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ORIGINAL RESEARCH ARTICLE

Toxicities with Immune Checkpoint Inhibitors: Emerging Priorities From Disproportionality Analysis of the FDA Adverse Event Reporting System

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Abstract

Background Immune checkpoint inhibitors (ICIs), including antibodies targeting cytotoxic T-lymphocyte associated protein 4 (CTLA4) and programmed cell death 1 or its ligand (PD1/PDL1), elicit different immune-related adverse events (irAEs), but their global safety is incompletely characterized.

Objective The aim of this study was to characterize the spectrum, frequency, and clinical features of ICI-related adverse events (AEs) reported to the FDA Adverse Event Reporting System (FAERS).

Patients and methods AEs from FAERS (up to June 2018) recording ICIs (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab) as suspect were extracted. Comprehensive disproportionality analyses were performed through the reporting odds ratio (ROR) with 95% confidence interval (95% CI), using other oncological drugs as comparison. An overview of systematic reviews (OoSRs) was also undertaken to identify irAEs with consistent positive associations.

Results ICIs were recorded in 47,266 reports, submitted mainly by consumers receiving monotherapy with anti-PD1/PDL1 drugs. Three areas of toxicity emerged from both disproportionality analysis and the OoSRs (32 studies): endocrine ($N = 2863$; ROR = 6.91; 95% CI 6.60–7.23), hepatobiliary (2632; 1.33; 1.28–1.39), and respiratory disorders (7240; 1.04; 1.01–1.06). Different reporting patterns emerged for anti-CTLA4 drugs (e.g., hypophysitis, adrenal insufficiency, hypopituitarism, and prescribed overdose) and anti-PD1/PDL1 agents (e.g., pneumonitis, cholangitis, vanishing bile duct syndrome, tumor pseudoprogression, and inappropriate schedule of drug administration). No increased reporting emerged when comparing combination with monotherapy regimens, but multiple hepatobiliary/endocrine/respiratory irAEs were recorded.

Conclusions This parallel approach through contemporary post-marketing analysis and OoSRs confirmed that ICIs are associated with a multitude of irAEs, with different reporting patterns between anti-CTLA4 and anti-PD1/PDL1 medications. Close clinical monitoring is warranted to early diagnose and timely manage irAEs, especially respiratory, endocrine, and hepatic toxicities, which warrant further characterization; patient- and drug-related risk factors should be assessed through analytical pharmaco-epidemiological studies and prospective multicenter registries.

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1 Introduction

Immunotherapy is changing the therapeutic landscape of several solid tumors. Immune checkpoint inhibitors (ICIs) represent the cornerstone of these novel targeted approaches: they increase antitumor immunity through blocking either cytotoxic T-lymphocyte antigen 4 (CTLA4), or programmed cell death 1 (PD1) or its ligand (PDL1) [1, 2]. Ipilimumab, the first anti-CTLA-4 drug, caused a paradigm shift in drug development of these drugs: lessons learnt with its novel response kinetics and delayed separation of Kaplan–Meier survival curves led to a change in primary outcomes from response-based end points (overall response rate or progression-free survival) to overall survival [3].

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Key Points

As anticipated from pre-approval clinical trials, immune checkpoint inhibitors (ICIs) are associated with large post-marketing reporting of diverse immune-related adverse events (irAEs), occurring in virtually any organ or tissue.

Gastrointestinal disorders, hypophysitis, and adrenal insufficiency were more frequently reported with anti-CTLA4 drugs, whereas thyroid dysfunction, pneumonitis, cholangitis, and vanishing bile duct syndrome were more frequently reported with anti-PD1/PDL1 agents.

This comprehensive analysis of the FDA Adverse Event Reporting System, together with a structured appraisal of published systematic reviews, identified endocrine, hepatic, and respiratory toxicities as emerging safety priorities.

These toxicities should be further characterized to verify the existence of a class effect (liver injury), assess incidence, and elucidate patient- and drug-related risk factors.

From a safety standpoint, the increased activity of the immune system results in a unique and distinct spectrum of side effects, the so-called immune-related adverse events (irAEs), which can affect different organs, especially the gastrointestinal tract, endocrine glands, lungs, and liver. Although irAEs are mild to moderate in severity and usually manageable [4], fulminant cases have been described [5], and the wide range of potential clinical manifestations requires a multidisciplinary collaborative team, with several unresolved questions [6], including recommendations for mitigating and management of specific toxicities [7], and optimal algorithms for personalized shut-off treatment [8]. Pre-approval trials have shown better safety than chemotherapy, although combination of both CTLA4 and PD1 inhibitors (acting on distinct lymphocyte subtypes and at different sites) caused a higher incidence and a broader spectrum of irAEs [9].

Considering that ICIs have entered clinical practice with great expectations, post-marketing monitoring is crucial, and the term 'immuno-vigilance' was recently coined [10]. Pivotal trials cannot fully assess rare adverse events (AEs) because of inconsistent reporting across trials [11], and case reports from the literature can only provide a partial epidemiological picture [12]. The analysis of international spontaneous reporting systems allows a broader perspective by collecting unpublished reports of AEs submitted worldwide occurring in real-world unselected oncological patients with comorbidities and poly-pharmacotherapy, even in the long-term; this ensures rapid detection of even rare irAEs and emerging clinical entities such as myocarditis and coronary toxicity [13, 14], especially for biological/biotechnological medicinal products with peculiar pharmacokinetics-pharmacodynamics [15].

In this pharmacovigilance study, we analyzed AEs submitted to the US FDA Adverse Event Reporting System (FAERS) in order to characterize their current safety profile (frequency, spectrum, clinical features), alone and in combination. Moreover, emerging toxicities were classified with relevant level of priority for further research, based on a structured literature appraisal.

2 Methods

2.1 Study Concept and Design

The study was conceived as an observational, retrospective pharmacovigilance analysis combined with literature appraisal to identify (expected or previously unknown) toxicities to be prioritized for further research (Fig. 1). The former was designed as a disproportionality approach based on unsolicited reports submitted to FAERS, whereas the latter was carried out as a purposive literature search for systematic reviews of randomized controlled trials (RCTs), now referred to as overview of systematic reviews (OoSRs). This mixed approach compared two different real-world datasets (those from observational practice and those from RCTs) and would allow to (a) identify previously unknown safety issues, (b) characterize known toxicities, and (c) provide a public health perspective to recognized irAEs.

2.1.1 FAERS: Features, Acquisition and Processing

FAERS is the US repository of AEs and medication errors spontaneously submitted by healthcare professionals, patients, and manufacturers, gathering worldwide reports (including European reports potentially related to serious events and other non-US non-European data). In the recent past, FAERS and other spontaneous reporting systems were exploited in a number of post-marketing drug safety studies to assess both short- and long-term AEs for heterogeneous pharmacological classes [16], including biological products [17–20]. FAERS is particularly attractive among international pharmacovigilance databases because it covers a heterogeneous catchment area (allowing broader generalization of findings) and offers public access to raw data that can be downloaded in a format suitable for customized analyses [21]. Moreover, previous studies have demonstrated great

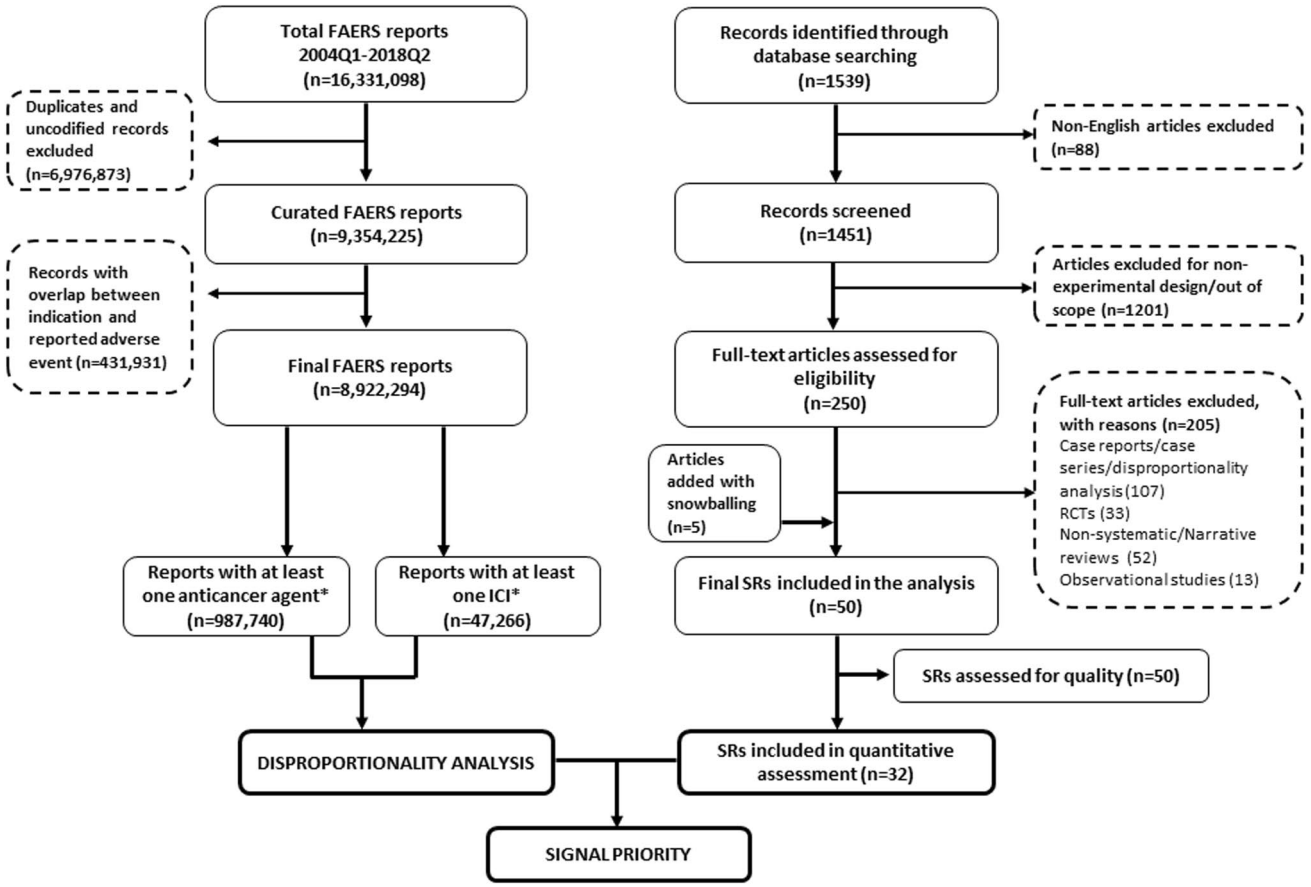

Fig. 1 Flow chart to compare the FAERS analysis with the literature assessment. *FAERS* FDA Adverse Event Reporting System, *ICI* immune checkpoint inhibitor, *RCTs* randomized controlled trials, *SRs* systematic reviews, *Primary Suspect or Secondary Suspect (see text for details)

accuracy in early detection of safety issues, especially for newly approved drugs (i.e., on the market for no more than 5 years) [22], as well as for AEs with low/rare background incidence [23].

