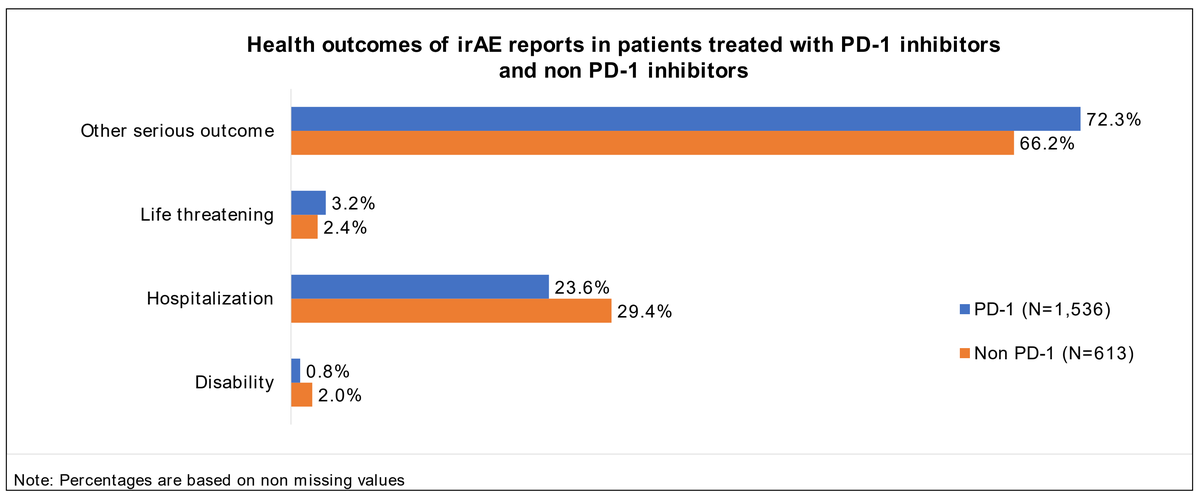
Figure 2: Reporting odds ratio of irAEs in PD-1 inhibitors



Health outcomes of irAE reports

- Health outcomes of irAEs among those who were treated with PD-1 inhibitors and non PD-1 inhibitors are shown in Figure 3. It is observed that there was a significant difference in outcomes reported in both the therapies.
- The proportion of hospitalization among patients who were treated with PD-1 inhibitors (23.6%) was lower than the patients who were treated with non PD-1 inhibitors (29.4%). The proportion of disability was also significantly lower in patients treated with PD-1 inhibitors (0.8% in PD-1 inhibitors vs. 2.0% in non PD-1 inhibitors).

Figure 3: Health outcomes in patients treated with PD-1 inhibitors and non PD-1 inhibitors patients



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