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Treatment-emergent antidrug antibodies related to PD-1, PD-L1, or CTLA-4 inhibitors across tumor types: a systematic review

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ABSTRACT

Background Increased understanding of how the immune system regulates tumor growth has innovated the use of immunotherapeutics to treat various cancers. The impact of such therapies, including programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, on the production of antidrug antibodies (ADAs) and their impact on outcomes, is poorly understood. This study aims to evaluate the clinical trial evidence on ADA incidence associated with PD-1, PD-L1, and CTLA-4 inhibitors in the treatment of cancer and to assess associations between treatment administered, ADA incidence, and treatment outcomes.

Methods Embase®, Medline®, and EBM Reviews were searched via the OVID® platform on February 15, 2022. Conference proceedings, clinical trial registries, and global regulatory and reimbursement body websites were also searched. Eligible publications included clinical trials enrolling patients receiving cancer treatment with either PD-1, PD-L1, or CTLA-4 reporting outcomes including incidence or prevalence of ADAs and the impact of immunogenicity on treatment safety and efficacy. Reference lists of eligible publications were also searched. The review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and evidence quality assessment was conducted using the appropriate Joanna Briggs Institute Critical Appraisal tool.

Results After screening 4160 records and reviewing 97 full publications, a total of 34 publications reporting on 68 trials were included. A further 41 relevant clinical trials were identified on ClinicalTrials.gov and a further 32 from searches of packaging inserts. In total, 141 relevant trials covering 15 different checkpoint inhibitors and 16 different tumor types were included. Across the included trials, atezolizumab was associated with the highest incidence of ADAs (29.6% of 639 patients), followed by nivolumab (11.2% of 2,085 patients). Combination checkpoint inhibitor treatment appeared to increase the rate of ADAs versus monotherapy. Only 17 trials reported on the impact of ADAs on treatment outcomes with mixed results for the impact of ADAs on treatment efficacy, safety, and pharmacokinetics.

Conclusions Checkpoint inhibitors for the treatment of cancer are immunogenic, with the incidence of treatment-emergent ADAs varying between individual therapies. It remains unclear what impact ADAs have on treatment outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The rates of treatment-emergent antidrug antibody (ADA) formation with cancer immunotherapies—and their impact on treatment outcomes—are poorly understood.

WHAT THIS STUDY ADDS

⇒ We systematically reviewed the literature on ADAs in trials of cancer immunotherapies, and assessed associations between treatment administered, ADA incidence rates, and treatment outcomes.

⇒ A total of 141 trials were included, covering a total of 15 treatment options across 16 different tumor types. Focusing on studies with a larger sample size, atezolizumab was associated with the highest incidence of treatment-emergent ADAs (29.6%), followed by nivolumab (11.2%). The effect ADAs had on treatment outcomes remains unclear.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ The full impact of ADAs on cancer immunotherapy efficacy and safety requires better characterization with larger studies conducted to permit robust statistical analyses.

BACKGROUND

The cell membrane proteins PD-1, PD-L1, and CTLA-4 play an important role in suppressing immune responses, preventing autoimmunity.[1–3] One way cancer cells survive is by exploiting immunosuppressive mechanisms such that they avoid detection and destruction by the immune system. A common feature among many cancer types is high levels of PD-1 expression, with higher PD-1-positive cell counts associated with more metastases, increased disease progression, and decreased patient survival.[4–13]

Cancer immunotherapies, including CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors, target the molecular mechanisms responsible for immunosuppression, inducing the immune system to recognize and target cancer cells.[3 14] A by-product of immunotherapies, however, is the formation of antidrug antibodies (ADAs). ADAs result from an immune response to the administered drug which, once in circulation, may bind to the immunogenic component(s) of the drug, potentially altering its pharmacokinetics and pharmacodynamics as well as its efficacy and safety.[15] Neutralizing antibodies (nAbs) are a subset of ADAs that bind to the specific region of the administered drug that would otherwise bind to its therapeutic target thereby inhibiting—or neutralizing—its pharmacological function.[16 17]

The rates of treatment-emergent ADA formation with the use of CTLA-4, PD-1, and PD-L1 inhibitors, and what impact they may have on treatment outcomes are poorly understood. The objective of this study was to systematically review the literature on treatment-emergent ADAs in trials of PD-1, PD-L1, or CTLA-4 antibodies for the treatment of cancer, and to assess associations between treatment administered, ADA/nAb incidence rates, and treatment outcomes.