A publicly released version of FAERS was downloaded from the relevant website (from the first quarter [Q1] of 2004 through Q2 of 2018). Before performing customized statistical analyses, FAERS was processed for data quality, including removal of duplicates (i.e., reports with overlaps in three out of four key fields, namely event date, age, gender, and reporter country), and standardization of drug names into relevant active substances [24]. AEs were analyzed through the standardized Medical Dictionary for Regulatory Activities (MedDRA) terminology (version 19); in FAERS, they are coded in terms of Preferred Terms (PTs), which identified specific signs/symptoms of a given clinical entity. The hierarchical structure of MedDRA allows grouping of PTs (high specificity) into relevant System Organ Class (SOC, high sensitivity).

2.1.2 Disproportionality Analysis

Disproportionality analysis is a validated concept in pharmacovigilance that compares the proportion of selected AEs reported for a single drug or drug class (e.g., ICIs) with the proportion of the same AEs for a control group of drugs (e.g., other anticancer agents). The denominator in these analyses is the total number of reports of AEs for each group of drugs. If the proportion of AEs is greater in patients exposed to a specific drug (cases) than in patients not exposed to this drug (non-cases), an association can be hypothesized between the specific drug and the event. Through this so-called *case/non-case* approach, which can be viewed as a case–control analysis, the reporting odds ratio (ROR) with relevant 95% confidence interval (CI) was calculated. Disproportionality was considered statistically significant when the lower limit of the 95% CI of the ROR exceeds 1, as recommended [24, 25]. Exposure assessment considered ICIs (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab approved as of June

2018) recorded as 'primary suspect' or 'secondary suspect'. Therefore, active substances and brand names represented our criteria to select reports relevant to ICIs.

Pharmacovigilance in oncology is not straightforward compared with other medical areas. Frequent use of multiple therapeutic regimens makes it difficult to disentangle side effects of individual drugs versus drug–drug interactions versus 'innocent bystander' effects [26]. Moreover, complexity of patient histories results in high potential for confounding and effect modification (i.e., drug–disease interactions). Finally, the unique benefit–risk consideration may result in a higher threshold for recognizing and reporting AEs. Therefore, different data-mining steps were specifically performed to refine disproportionality analysis and minimize biases as follows: (a) to reduce the likelihood of false positives, disproportionality was calculated only when at least five cases of interest were reported, instead of the traditional signaling criterion of three cases [27]; (b) to provide a clinical perspective, the so-called analysis by therapeutic area (main analysis) was adopted by comparing ICIs versus other oncological drugs (using AEs recorded for at least one anticancer agent) [28]; (c) to minimize the existence of an 'indication bias' (i.e., the indication for which the drug is prescribed is reported as an AE), reports with overlap between therapeutic indication and reported AE were removed a priori from the whole FAERS database (e.g., melanoma reported as an AE in patients receiving nivolumab for melanoma).

Analyses were first performed at the SOC level to describe the spectrum of toxicities. Subsequently, key toxicities emerging from the combined assessment with the literature were characterized in terms of specific signs/symptoms (PT level) and ICI regimens (anti-CTLA4 and anti-PD1/PDL1 drugs, monotherapy vs combination therapy). Additional analyses were also performed to test the consistency of results by selecting only data after April 2011 (i.e., considering the affective period on the market of ICIs, with the approval of the first-in-class ipilimumab on March 23, 2011); and comparing ICIs with monoclonal antibodies (considering the biotechnological nature of these drugs and pharmacological similarities). Statistical analyses were performed through PostgreSQL software version 9.5 and RStudio.

2.2 Literature Selection and Appraisal

The OoSRs was conducted in MEDLINE (via PubMed, on 29 October 2018) to find SRs of RCTs on the safety of ICI, with restriction to English articles published up to June 2018. Detailed criteria for article retrieval (search strategy) and eligibility are provided as electronic supplementary material (ESM, Supplementary Material 1).

This OoSRs adopts an 'evidence summary' approach. First, potentially eligible SRs were assessed for quality by applying the validated AMSTAR tool [29]. Second, SRs were assessed for actual eligibility as follows: only direct comparisons between ICIs (as a class or as a single drug) and chemotherapy were selected (indirect network meta-analyses were excluded); meta-analysis without SRs (e.g., pooled analysis) or meta-analysis on the overall safety without specifying/separating AEs in terms of affected organ/system (e.g., fatal irAEs) were excluded. Third, risk estimates were extracted for the various safety outcomes, and used to assess study results. If a statistically significant odds ratio/hazard ratio was found, the study was deemed as 'positive', namely it demonstrated an increased occurrence/risk of a given AE with ICIs; 'negative' studies were those with a statistically significant reduced occurrence/risk with ICIs; 'neutral' studies were defined when there was no evidence of a significant difference (ICIs as safe as comparator) or these was uncertainty/inconclusive data (e.g., high heterogeneity or inconsistencies across sensitivity analyses). SRs reporting only incidence rates were not evaluated, whereas SRs investigating multiple AEs counted as many-fold as the number of outcomes investigated. In case of multiple analyses, data on grade 3–4 severity were preferred.

Because multiple SRs were identified on the same topic, the totality of SRs was evaluated for robustness (consistency of the findings among SRs in relation to the number of published studies). The following assessment was finally adopted:

Consistent Positive Association—more than half of SRs were concordant in documenting an increased occurrence with ICIs;

Consistent Negative Association—more than half of SRs were concordant in documenting a reduced occurrence with ICIs;

Neutral Association—more than half of SRs were concordant in documenting no evidence of risk;

Uncertain Association—a single SR was available, or conflicting results from two or more SRs.

2.3 Definition of the Level of Priority

Data from the literature appraisal and disproportionality analysis were compared for consistency of findings, and four levels of priority were assigned to the different toxicities.

(a) *Top priority:* toxicity emerging from disproportionality, with consistent positive association from the OoSRs (i.e., concordance between pre-approval and post-marketing evidence).
(b) *High priority:* toxicity emerging from disproportionality without data from OoSRs (i.e., only evidence from post-marketing data).
(c) *Intermediate priority:* toxicity without disproportionality but consistent positive association from the OoSRs (i.e., only evidence from pre-approval data).

(d) *Low priority:* toxicity without disproportionality and neutral/uncertain association from OoSRs.

As anticipated, top and high priorities were further characterized through additional disproportionality analyses in terms of specific signs/symptoms and ICI regimens.

3 Results

3.1 Descriptive Analysis of FAERS and Literature Appraisal

Over the 15-year period, 16,331,098 FAERS reports were initially processed for drug codification, duplicate removal, and aforementioned quality criteria; 8922,294 reports were finally retained, of which 47,266 (0.53%) included at least one ICI (Fig. 1). The highest number of reports emerged for nivolumab ($N = 24,560$) followed by ipilimumab ($N = 13,971$) and pembrolizumab ($N = 10,425$). The reported country was US in 57% of reports. Young adults and subjects aged > 65 years old were similarly represented (30–33%), with slight male preponderance (53%, with very similar proportions across various medications) (Table 1). The majority of reports were serious (> 80%), namely resulting in hospitalization (30%), death (29%), or life-threatening events (3%). A peak in reporting of death was noted for atezolizumab (50%). Notably, consumers were the main source of reports (34%, peaking at 79% for atezolizumab), followed by other healthcare professionals and clinicians (30% each). Over the years, there was an exponential increase in the number of submitted reports, especially for monotherapy regimens with anti-PD1/PDL1 drugs, with two remarkable peaks in the first quarter of 2017 and second quarter of 2018 (Fig. 2). *General disorders and administration site conditions* was the SOC with the highest number of reports (16,449), followed by *gastrointestinal disorders* (9124) and *neoplasms benign, malignant and unspecified (incl. cysts and polyps)* (8773).

The literature search yielded 1539 studies, which were screened based on the aforementioned exclusion criteria: 50 SRs were retained and evaluated for quality, of which 32 were used for quantitative assessment (Fig. 1). The overall quality according to the AMSTAR tool was judged high (≥ 9) for 25 SRs (Supplementary Material 1, see ESM). Skin (13 studies), gastrointestinal (11), respiratory (10), hepatobiliary (9), and endocrine disorders (8) were the most frequently investigated toxicities. Consistent positive associations finally emerged for endocrine, hepatobiliary, gastrointestinal, skin, and respiratory disorders, whereas blood/lymphatic system disorders and general disorders and administration site conditions were deemed to be consistent negative associations.

