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Bullous disorders associated with PD-1 and PD-L1 inhibitors: pharmacovigilance analysis of the FDA Adverse Event Reporting System (FAERS) from the Research on Adverse Drug events And Reports (RADAR) Program

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To the Editor:

Although bullous disorders (BDs) are increasingly recognized as associated with PD-1 (nivolumab [NI], pembrolizumab [PE]) and PD-L1 inhibitors (atezolizumab [AT], avelumab [AV], durvalumab [DU]), the characterization of BD events in the Full Prescribing Information (FPI) for these agents is not well-delineated as represented by the FPIs for NI (PD-1)[1] and AV (PD-L1)[2].

When used as monotherapy, the most recent FPIs for these agents, collectively through 2018, simply report dermatologic events as “Rash, All Grades” (up to 40% of patients) and “Rash, Grades 3-4” (up to 1.6% of patients). Moreover, although “Rash, Grades 3-4” is variously described, it is not specific to BDs. Yet, a retrospective analysis of data from 853 oncodermatology patients [each of whom were treated with one of the five PD-1 or PD-L1 inhibitors] found nearly 1% of patients experienced a BD[3].

We therefore aimed to determine if an association exists between PD-1/PD-L1 agents and BDs in the FDA Adverse Event Reporting System (FAERS). Using RADAR methodology[4], we searched FAERS from the first FDA approval date (table 1) to the last quarter for which data were available (Q1 2018).

The FAERS database was searched using MedDRA BD terms (Pemphigoid, Pemphigus, and Bullous Dermatitis) for patients receiving PD-1 (nivolumab, pembrolizumab) and PD-L1 inhibitors (atezolizumab, avelumab, durvalumab) and linked to a serious outcome (Death,

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Disability, Hospitalization, Life-Threatening, Required Intervention to Prevent Permanent Impairment/Damage, or Other Serious). Proportional Reporting Ratio (PRR) was used for detection of a safety signal. PRR corresponds to the ratio of observed frequency (occurrence of the adverse event(s) of interest) in the exposed population (drug(s) of interest) to the non-exposed population (table 2). It is a measure of association and may be considered by some to be the equivalent of the Relative Risk (RR) used for cohort studies. A safety signal is detected if the follow criteria are met: number of events >3, chi-square result >4, and PRR >2 [5].

A safety signal was detected in FAERS for PD-1 inhibitors: NI (N=99; PRR: 5.87; 95 %CI: 4.88-7.29), PE (N=43; PRR: 6.36; 95%CI: 4.71-8.59), and for 2 of 3 PD-L1 inhibitors: AT (N=7; PRR: 3.31; 95%CI: 1.58-6.95) and DU (N=4; PRR: 7.87; 95%CI: 2.96-20.96). Although there were no reports for BDs with AV, this finding may or may not indicate there is a lower risk for BDs with AV. Importantly, for all agents, these findings do not indicate causality and cannot be used to determine incidence or risk ratio [5].

A limitation for this study includes reporting bias within a voluntary reporting system such as FAERS along with possible report redundancy. Also, the retrospective nature of this study precludes chart review and verification of previously collected data collected.

This post-marketing real-world data analysis revealed an association between BDs and exposure to a PD-1/PD-L1 inhibitor, in aggregate. Given that additional data are emerging for BDs and PD-1/PD-L1 inhibitors, these current findings from the FAERS database serve to further inform practitioners of newly evolving information about the risk for bullous disorders associated with these agents.

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Table 1.

FAERS data through Q1 2018: Reports for bullous disorders by drug name

Drug (Class)	N	Safety Signal [5] for BD	Date of FDA Approval
Nivolumab (PD-1)	99	Yes	Dec 22, 2014
Pembrolizumab (PD-1)	43	Yes	Sep 2, 2014
Atezolizumab (PD-L1)	7	Yes	May 18, 2016
Durvalumab (PD-L1)	4	Yes	May 1, 2017
Avelumab (PD-L1)	0	No	Mar 23, 2017

Table 2.

Calculation of the proportional reporting ratio (PRR)[5]

2x2 Table		
	Drug of Interest	**All Other drugs**
Adverse Event of Interest	a	b
All other Adverse Events	c	d

PRR = a/(a + c) divided by b/(b + d)

The Chi-square is calculated as per standard statistical formula: $[(\text{observed-expected})^2/\text{expected}]$. Yates correction is recommended. Using the PRR, a signal is detected if the number of co-occurrences is 3 or more and the PRR is 2 or more with an associated $\chi 2$ value of 4 or more[5].