METHODS

The systematic literature search was performed on February 15, 2022 and conformed with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[18] Electronic databases searched included Embase®, Medline® and Medline Epub Ahead of Print (In-process & Other Non-Indexed Citations). Searches of health technology assessment body websites, conference proceedings from the last 3 years, clinical trial registries, registrational/regulatory websites, package inserts/summaries of product characteristics, and reference lists of studies included at full publication screening were also performed.

Eligible publications were those enrolling patients receiving treatment for cancer with either PD-1, PD-L1, or CTLA-4 inhibitors, and which reported outcomes including incidence or prevalence of ADAs and the impact of immunogenicity on treatment efficacy. The full eligibility criteria for inclusion in the systematic review are presented in table 1.

Potentially eligible publications were first screened based on their title and abstract. Publications still included following the initial screen were then subject to full text review. Screening was performed by a single analyst and independently checked by a second analyst. Discrepancies in screening results were resolved by consensus. Data extraction was conducted by an analyst and all extracted data were independently checked against the source publication by a second analyst.

Quality assessment of included publications was performed using the appropriate checklist from the Joanna Briggs Institute.[19]

RESULTS

Search results

The electronic database search identified a total of 4612 publications. Following the removal of 452 duplicates, 4160 publications were screened based on title and abstract, resulting in 4063 being excluded. The remaining 97 potentially relevant publications were screened based on their full publication of which 28 were included and 69 were excluded. Handsearching of conference proceedings and reference lists of included studies yielded six additional relevant publications for inclusion. Thus, a total of 34 publications were included in the systematic review.[20–53] These 34 publications reported data from a total of 68 trials. An additional 41 clinical trials on ClinicalTrials.gov reported relevant data and searches of Food and Drug Administration (FDA) packaging inserts identified a further 32 trials. In total, therefore, data from 141 trials reporting on the incidence of treatment-emergent ADAs or the impact of ADAs on outcomes were captured in this review[20–42 44–96] (online supplemental figure 1 and table 1).

Quality assessment

Quality assessment was performed on 23 of the 34 included publications.[21–25 28 30–32 34–36 38–42 45–47 51–53] No quality assessment was performed on the remaining 11 publications as six were pooled analyses[20 44 46 48–50] and five were abstracts or posters.[26 27 29 33 37] All 23 publications that underwent quality assessment were deemed to be of high quality with low risk of bias (online supplemental tables 2 and 3).

Characteristics of included trials

Of the 141 trials included in the systematic review, 66 were randomized controlled trials (RCTs), 30 were open-label comparative studies, 36 were single-arm studies, seven were open-label sequential studies, one was a retrospective observational study, and one did not report study design.

Overall, the 141 trials covered a total of 15 different treatment options (online supplemental figure 1) and 16 different tumor types (online supplemental table 1). Most studies (131/141) reported data for solid tumors, with only eight studies (390 patients) reporting data in liquid tumors and two including both solid and liquid tumors (patient numbers not consistently reported by tumor type) (online supplemental table 1). Most of the included trials were reported in trial registries (ClinicalTrials.gov) and FDA packaging inserts as opposed to in peer-reviewed journals. The definition of ADA varied across the included studies (online supplemental table 4). Across the 141 included studies, the incidence of treatment-emergent ADAs among enrolled patients ranged from 0% to 100% depending on the study and the treatment being administered (online supplemental figure 2A,table 1).

The study sample size varied considerably from six to 2085 patients when considering pooled data (online

Table 1 Eligibility criteria for inclusion in the systematic review

Criteria	Include
Population	Subjects receiving treatment for cancer with no restriction on patient characteristics, indication (including tumor type, ie, solid vs liquid tumors), or line of therapy (Papers reporting relevant ADA-related data in other indications, eg, rheumatoid arthritis, multiple sclerosis, lupus were tagged but were not eligible for inclusion)
Intervention and comparator(s)	► PD-1 inhibitors ► PD-L1 inhibitors ► CTLA-4 inhibitors No restriction on treatment regimen and may be administered as monotherapy or in combination
Outcomes	► Impact of immunogenicity on: – Pharmacokinetics – Safety/tolerability, including hypersensitivity reactions – Anaphylaxis – Infusion reactions – Immune-complex mediated diseases – Efficacy – Target binding – Drug clearance ► Incidence and prevalence of ADAs/nAbs (no restriction on assay employed) and link to patient outcome ► Type of antibody, that is, IgM vs IgG ► Predictors of ADA production ► Mechanisms underlying ADA formation ► Impact of assay used to detect ADAs on outcomes of interest
Study design	► Randomized controlled trials (all phases) ► Long-term extensions to randomized controlled trials ► Non-randomized clinical studies ► Observational studies (prospective and retrospective) ► Post hoc analysis of clinical studies ► SR and meta-analysis publications (Single patient case studies were tagged but not extracted)
Geography	No restriction
Date of publication	No restriction
Language of publication	No restriction. The primary focus was English language publications or non-English language publications with an English abstract