3.2 Disproportionality Analysis of FAERS

The disproportionality analysis highlighted six areas of toxicity with statistically significant ROR: *endocrine disorders* ($N = 2863$; ROR = 6.91; 95% CI 6.60–7.23), *hepatobiliary disorders* (2632; 1.33; 1.28–1.39), *injury, poisoning and procedural complications* (6776; 1.20; 1.17–1.23), *neoplasms benign, malignant and unspecified (incl. cysts and polyps)* (8773; 1.85; 1.81–1.90), *respiratory, thoracic and mediastinal disorders* (7240; 1.04; 1.01–1.06), *surgical and medical procedures* (1298; 1.20; 1.13–1.27) (Table 2).

Results were consistent across sensitivity analyses. Specifically, the ROR remained statistically significant when ICIs were compared with monoclonal antibodies, with the exception of *respiratory, thoracic and mediastinal disorders* (ROR = 0.92; 95% CI 0.90–0.95); likewise, no major changes to the RORs emerged when the analyses were restricted to the 2011Q2–2018Q2 period, with the exception of *metabolism and nutrition disorders,* which reached the threshold for statistical significance (1.13; 1.10–1.17). No disproportionate reporting was found when comparing monotherapy with combination regimens, whereas a different reporting frequency (i.e., statistically significant ROR) emerged when anti-CTLA4 agents were compared with anti-PD1/PDL1 medications for different toxicities, including *endocrine disorders* (1.60; 1.46–1.75), *eye disorders* (1.21; 1.05–1.39), *gastrointestinal disorders* (2.03; 1.93–2.15), *metabolism and nutrition* (1.15; 1.06–1.25), *pregnancy, puerperium and perinatal conditions* (2.28; 1.07–4.86), and *skin and subcutaneous tissue disorders* (1.28; 1.19–1.37).

3.3 Characterization of Emerging Toxicities

The combined analysis of FAERS data with the literature appraisal highlighted *endocrine, hepatobiliary*, and *respiratory disorders* as top priorities, whereas *injury, poisoning and procedural complications*, *neoplasm (benign, malignant and unspecified) disorders,* and *surgical/medical procedures* emerged as high priorities (Table 3). The most frequently reported AEs with disproportionality for all ICIs were *hypothyroidism* ($N = 777$; ROR = 6.36; 95% CI 5.85–6.93), *hypophysitis* (594; 20.80; 11.13–38.86), and *adrenal insufficiency* (493; 10.03; 8.88–11.33) for endocrine events, with higher reporting with anti-CTLA4 agents; conversely, thyroid dysfunctions were more frequent with anti-PD1/PDL1 drugs. For liver injuries, the ranking was *hepatitis* (420; 3.12; 2.81–3.47), *hepatic function abnormal* (385; 1.55; 1.39–1.72), and *autoimmune hepatitis* (373; 14.23; 11.90–17.00), with higher reporting for *cholangitis* with anti-PD1/PDL1 medicines (106; 2.51; 2.05–3.07). For respiratory toxicities, disproportionality was found for *pneumonitis* (1289; 4.06; 3.82–4.32) and *interstitial lung disease* (794; 1.63; 1.52–1.75), with higher reporting frequency for

Table 1 Demographic data

Total reports		ICI as a class 47,266 (%)	Nivolumab 24,560 (%)	Ipilimumab 13,971 (%)	Pembrolizumab 10,425 (%)	Atezolizumab 2663 (%)	Durvalumab 405 (%)	Avelumab 383 (%)
Geographical distribution	EU	11,437 (24.20)	6718 (27.35)	3270 (23.41)	1816 (17.42)	896 (33.65)	149 (36.79)	145 (37.86)
	Non EU							
	Africa	83 (0.18)	50 (0.20)	13 (0.09)	19 (0.18)	4 (0.15)		
	Americas	27,134 (57.41)	12,974 (52.83)	9363 (67.02)	6058 (58.11)	1286 (48.29)	228 (56.3)	143 (37.34)
	Asia	7298 (15.44)	4150 (16.90)	876 (6.27)	2197 (21.07)	424 (15.92)	20 (4.94)	72 (18.80)
	Oceania	1253 (2.65)	636 (2.59)	419 (3.00)	327 (3.14)	52 (1.95)	7 (1.73)	23 (6.01)
Age group distribution	0–17 y	118 (0.25)	73 (0.30)	31 (0.22)	21 (0.20)	6 (0.23)		
	18–64 y	14,261 (30.17)	7089 (28.86)	5046 (36.12)	2968 (28.47)	1052 (39.50)	135 (33.33)	171 (44.65)
	>65 y	15,489 (32.77)	7801 (31.76)	4013 (28.72)	3980 (38.18)	1029 (38.64)	166 (40.99)	168 (43.86)
	UKW	17,401 (36.82)	9597 (39.08)	4881 (34.94)	3456 (33.15)	576 (21.63)	104 (25.68)	44 (11.49)
Patient sex distribution	Male	25,247 (53.41)	13,062 (53.18)	7561 (54.12)	5629 (54.00)	1425 (53.51)	218 (53.83)	205 (53.52)
	Female	15,329 (32.43)	7605 (30.96)	4481 (32.07)	3699 (35.48)	1002 (37.63)	151 (37.28)	158 (41.25)
	UKW	6694 (14.16)	3893 (15.85)	1929 (13.81)	1097 (10.52)	236 (8.86)	36 (8.89)	20 (5.22)
Outcome distribution[a]	HO	14,034 (29.69)	7096 (28.89)	5204 (37.25)	2567 (24.62)	1335 (50.13)	188 (46.42)	226 (59.01)
	DE	13,787 (29.17)	8068 (32.85)	3014 (21.57)	3160 (30.31)	521 (19.56)	64 (15.80)	87 (22.72)
	OT	10,560 (22.34)	5861 (23.86)	3032 (21.70)	2138 (20.51)	343 (12.88)	63 (15.56)	30 (7.83)
	LT	1632 (3.45)	839 (3.42)	423 (3.03)	426 (4.09)	130 (4.88)	17 (4.20)	21 (5.48)
	DS	287 (0.61)	123 (0.50)	51 (0.37)	108 (1.04)	14 (0.53)	2 (0.49)	1 (0.26)
	CA	3 (0.01)		1 (0.01)	2 (0.02)			
	UKW	6966 (14.74)	2573 (10.48)	2246 (16.08)	2024 (19.41)	320 (12.02)	71 (17.53)	18 (4.70)
Reporter's occupation distribution	CN	16,292 (34.47)	6919 (28.17)	5085 (36.40)	5141 (49.31)	167 (6.27)	21 (5.19)	10 (2.61)
	OT	14,241 (30.13)	9344 (38.05)	5750 (41.16)	1736 (16.65)	260 (9.76)	90 (22.22)	90 (23.50)
	MD	14,231 (30.11)	6855 (27.91)	2617 (18.73)	3049 (29.25)	2108 (79.16)	260 (64.20)	277 (72.32)
	PH	2284 (4.83)	1359 (5.53)	453 (3.24)	441 (4.23)	119 (4.47)	15 (3.70)	6 (1.57)
	LW	14 (0.03)	10 (0.04)		4 (0.04)			
	UKW	210 (0.44)	73 (0.30)	66 (0.47)	54 (0.52)	9 (0.34)	19 (4.69)	(0)
Therapeutic regimen	Monotherapy	42,156 (89.19)	19,606 (79.83)	8903 (63.72)	10,209 (97.93)	2652 (99.59)	404 (99.75)	382 (99.74)
	Combination	5110 (10.81)	4954 (20.17)	5068 (36.28)	216 (2.07)	11 (0.41)	1 (0.25)	1 (0.26)

Table 1 (continued)

Total reports		ICI as a class 47,266 (%)	Nivolumab 24,560 (%)	Ipilimumab 13,971 (%)	Pembrolizumab 10,425 (%)	Atezolizumab 2663 (%)	Durvalumab 405 (%)	Avelumab 383 (%)
Reporting year	Before 2011	68 (0.14)		68 (0.49)				
	2011	652 (1.38)	1 (0)	652 (4.67)				
	2012	1189 (2.52)	5 (0.02)	1187 (8.50)				
	2013	1080 (2.28)	26 (0.11)	1073 (7.68)				
	2014	2046 (4.33)	119 (0.48)	1646 (11.78)	393 (3.77)	3 (0.11)		
	2015	5157 (10.91)	2462 (10.02)	2111 (15.11)	1295 (12.42)	20 (0.75)		
	2016	10,989 (23.25)	7037 (28.65)	2079 (14.88)	2290 (21.97)	553 (20.77)	14 (3.46)	6 (1.57)
	2017	15,769 (33.36)	9098 (37.04)	3245 (23.23)	3777 (36.23)	1158 (43.48)	136 (33.58)	186 (48.56)
	2018[b]	10,316 (21.83)	5812 (23.66)	1910 (13.67)	2670 (25.61)	929 (34.89)	255 (62.96)	191 (49.87)

Relevant percentages are provided in parentheses (out of total reports). The sum of the number of cases for the different ICIs may be higher than the total number of cases for the drug class because a patient may have received more than one drug (combination regimen)

CA congenital anomaly, *CN* consumer, *DE* death, *DS* disability, *EU* European Union, *HO* hospitalization (initial or prolonged), *ICI* immune checkpoint inhibitor, *LT* life-threatening, *LW* lawyer, *MD* medical doctor, *OT (outcome distribution)* other serious (important medical event), *OT (reporter's occupation distribution)* other health professional, *PH* pharmacist, *UKW* unknown (missing data)

[a]Because different degrees of seriousness may be recorded in a single report, the final level of seriousness was assigned based on the following ranking: death > life-threatening > hospitalization > disability > congenital anomaly > other serious

[b]Up to Q2 (June 2018)

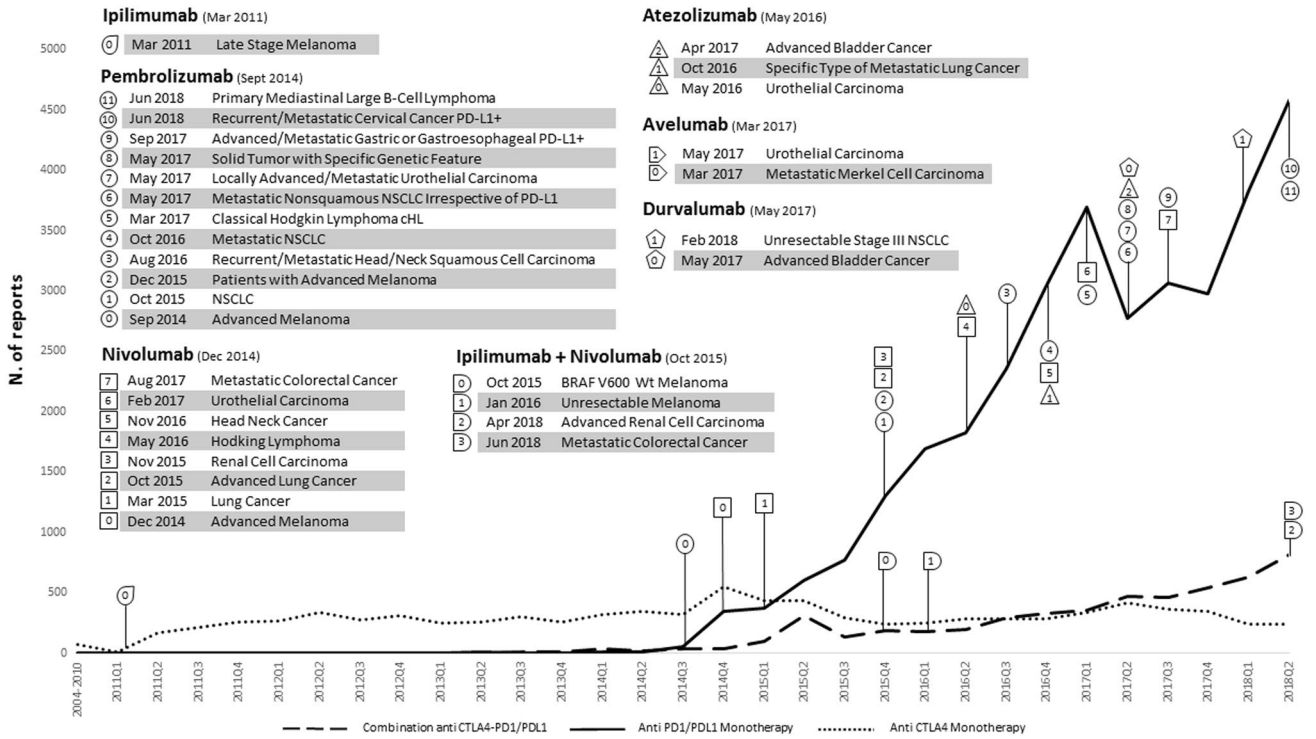

Fig. 2 Time trends of spontaneous reports collected for ICIs, according to the therapeutic regimen. Approval dates and therapeutic indications are also presented, according to the Food and Drug Administration. *CTLA4* cytotoxic T-lymphocyte associated protein 4, *ICIs* immune checkpoint inhibitors, *NSCLC* non-small cell lung cancer, *PD1/PDL1* programmed cell death 1 or its ligand

anti-PD1/PDL1 drugs (Table 4). Frequency of co-reporting among *endocrine*, *hepatobiliary* and *respiratory disorders* are presented in Fig. 3.

Among toxicities receiving high priority, the most frequently reported AEs were *malignant neoplasm progression* (6691; 5.94; 5.77–6.12), *product use in unapproved indication* (1734; 6.29; 5.94–6.66), and *transfusion* (172; 5.19; 4.37–6.16). Different reporting frequencies were observed for tumor pseudoprogression and inappropriate schedule of drug administration with anti-PD1/PDL1 drugs, and prescribed overdose for anti-CTLA4 agents. The full list of AEs (top and high priorities) with relevant disproportionality is provided in Supplementary Material 2, see ESM.

4 Discussion

To our knowledge, this is the largest comprehensive analysis of post-marketing AEs attributed to ICIs collected from a worldwide pharmacovigilance database; apart from recently approved avelumab and durvalumab, there is a considerable amount of data for nivolumab, ipilimumab (alone and in combination), and pembrolizumab.

Overall, four main findings emerged. First, the exponential increase in the number of AEs, especially since 2017, is noteworthy (ICIs account for 4.8% of total reports with anticancer drugs collected over 13 years). This may be ascribable to various reasons, including the perceived expectations of this immunotherapy, which reduced the phenomenon of 'clinical inertia' usually observed for non-anticancer drugs, and the rapid extension of therapeutic indications in different oncological settings for anti-PD1/PDL1 agents, as well as the case of agnostic approval for pembrolizumab.

Second, the spectrum of irAEs is variegate and virtually any organ or tissue can be involved: endocrine systems, liver, lung, gastrointestinal tract, and skin, among others, thus emphasizing the importance of timely identification and early personalized management through a multidisciplinary tumor board [7, 8]. Notably, individuals receiving ICIs may experience a unique set of AEs in comparison with first- and second-generation anticancer agents, including monoclonal antibodies; 'traditional' biologics are associated with a high frequency of reports related to general disorders/administration site condition (owing to the parenteral administration) and predictable toxicities such as infections and neoplasms due to an immune compromising

Table 2 Primary and secondary disproportionality analyses

Toxicity of interest	ICI versus other anti-cancer drugs (Q2/2004–Q2/2018)		ICIs versus other anti-cancer drugs (Q2/2011–Q2/2018)		ICIs versus monoclonal antibodies (Q2/2004–Q2/2018)		Monotherapy versus combination ($N=42,156$)		Anti-CTLA4 monotherapy versus anti-PD1/PDL1 monotherapy ($N=8903$)	
	n	ROR (95% CI)	*n*	ROR (95% CI)	*n*	ROR (95% CI)	*n*	ROR (95% CI)	*n*	ROR (95% CI)
Blood and lymphatic system disorders	3134	0.48 (0.47–0.50)	3125	0.54 (0.52–0.56)	3134	0.46 (0.44–0.48)	2780	0.99 (0.89–1.11)	513	0.87 (0.78–0.96)
Cardiac disorders	2589	0.67 (0.64–0.70)	2583	0.85 (0.81–0.88)	2589	0.67 (0.64–0.70)	2238	0.97 (0.86–1.09)	328	0.68 (0.61–0.77)
Congenital, familial, and genetic disorders	36	0.18 (0.13–0.25)	36	0.21 (0.15–0.29)	36	0.28 (0.20–0.39)	34	1.06 (0.25–4.41)	5	0.70 (0.27–1.80)
Ear and labyrinth disorders	226	0.54 (0.48–0.62)	226	0.54 (0.47–0.62)	226	0.62 (0.54–0.72)	196	0.97 (0.66–1.43)	52	1.26 (0.92–1.73)
Endocrine disorders	2863	**6.91 (6.60–7.23)**	2856	**6.69 (6.38–7.02)**	2863	**3.99 (3.69–4.30)**	2275	0.88 (0.80–0.97)	744	**1.60 (1.46–1.75)**
Eye disorders	1194	0.69 (0.65–0.73)	1192	0.68 (0.64–0.72)	1194	0.66 (0.62–0.70)	1067	1.00 (0.83–1.21)	271	**1.21 (1.05–1.39)**
Gastrointestinal disorders	9124	0.82 (0.80–0.84)	9094	0.85 (0.83–0.87)	9124	0.91 (0.89–0.94)	7773	0.95 (0.88–1.01)	2803	**2.03 (1.93–2.15)**
General disorders and administration site conditions	16,449	0.80 (0.78–0.81)	16,420	0.76 (0.74–0.77)	16,449	0.93 (0.91–0.95)	15,066	1.04 (0.98–1.11)	2894	0.87 (0.82–0.91)
Hepatobiliary disorders	2632	**1.33 (1.28–1.39)**	2622	**1.45 (1.39–1.51)**	2632	**1.32 (1.26–1.38)**	2149	0.91 (0.82–1.01)	426	0.94 (0.84–1.04)
Immune system disorders	820	0.51 (0.48–0.55)	817	0.52 (0.48–0.56)	820	0.48 (0.45–0.52)	730	1.00 (0.80–1.24)	138	0.89 (0.74–1.08)
Infections and infestations	5795	0.68 (0.67–0.70)	5781	0.73 (0.71–0.76)	5795	0.59 (0.57–0.60)	5036	0.97 (0.89–1.05)	1063	1.00 (0.93–1.07)
Injury, poisoning, and procedural complications	6776	**1.20 (1.17–1.23)**	6767	**1.13 (1.10–1.16)**	6776	**1.09 (1.06–1.12)**	6185	1.03 (0.94–1.12)	797	0.57 (0.53–0.62)
Investigations	5147	0.63 (0.61–0.65)	5123	0.70 (0.68–0.72)	5147	0.71 (0.69–0.74)	4588	1.00 (0.91–1.10)	984	1.02 (0.94–1.10)
Metabolism and nutrition disorders	4196	1.03 (1.00–1.07)	4180	**1.13 (1.10–1.17)**	4196	**1.05 (1.01–1.08)**	3496	0.93 (0.85–1.01)	840	**1.15 (1.06–1.25)**
Musculoskeletal and connective tissue disorders	3759	0.89 (0.86–0.92)	3751	0.86 (0.83–0.89)	3759	0.97 (0.93–1.00)	3332	0.99 (0.89–1.10)	539	0.75 (0.68–0.83)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	8773	**1.85 (1.81–1.90)**	8762	**1.85 (1.80–1.89)**	8773	**1.67 (1.63–1.72)**	8064	1.04 (0.96–1.13)	1380	0.78 (0.73–0.83)
Nervous system disorders	5402	0.71 (0.69–0.73)	5386	0.76 (0.74–0.78)	5402	0.76 (0.73–0.78)	4817	1.00 (0.91–1.10)	1088	1.08 (1.00–1.16)
Pregnancy, puerperium, and perinatal conditions	50	0.29 (0.22–0.38)	50	0.31 (0.23–0.40)	50	0.32 (0.24–0.43)	27	0.61 (0.35–1.06)	13	**2.28 (1.07–4.86)**
Product issues	51	0.23 (0.17–0.30)	51	0.22 (0.17–0.29)	51	0.27 (0.20–0.36)	51	NA	3	NC
Psychiatric disorders	1432	0.61 (0.58–0.65)	1423	0.63 (0.60–0.67)	1432	0.78 (0.74–0.83)	1303	1.02 (0.85–1.23)	254	0.92 (0.80–1.06)
Renal and urinary disorders	2377	0.87 (0.83–0.91)	2370	0.96 (0.92–1.00)	2377	0.90 (0.86–0.95)	2060	0.97 (0.86–1.10)	365	0.83 (0.74–0.93)
Reproductive system and breast disorders	188	0.44 (0.38–0.51)	187	0.46 (0.40–0.53)	188	0.50 (0.43–0.58)	170	1.01 (0.62–1.65)	23	0.64 (0.41–0.99)
Respiratory, thoracic, and mediastinal disorders	7240	**1.04 (1.01–1.06)**	7227	**1.15 (1.12–1.18)**	7240	0.92 (0.90–0.95)	6473	1.00 (0.92–1.09)	728	0.49 (0.45–0.53)
Skin and subcutaneous tissue disorders	4618	0.66 (0.64–0.68)	4614	0.64 (0.62–0.66)	4618	0.83 (0.80–0.86)	4128	1.00 (0.91–1.11)	1084	**1.28 (1.19–1.37)**
Social circumstances	107	0.25 (0.20–0.30)	107	0.26 (0.21–0.31)	107	0.38 (0.31–0.46)	104	1.09 (0.35–3.44)	15	0.68 (0.39–1.18)
Surgical and medical procedures	1298	**1.20 (1.13–1.27)**	1298	**1.37 (1.30–1.45)**	1298	**1.64 (1.53–1.75)**	1180	1.02 (0.84–1.24)	186	0.74 (0.63–0.87)
Vascular disorders	1845	0.49 (0.46–0.51)	1836	0.56 (0.53–0.58)	1845	0.43 (0.41–0.45)	1632	0.99 (0.86–1.15)	378	1.10 (0.98–1.24)

Statistically significant disproportionality (i.e., lower limit of the 95% CI of the ROR > 1) is shown in bold

CI confidence interval, *CTLA4* cytotoxic T-lymphocyte associated protein 4, *ICIs* immune checkpoint inhibitors, *NA* not applicable because the ROR cannot be calculated (no cases in combination regimen), *NC* not calculated because the number of cases was < 5 (see methods for details), *PD1/PDL1* programmed cell death 1 or its ligand, *Q2* second quarter, *ROR* reporting odds ratio

Table 3 Disproportionality analysis in FAERS (ICIs compared with other oncological agents) and literature appraisal

System organ class	FAERS*	Literature appraisal (OoSRs)				Combined assessment
		Outcome investigated as for the original studies	N. of studies on the outcome of interest	N. of positive/neutral/negative studies	Evaluation	
Blood and lymphatic system disorders	×	Anemia, neutropenia, leukopenia, hypophosphatemia, lymphopenia, thrombocytopenia	6	0/0/6	Consistent negative association	Low priority
Cardiac disorders	×	Cardiorespiratory arrest, cardiac failure, myocardial infarction, stroke	2	0/1/1	Uncertain association	Low priority
Endocrine disorders	✓	**Hypothyroidism, hyperthyroidism, hypophysitis, adrenal insufficiency, thyroiditis**	**9**	**9/0/0**	**Consistent positive association**	**Top priority**
Eye disorders	×	Uveitis, dry eyes	1	1/0/0	Uncertain association	Low priority
Gastrointestinal disorders	×	Colitis, diarrhea, nausea, vomiting	11	6/2/3	Consistent positive association	Intermediate priority
General disorders and administration site conditions	×	Fatigue, asthenia	6	0/2/4	Consistent negative association	Low priority
Hepatobiliary disorders	✓	**Increased transaminases, hepatitis**	**9**	**6/3/0**	**Consistent positive association**	**Top priority**
Injury, poisoning, and procedural complications	✓					High priority
Investigations	×	Lipase increased	1	0/1/0	Uncertain association	Low priority
Musculoskeletal and connective tissue disorders	×	Arthritis, vasculitis, myositis	1	0/0/1	Uncertain association	Low priority
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	✓					High priority
Respiratory, thoracic, and mediastinal disorders	✓	**Pneumonitis, interstitial lung disease**	**10**	**7/3/0**	**Consistent positive association**	**Top priority**
Skin and subcutaneous tissue disorders	×	Rash, pruritus, vitiligo, dermatitis	13	9/3/1	Consistent positive association	Intermediate priority
Surgical and medical procedures	✓					High priority

Top priorities are shown in bold

*×no statistically significant disproportionality emerged in primary analysis, ✓ statistically significant disproportionality emerged in primary analysis. See Table 2 for details

FAERS FDA Adverse Event Reporting System, *ICIs* immune checkpoint inhibitors, *OoSRs* overview of systematic reviews

effect [17–20]. From a pharmacological viewpoint, the question arises as to whether or not these irAEs are actually predictable. According to RCTs, ipilimumab exhibits a clear dose-dependent relationship with regards to incidence and severity of irAEs, although the mechanistic basis of toxicity may vary depending on the damaged organ [30].

Third, different reporting frequencies were observed between anti-CTLA4 drugs and anti-PD1/PDL1 agents: gastrointestinal disorders, endocrine and skin disorders

Table 4 Toxicities emerging as top and high priority: disproportionality analyses performed on the 2004Q1–2018Q2 period at PT level (signs/symptoms) and distinguishing anti-CTLA4 from anti-PD1/PDL1 agents (see methods for details)

Toxicity	ICI as class versus other anticancer agents		Anti-CTLA4 versus other anticancer agents, including anti-PD1/PDL1 drugs		Anti-PD1/PDL1 versus other anticancer agents, including anti-CTLA4 drugs	
	N. cases	ROR (95% CI)	N. cases	ROR (95% CI)	N. cases	ROR (95% CI)
Endocrine disorders						
Hypothyroidism	777	**6.36 (5.85–6.93)**	214	**5.92 (5.15–6.82)**	680	**6.87 (6.29–7.50)**
Hypophysitis	594	**20.80 (11.13–38.86)**	466	***56.39 (46.60–68.24)***	284	**12.19 (10.38–14.30)**
Adrenal insufficiency	493	**10.03 (8.88–11.33)**	264	***18.33 (15.92–21.10)***	346	**8.66 (7.61–9.86)**
Hyperthyroidism	422	**10.09 (8.84–11.52)**	159	**12.89 (10.85–15.32)**	370	**10.91 (9.54–12.47)**
Hypopituitarism	197	**16.60 (12.23–22.53)**	128	***36.67 (28.58–47.04)***	110	**11.40 (8.88–14.65)**
Thyroiditis	170	**12.91 (10.13–16.46)**	74	**19.05 (14.59–24.88)**	147	**13.76 (10.86–17.44)**
Thyroid disorder	151	**4.09 (3.42–4.88)**	43	**3.94 (2.89–5.36)**	127	**4.24 (3.50–5.12)**
Autoimmune thyroiditis	89	**9.60 (7.24–12.74)**	30	**10.95 (7.42–16.17)**	78	**10.37 (7.78–13.82)**
Endocrine disorder	65	**12.59 (8.57–18.51)**	47	***30.87 (21.09–45.17)***	29	**6.92 (4.52–10.59)**
Hypothalamo-pituitary disorder	63	**14.02 (9.12–21.56)**	40	***30.17 (20.04–45.42)***	39	**10.69 (7.09–16.12)**
Hepatobiliary disorders						
Hepatitis	420	**3.12 (2.81–3.47)**	188	**4.75 (4.09–5.52)**	333	**3.05 (2.72–3.42)**
Hepatic function abnormal	385	**1.55 (1.39–1.72)**	75	1.02 (0.81–1.28)	364	**1.80 (1.62–2.01)**
Autoimmune hepatitis	373	**14.23 (11.90–17.00)**	161	**20.85 (17.34–25.07)**	303	**14.24 (12.04–16.84)**
Liver disorder	241	**1.18 (1.04–1.35)**	102	**1.70 (1.39–2.07)**	196	**1.19 (1.03–1.37)**
Hepatic failure	193	0.91 (0.78–1.05)	72	1.14 (0.91–1.45)	151	0.87 (0.74–1.03)
Hepatotoxicity	154	1.04 (0.88–1.22)	70	**1.59 (1.26–2.02)**	116	0.96 (0.80–1.16)
Drug-induced liver injury	123	**2.37 (1.96–2.86)**	47	**3.06 (2.28–4.10)**	102	**2.42 (1.97–2.96)**
Hepatocellular injury	117	**1.45 (1.20–1.75)**	42	**1.76 (1.30–2.40)**	97	**1.48 (1.21–1.82)**
Cholestasis	116	**1.41 (1.17–1.70)**	36	**1.48 (1.06–2.06)**	101	**1.51 (1.24–1.85)**
Cholangitis	110	**2.11 (1.73–2.57)**	11	0.71 (0.39–1.29)	106	***2.51 (2.05–3.07)***
Respiratory disorders						
Dyspnea	1614	0.91 (0.87–0.96)	411	0.78 (0.71–0.86)	1423	0.99 (0.94–1.05)
Pneumonitis	1289	**4.06 (3.82–4.32)**	304	**3.22 (2.87–3.62)**	1196	**4.66 (4.38–4.97)**
Interstitial lung disease	794	**1.63 (1.52–1.75)**	74	0.51 (0.40–0.64)	761	***1.93 (1.79–2.08)***
Pleural effusion	656	0.97 (0.90–1.05)	136	0.68 (0.57–0.81)	598	**1.09 (1.01–1.19)**
Cough	646	0.88 (0.82–0.96)	128	0.59 (0.49–0.70)	580	0.98 (0.90–1.06)
Respiratory failure	537	1.08 (0.99–1.18)	103	0.70 (0.58–0.85)	482	**1.20 (1.09–1.31)**
Pulmonary embolism	413	0.80 (0.72–0.88)	131	0.86 (0.72–1.02)	325	0.77 (0.69–0.87)
Lung disorder	330	**1.28 (1.14–1.43)**	37	0.48 (0.35–0.67)	311	**1.49 (1.33–1.67)**
Hemoptysis	256	**1.54 (1.36–1.75)**	29	0.59 (0.41–0.85)	241	**1.79 (1.57–2.04)**
Hypoxia	217	0.96 (0.84–1.10)	61	0.91 (0.71–1.18)	198	1.08 (0.94–1.25)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)						
Malignant neoplasm progression	6691	**5.94 (5.77–6.12)**	1416	**4.06 (3.84–4.30)**	5806	**6.42 (6.23–6.63)**
Metastases to central nervous system	343	**2.03 (1.81–2.27)**	132	**2.65 (2.22–3.15)**	252	**1.83 (1.61–2.09)**
Neoplasm malignant	280	1.11 (0.98–1.25)	229	***3.10 (2.72–3.55)***	53	0.26 (0.20–0.34)
Neoplasm progression	140	0.36 (0.31–0.43)	45	0.40 (0.30–0.53)	102	0.33 (0.27–0.40)
Metastases to bone	105	0.85 (0.70–1.04)	21	0.58 (0.37–0.89)	98	0.98 (0.80–1.20)
Metastases to liver	94	0.52 (0.42–0.63)	39	0.72 (0.53–0.99)	74	0.50 (0.40–0.63)
Tumor pseudoprogression	94	**17.42 (10.64–28.52)**	8	**5.01 (2.44–10.28)**	94	***21.47 (13.11–35.15)***
Metastases to lung	81	0.60 (0.48–0.75)	36	0.91 (0.65–1.26)	64	0.59 (0.46–0.75)
Neoplasm	79	0.91 (0.73–1.15)	28	1.10 (0.76–1.59)	60	0.86 (0.66–1.11)
Tumor hemorrhage	68	**1.70 (1.33–2.18)**	22	**1.86 (1.22–2.85)**	53	**1.64 (1.24–2.16)**

Table 4 (continued)

Toxicity	ICI as class versus other anticancer agents		Anti-CTLA4 versus other anticancer agents, including anti-PD1/PDL1 drugs		Anti-PD1/PDL1 versus other anticancer agents, including anti-CTLA4 drugs	
	N. cases	ROR (95% CI)	N. cases	ROR (95% CI)	N. cases	ROR (95% CI)
Injury, poisoning, and procedural complications						
Product use in unapproved indication	1734	**6.29 (5.94–6.66)**	312	**3.77 (3.36–4.23)**	1687	***7.60 (7.17–8.04)***
Product use issue	1365	**3.99 (3.76–4.23)**	69	0.67 (0.52–0.84)	1342	***4.86 (4.58–5.16)***
Off-label use	1183	0.88 (0.83–0.93)	266	0.67 (0.59–0.75)	1015	0.93 (0.88–0.99)
Infusion-related reaction	365	1.05 (0.94–1.16)	79	0.77 (0.61–0.96)	315	1.11 (0.99–1.25)
Fall	320	0.6 (0.54–0.67)	78	0.49 (0.39–0.62)	263	0.61 (0.54–0.69)
Prescribed overdose	262	**14.64 (11.75–18.24)**	232	***44.34 (35.99–54.63)***	51	**3.50 (2.60–4.70)**
Incorrect product storage	241	**6.25 (5.38–7.27)**	50	**4.38 (3.29–5.84)**	201	**6.42 (5.48–7.54)**
Inappropriate schedule of drug administration	180	**1.67 (1.43–1.94)**	17	0.53 (0.33–0.86)	177	***2.02 (1.73–2.36)***
Toxicity to various agents	174	0.41 (0.35–0.47)	79	0.63 (0.50–0.78)	114	0.33 (0.27–0.40)
Drug dose omission	137	0.49 (0.41–0.58)	18	0.22 (0.14–0.34)	120	0.53 (0.44–0.63)
Surgical and medical procedures						
Transfusion	172	**5.19 (4.37–6.16)**	37	**3.77 (2.71–5.25)**	155	**5.76 (4.82–6.89)**
Hospitalization	139	0.82 (0.69–0.97)	56	1.12 (0.86–1.45)	103	0.75 (0.61–0.91)
Hospice care	99	**3.10 (2.50–3.83)**	16	**1.69 (1.03–2.78)**	93	***3.59 (2.88–4.46)***
Surgery	98	**1.46 (1.19–1.79)**	21	1.05 (0.69–1.62)	82	**1.50 (1.20–1.88)**
Therapy cessation	55	0.95 (0.73–1.25)	22	1.29 (0.85–1.97)	33	0.71 (0.50–1.00)
Packed red blood cell transfusion	47	**7.62 (5.32–10.91)**	10	**5.48 (2.88–10.46)**	43	**8.59 (5.96–12.39)**
Platelet transfusion	33	4.31 (2.94–6.33)	5	2.21 (0.91–5.38)	31	***4.99 (3.37–7.39)***
Dialysis	26	0.54 (0.36–0.79)	3	NC	23	0.58 (0.39–0.88)
Thoracic cavity drainage	26	**7.15 (4.45–11.49)**	1	NC	25	***8.47 (5.25–13.68)***
Cardiac pacemaker insertion	23	**2.88 (1.85–4.47)**	6	**2.54 (1.12–5.74)**	21	**3.24 (2.05–5.12)**

Statistically significant RORs (i.e., lower limit of the 95% CI of the RORs > 1) are shown in bold. Only the top 10 adverse events are listed in decreasing order of frequency (ICI as a class). The sum of the number of cases for the different groups of ICIs may be higher than the total number of cases for the drug class because a patient may have received more than one drug (anticancer combination regimen). The full list of adverse events is provided in supplementary material 2 (see ESM). The largest differences in terms of frequency between anti-CTLA4 and anti-PD1/PDL1 drugs (ROR value at least 2-fold higher) are shown in bold italics

CI confidence interval, *CTLA4* cytotoxic T-lymphocyte associated protein 4, *ICIs* immune checkpoint inhibitors, *NC* not calculated because the number of cases was < 5 (see methods for details), *PD1/PDL1* programmed cell death 1 or its ligand, *PT* preferred term, *Q* quarter, *ROR* reporting odds ratio

were more frequently reported with anti-CTLA4 drugs (ipilimumab), especially hypophysitis, adrenal insufficiency, hypopituitarism, and prescribed overdose, whereas thyroid dysfunction, pneumonitis, cholangitis, tumor pseudoprogression, and inappropriate schedule of drug administration were more frequent with anti-PD1/PDL1 agents. Similar frequencies were reported for autoimmune hepatitis and malignant neoplasm progression. These figures are strongly in agreement with the evidence from previous studies, including SRs of RCTs [11, 31, 32] and other pharmacovigilance analyses [33–35], thus confirming a close correlation between relative risks/hazard ratios and disproportionality measures in the modern FAERS [36]. Although the reasons for the observed reporting pattern remain obscure (and only partially reside in the different mechanisms of action), these differences in observed toxicities should be carefully considered by clinicians during monitoring to intercept serious irAEs early and to optimize treatment in a timely manner.

Fourth, we obtained some unique findings, including the following:

(a) No increased reporting with combination regimens, which is likely to be related to the remarkable reporting frequency of anti-PD1/PDL1 monoclonal antibodies.
(b) Overlap in co-reporting of endocrine, hepatobiliary, and respiratory irAEs, which carries important implications in clinical monitoring. Based on pre-approval RCTs, most of these irAEs observed with ICIs (especially ipilimumab) typically follow a chronological pattern; they start within the first 8–12 weeks after treatment initiation, with endocrine gland involvement usually appearing later at around 9 weeks [37]. Therefore,

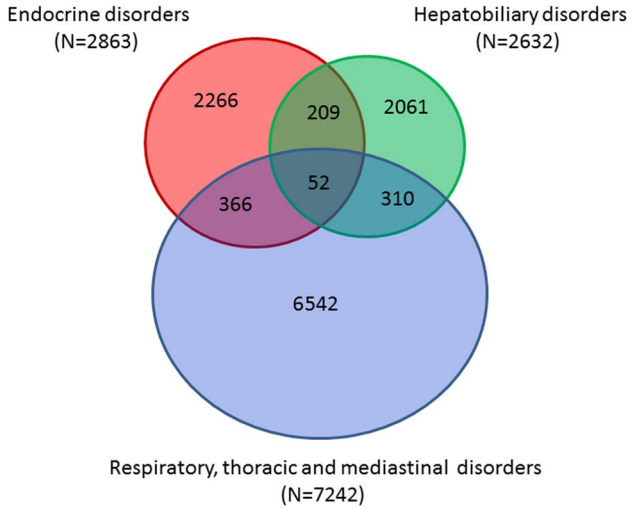

Fig. 3 Overlap among adverse events reported for endocrine, hepatobiliary, and respiratory disorders. Areas of the circles are rougly proportional to the number of reported adverse events

regular monitoring is required to promptly assess and manage these toxicities while avoiding therapy interruption.

(c) Higher reporting of cholangitis and vanishing bile duct syndrome with anti-PD1/PDL1 monoclonal antibodies. Drug-induced liver injury with ICIs represents an emerging area of research [38]; recent data from a pharmacovigilance register in France characterized 536 patients with grade 3 hepatitis and highlighted the importance of liver biopsy for a patient-guided approach to avoid corticosteroids [39]. While previous data suggested that ipilimumab may be associated with higher liver toxicity rates compared with ICIs blocking PD-1 [40], our findings support the existence of a specific pattern of liver damage for the different ICIs. In fact, while a signal of autoimmune hepatitis consistently emerged for all checkpoint inhibitors, an increased reporting of cholangitis was found for anti-PD1 drugs (nivolumab) in line with recent case series [41–45]. This form of severe and prolonged liver toxicity can manifest as 'large-duct or small-duct cholangitis', and may have different clinical presentation, biochemical evolution, and outcome, including secondary sclerosing cholangitis [46]. The occurrence of immune-related cholangitis has been described in subjects receiving nivolumab and avelumab, with late onset not only after administration of the treatment, but also after discontinuation of nivolumab [47]. Notably, we also found in FAERS six cases of vanishing bile duct syndrome with statistically significant disproportionality (ROR = 3.51; 95% CI 1.48–8.31; Electronic Supplementary Material 2, see ESM). To our knowledge, this is the first documentation of this pattern of liver injury with ICIs [48]. Taken together, this collated body of evidence calls for analytical pharmaco-epidemiological research to assess the risk at the population level and multicenter prospective registries to define the optimal treatment strategy in the individual patient and elucidate risk factors.

Disproportionalities found in our study for medical/surgical procedures, injury/poisoning/procedural complications, and neoplasms received a high priority, as they appear to be previously unknown safety aspects. The first area of toxicity can be interpreted as underlying cancer-related complications rather than a specific drug-related issue, whereas the second area of toxicity is mainly related to aspects dealing with drug administration (over- and under-dosing, use in unapproved indications, schedule of administration) and may be a potential consequence of the recent European pharmacovigilance legislation, which modified the definition of adverse drug reaction by including issues related to quality aspects, lack of efficacy and 'non-normal use' (i.e., abuse, misuse, overdose, occupational exposure, and medication errors) of medicines. We can therefore hypothesize that this regulatory context might result in increased awareness by clinicians of the importance of submitting AEs, thus creating a new type of *notoriety bias*.

Conversely, different clinical reasons may explain the high reporting of AEs potentially suggestive of 'drug ineffective' (i.e., malignant recurrence).

1. The aforementioned *notoriety bias*. This hypothesis is supported by recent data highlighting 'drug ineffective' as the most commonly reported AE in FAERS [49]. Additional studies performed on WHO-Vigibase data indicated that clusters of substandard medicines can be identified via a specific algorithm, although under stringent key prerequisites [50, 51]. Patient reporting in social media may complement information from clinicians to describe quality issues and the impact on quality of life [52].
2. The atypical delayed therapeutic response with ICIs, as compared with other targeted anticancer drugs.
3. The recently described phenomenon of 'pseudoprogression' (or even an aggressive pattern of hyperprogression [53]), a distinct immune-related pattern of response caused by the infiltration of immune cells to the tumor site that can manifest in the form of an apparent relapse (e.g., increase in tumor size, the development of new lesions [54]). Therefore, occurrence of irAEs in an early phase of therapy, including the aforementioned pseudoprogression, without apparent clinical benefit might discourage clinicians in pursuing ICI treatment while reporting a potential lack of efficacy. Oncologists should be reminded that the therapeutic effect occurs

later compared with the onset of irAEs, and that current data support positive association between these immunological events and survival outcome, as documented for nivolumab in non-small-cell lung cancer [55–57].

Among toxicities with intermediate priority, gastrointestinal and skin disorders warrant brief discussion. Our data indicated that these safety issues have non-negligible reporting, but did not result in significant disproportionality. Clinicians should be reminded that these toxicities do occur and may even be fatal, especially colitis: initial assessment is crucial when starting ICI treatment, since early management might prevent progression to more severe toxicity [37].

4.1 Strengths and Limitations

We exploited different data sources for safety assessment, including an OoSRs and a contemporary disproportionality analysis of the largest open-source worldwide database of unsolicited reports. To the best of our knowledge, only one integrated approach was recently carried out to assess ICI safety, although it was specifically focused on fatal toxic effects, thus making actual characterization and generalizability challenging [34].

We provided the most updated and comprehensive characterization of irAEs, and further raised debate on whether or not analysis of a spontaneous reporting system can be used to highlight clinical importance of toxic effects or suggest *foci* of potential drug misuse, unconventional uses and, most intriguingly, lack of efficacy. Although RCTs remain the best experimental approach to actually inform on the efficacy of medications, our study provided the public health perspective of toxicities that received attention and were largely investigated in the recent past with consistent data; hepatic, endocrine and respiratory irAEs warrant further prospective assessment to quantify and evaluate actual risk (class effect versus individual drug), including strategies for optimal management.

The vast number of SRs on irAEs (i.e., multiple reviews on the same topic) is a double-edge sword: on one hand, it prompted us to verify consistency of findings; on the other hand, it challenged the decision-making process of both clinicians and regulators. Our critical appraisal highlights the need to move from systematic reanalysis of the existent literature towards a new era of evidence-based medicine through comparative effectiveness/safety research and a combination of multiple sources of real-world data.

We acknowledge the limitations of FAERS data, in particular the inability to inform a causal relationship between drug exposure and occurrence of AE [21]. The ROR does not inform the real risk in clinical practice, mainly because of the lack of a denominator and under-reporting, but only indicates an increased risk of AE reporting and not a risk of AE occurrence. Therefore, incidence rates and risk ranking cannot be inferred from spontaneous reports. These aspects are shared by all pharmacovigilance databases and a causal inference is also an inherent limitation of cohort studies. We cannot exclude the so-called channeling bias (i.e., the possibility that drugs may be differently prescribed in relation to the severity of disease). In fact, clinical information such as cancer severity and duration is lacking, as well as laboratory and radiological findings and incomplete reporting of dosing and time to onset, thus making a firm comparison among ICIs inappropriate [58]. We also recognized that residual confounders may exist, including synergy with comorbidities and co-medications resulting in potential drug–drug interactions [59], although a number of measures were planned to minimize biases. We also acknowledge that both false-positive and false-negative results might exist. We cannot exclude that some AEs such as metastasis do not represent an indication bias considering that ICIs are also indicated in metastatic settings. Conversely, some AEs might not be identified because of their rarity or due to methodological issues: disproportionality measures are interdependent and the literature assessment was not intended to be a systematic review but an OoSRs of RCTs; this may explain the reason why cardiovascular toxicity did not emerge as top priority [60].

Notwithstanding these limitations, pharmacovigilance assessment represents an invaluable opportunity to monitor drug safety and identify new rare signals. We have described the worldwide safety profile of ICIs in an unselected population; major confounders were accounted for by applying multiple 'quality criteria' to minimize the likelihood of false positives and other sources of bias (e.g., selection of five cases as the threshold for calculating disproportionality, removal of reports suggestive of potential indication bias). There are no reasons to support the existence of stimulated reporting/notoriety bias specifically referring to a given AE (regulatory warnings are largely homogeneous across pharmacological classes), and the Weber effect (i.e., a peak in reporting early after approval and a decline thereafter) was not demonstrated for oncological drugs, and did not emerge from our data [61].

Taken together, our findings and the overall body of evidence call for proactive immuno-vigilance and post-authorization studies should be conducted, as recommended by the European Medicines Agency, to define the magnitude and extent of irAEs and actual clinical effectiveness, especially in the metastatic setting. In particular, oncology research should move beyond adaptive designs and pragmatic clinical trials to embrace new avenues of Big Smart data [62], such as combining population-based registries with health record systems [63].

5 Conclusions

Notwithstanding limitations, these real-world FAERS data corroborated the usefulness of pharmacovigilance research and confirmed that irAEs with ICIs may virtually occur in any organ/tissue, including co-occurrences, with different reporting frequencies between anti-CTLA4 drugs (hypophysitis, adrenal insufficiency) and anti-PD1/PDL1 agents (thyroid dysfunction, pneumonitis, cholangitis, vanishing bile duct syndrome).

These findings strengthen the importance of (a) close clinical monitoring of patients for early diagnosis and timely management of irAEs while awaiting a delayed therapeutic response; (b) proactive multidisciplinary pharmacovigilance to maintain 'real-time' surveillance (especially for recently approved ICIs such as avelumab and durvalumab, and considering emerging combination regimens with other oncological agents); and (c) prioritizing respiratory, endocrine, and liver toxicities to assess and further characterize patient- and drug-related risk factors through analytical pharmacoepidemiological research and multicenter registries.

Compliance with Ethical Standards

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Conflict of interest Emanuel Raschi, Alessandra Mazzarella, Ippazio Cosimo Antonazzo, Nicolò Bendinelli, Emanuele Forcesi, Marco Tuccori, Ugo Moretti, Elisabetta Poluzzi, and Fabrizio De Ponti declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

References

1. Clarke JM, George DJ, Lisi S, Salama AKS. Immune checkpoint blockade: the new frontier in cancer treatment. Targ Oncol. 2018;13:1–20.
2. Martin-Liberal J, Hierro C, de Ochoa OM, Rodon J. Immuno-oncology: the third paradigm in early drug development. Targ Oncol. 2017;12:125–38.
3. Hoos A. Development of immuno-oncology drugs—from CTLA4 to PD1 to the next generations. Nat Rev Drug Discov. 2016;15:235–47.
4. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. JAMA Oncol. 2016;2:1346–53.
5. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016;375:1749–55.
6. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378:158–68.
7. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36:1714–68.
8. Martins F, Sykiotis GP, Maillard M, Fraga M, Ribi C, Kuntzer T, et al. New therapeutic perspectives to manage refractory immune checkpoint-related toxicities. Lancet Oncol. 2019;20:e54–64.
9. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol. 2016;13:473–86.
10. Raschi E, Diemberger I, Cosmi B, De Ponti F. ESC position paper on cardiovascular toxicity of cancer treatments: challenges and expectations. Intern Emerg Med. 2018;13:1–9.
11. Baxi S, Yang A, Gennarelli RL, Khan N, Wang Z, Boyce L, et al. Immune-related adverse events for anti-PD-1 and anti-PD-L1 drugs: systematic review and meta-analysis. BMJ. 2018;360:k793.
12. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. Ann Intern Med. 2018;168:121–30.
13. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet. 2018;391:933.
14. Ferreira M, Pichon E, Carmier D, Bouquet E, Pageot C, Bejan-Angoulvant T, et al. Coronary toxicities of anti-PD-1 and anti-PD-L1 immunotherapies: a case report and review of the literature and international registries. Targ Oncol. 2018;13:509–15.
15. Centanni M, Moes DJAR, Troconiz IF, Ciccolini J, van Hasselt JGC. Clinical Pharmacokinetics and Pharmacodynamics of Immune Checkpoint Inhibitors. Clin Pharmacokinet. 2019. https://doi.org/10.1007/s40262-019-00748-2.
16. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA Adverse Event Reporting System. Int J Med Sci. 2013;10:796–803.
17. Giezen TJ, Mantel-Teeuwisse AK, Meyboom RH, Straus SM, Leufkens HG, Egberts TC. Mapping the safety profile of biologicals: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. Drug Saf. 2010;33:865–78.
18. Cutroneo PM, Isgro V, Russo A, Ientile V, Sottosanti L, Pimpinella G, et al. Safety profile of biological medicines as compared with non-biologicals: an analysis of the italian spontaneous reporting system database. Drug Saf. 2014;37:961–70.
19. Gouverneur A, Claraz P, Rousset M, Arnaud M, Fourrier-Reglat A, Pariente A, et al. Comparative safety of targeted therapies for metastatic colorectal cancer between elderly and younger patients: a study using the international pharmacovigilance database. Target Oncol. 2017;12:805–14.
20. Araujo AGS, Borba HHL, Tonin FS, Lenzi L, Venson R, Pontarolo R, et al. Safety of biologics approved for the treatment of rheumatoid arthritis and other autoimmune diseases: a disproportionality analysis from the FDA adverse event reporting system (FAERS). BioDrugs. 2018;32:377–90.
21. Raschi E, Poluzzi E, Salvo F, Pariente A, De Ponti F, Marchesini G, et al. Pharmacovigilance of sodium-glucose co-transporter-2 inhibitors: what a clinician should know on disproportionality analysis of spontaneous reporting systems. Nutr Metab Cardiovasc Dis. 2018;28:533–42.
22. Fukazawa C, Hinomura Y, Kaneko M, Narukawa M. Significance of data mining in routine signal detection: analysis based on the safety signals identified by the FDA. Pharmacoepidemiol Drug Saf. 2018;27:1402–8.
23. Harpaz R, DuMouchel W, LePendu P, Bauer-Mehren A, Ryan P, Shah NH. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system. Clin Pharmacol Ther. 2013;93:539–46.

24. Poluzzi E, Raschi E, Piccinni C, De Ponti F. Data mining techniques in pharmacovigilance: analysis of the publicly accessible FDA adverse event reporting system (AERS). In: Karahoca A, editor. Data mining applications in engineering and medicine. Croatia: InTech; 2012. p. 265–302.
25. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18:427–36.
26. Tuccori M, Montagnani S, Capogrosso-Sansone A, Mantarro S, Antonioli L, Fornai M, et al. Adverse reactions to oncologic drugs: spontaneous reporting and signal detection. Expert Rev Clin Pharmacol. 2015;8:61–75.
27. Slattery J, Alvarez Y, Hidalgo A. Choosing thresholds for statistical signal detection with the proportional reporting ratio. Drug Saf. 2013;36:687–92.
28. Hauben M, Hung E, Wood J, Soitkar A, Reshef D. The impact of database restriction on pharmacovigilance signal detection of selected cancer therapies. Ther Adv Drug Saf. 2017;8:145–56.
29. Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL. The Global Evidence Mapping Initiative: scoping research in broad topic areas. BMC Med Res Methodol. 2011;11:92.
30. Baraibar I, Melero I, Ponz-Sarvise M, Castanon E. Safety and Tolerability of Immune Checkpoint Inhibitors (PD-1 and PD-L1) in Cancer. Drug Saf. 2019. https://doi.org/10.1007/s40264-018-0774-8.
31. Khoja L, Day D, Wei-Wu CT, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol. 2017;28:2377–85.
32. Xu C, Chen YP, Du XJ, Liu JQ, Huang CL, Chen L, et al. Comparative safety of immune checkpoint inhibitors in cancer: systematic review and network meta-analysis. BMJ. 2018;363:k4226.
33. Ali AK, Watson DE. Pharmacovigilance assessment of immune-mediated reactions reported for checkpoint inhibitor cancer immunotherapies. Pharmacotherapy. 2017;37:1383–90.
34. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4:1721–8.
35. Ji HH, Tang XW, Dong Z, Song L, Jia YT. Adverse event profiles of anti-CTLA-4 and anti-PD-1 monoclonal antibodies alone or in combination: analysis of spontaneous reports submitted to FAERS. Clin Drug Investig. 2019. https://doi.org/10.1007/s40261-018-0735-0.
36. Macia-Martinez MA, de Abajo FJ, Roberts G, Slattery J, Thakrar B, Wisniewski AF. An empirical approach to explore the relationship between measures of disproportionate reporting and relative risks from analytical studies. Drug Saf. 2016;39:29–43.
37. Sosa A, Lopez CE, Simon OC, Karachaliou N, Rosell R. Clinical assessment of immune-related adverse events. Ther Adv Med Oncol. 2018;10:1758835918764628.
38. Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int. 2018;38:976–87.
39. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68:1181–90.
40. Wang W, Lie P, Guo M, He J. Risk of hepatotoxicity in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis of published data. Int J Cancer. 2017;141:1018–28.
41. Gelsomino F, Vitale G, D'Errico A, Bertuzzi C, Andreone P, Ardizzoni A. Nivolumab-induced cholangitic liver disease: a novel form of serious liver injury. Ann Oncol. 2017;28:671–2.
42. Gelsomino F, Vitale G, Ardizzoni A. Immune-mediated cholangitis: is it always nivolumab's fault? Cancer Immunol Immunother. 2018;67:1325–7.
43. Kawakami H, Tanizaki J, Tanaka K, Haratani K, Hayashi H, Takeda M, et al. Imaging and clinicopathological features of nivolumab-related cholangitis in patients with non-small cell lung cancer. Invest New Drugs. 2017;35:529–36.
44. Kashima J, Okuma Y, Shimizuguchi R, Chiba K. Bile duct obstruction in a patient treated with nivolumab as second-line chemotherapy for advanced non-small-cell lung cancer: a case report. Cancer Immunol Immunother. 2018;67:61–5.
45. Gelsomino F, Vitale G, Ardizzoni A. A case of nivolumab-related cholangitis and literature review: how to look for the right tools for a correct diagnosis of this rare immune-related adverse event. Invest New Drugs. 2018;36:144–6.
46. Ogawa K, Kamimura K, Terai S. Anti-programmed cell death-1 immunotherapy-related secondary sclerosing cholangitis. Hepatology. 2018;69:914–6.
47. Noda-Narita S, Mizuno S, Noguchi S, Watanabe K, Nakai Y, Koike K, et al. Development of mild drug-induced sclerosing cholangitis after discontinuation of nivolumab. Eur J Cancer. 2019;107:93–6.
48. Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology. 2017;65:1267–77.
49. Misu T, Kortepeter CM, Munoz MA, Wu E, Dal Pan GJ. An evaluation of "drug ineffective" postmarketing reports in drug safety surveillance. Drugs Real World Outcomes. 2018;5:91–9.
50. Juhlin K, Karimi G, Ander M, Camilli S, Dheda M, Har TS, et al. Using VigiBase to identify substandard medicines: detection capacity and key prerequisites. Drug Saf. 2015;38:373–82.
51. Trippe ZA, Brendani B, Meier C, Lewis D. Identification of substandard medicines via disproportionality analysis of individual case safety reports. Drug Saf. 2017;40:293–303.
52. Inacio P, Cavaco A, Airaksinen M. The value of patient reporting to the pharmacovigilance system: a systematic review. Br J Clin Pharmacol. 2017;83:227–46.
53. Champiat S, Dercle L, Ammari S, Massard C, Hollebecque A, Postel-Vinay S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res. 2017;23:1920–8.
54. Chiou VL, Burotto M. Pseudoprogression and immune-related response in solid tumors. J Clin Oncol. 2015;33:3541–3.
55. Sato K, Akamatsu H, Murakami E, Sasaki S, Kanai K, Hayata A, et al. Correlation between immune-related adverse events and efficacy in non-small cell lung cancer treated with nivolumab. Lung Cancer. 2018;115:71–4.
56. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol. 2018;4:374–8.
57. Teraoka S, Fujimoto D, Morimoto T, Kawachi H, Ito M, Sato Y, et al. Early immune-related adverse events and association with outcome in advanced non-small cell lung cancer patients treated with nivolumab: a prospective cohort study. J Thorac Oncol. 2017;12:1798–805.
58. Michel C, Scosyrev E, Petrin M, Schmouder R. Can disproportionality analysis of post-marketing case reports be used for comparison of drug safety profiles? Clin Drug Investig. 2017;37:415–22.
59. Oshima Y, Tanimoto T, Yuji K, Tojo A. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. JAMA Oncol. 2018;4:1112–5.
60. Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated

with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol. 2018;19:1579–89.
61. Arora A, Jalali RK, Vohora D. Relevance of the Weber effect in contemporary pharmacovigilance of oncology drugs. Ther Clin Risk Manag. 2017;13:1195–203.
62. Trifiro G, Sultana J, Bate A. From big data to smart data for pharmacovigilance: the role of healthcare databases and other emerging sources. Drug Saf. 2018;41:143–9.
63. Kibbelaar RE, Oortgiesen BE, van der Wal-Oost AM, Boslooper K, Coebergh JW, Veeger NJGM, et al. Bridging the gap between the randomised clinical trial world and the real world by combination of population-based registry and electronic health record data: a case study in haemato-oncology. Eur J Cancer. 2017;86:178–85.