ADA, antidrug antibody; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Ig, immunoglobulin; nAb, neutralizing antibody; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; SR, systematic review.

supplemental table 1). Focusing on the studies/datasets with the largest samples sizes (table 2), atezolizumab treatment (PD-L1 inhibitor) was observed to induce the highest incidence of ADAs with 29.6% of enrolled patients affected (NCT02031458; sample size of 639 patients with hepatocellular carcinoma),[44 50] followed by nivolumab (PD-1 inhibitor) with 11.2% of patients exhibiting antibodies (pooled data from FDA packaging leaflet; sample size of 2085 patients with advanced tumors).[57] The remaining treatments were associated with lower levels of ADAs, ranging from 0.52% (in 381 patients) with sintilimab treatment (PD-1 inhibitor[97]) to 4.4% (in 1609 patients) with avelumab.[49]

Trials in which PD-1, PD-L1, or CTLA-4 inhibitors were administered in combination appeared to show higher incidence of ADAs than when these treatments were administered alone (table 2). The same effect was not obvious when these treatments were coadministered with other chemotherapy or targeted drugs (online supplemental figure 2B).

Incidence of treatment-emergent nAbs

The incidence of nAbs was highest in atezolizumab trials compared with those of the other treatments of interest, with up to 27.5% of atezolizumab-treated subjects exhibiting nAbs (table 2).[44 50] The highest proportions of ADAs that were nAbs (23.1%–100%) were in patients treated with atezolizumab compared with other treatments (online supplemental figure 2C).

Impact of assay on incidence of ADAs

The assay used to detect treatment-emergent ADAs was poorly reported across trials. Of the 141 included trials, only 54 identified the assay used to evaluate the presence

Table 2 Summary of treatment-emergent ADA incidence by treatment (in trials with largest sample sizes)

Treatment	No of trials identified	Reported incidence (%) of ADAs			Range (%) of reported incidence of nAbs
		Range	Incidence in largest sample size (n) (ref)	Incidence in FDA package insert (n) (ref)	
CTLA-4 inhibitors					
Ipilimumab	12	0–26	1.1 (1024)[61]	1.1 (1024)[61] 5.4 (499) 8.5 (483)	0–1.6
Tremelimumab	4	3.98–71.4	3.98 (377)[96]	NA	NR
PD-1 inhibitors					
Avelumab	13	0–39.9	4.4 (1609)[49]	4.1 (1558)[56] 15 (453)	0–3.6
Cemiplimab	6	0–2.6	2.6 (39)[51]	2.2 (823)[58]	0
Dorsalimab	1	2.5–3.7	3.7 (349)[40]	2.5 (315)[59]	2.0
JTX-4014	1	0	0 (18)[43]	NA	NR
Nivolumab	27	0–42.9	12.7 (1086)[20]	11.2 (2085)[57]	0–2.8
Pembrolizumab	31	0–20	1.8 (2000)[48]	2.1 (1289)[54] 1.8 (2034)	0–0.7
Pucotenlimab	1	3.3	3.3 (30)[39]	NA	NR
Sasanlimab	1	8.6	8.6 (35)[34]	NA	0
Sintilimab	4	0–1.05	0.52 (381)[46]	NA	0–1.05
PD-1 inhibitors					
Atezolizumab	31	0–54.1	29.6 (639)[44 50]	28 (241)[55]	4.3–27.5
Durvalumab	14	0–74	0 (416)[98]	2.9 (1,570)[60]	0–0.9
LY3415244	1	100	100 (12)[31]	NA	NR
Lodapolimab	1	17	17 (65)[52]	NA	11
Combination therapies					
Durvalumab+tremelimumab	6	0–9.6	9.6 (293)[93]	NA	0.4–1.0
		0–18.5	18.5 (293)[93]		11.4–17.1
Ipilimumab+nivolumab	2	2.4–9.3	2.4 (86)[73]	NA	0
		27.3–39.4	27.3 (154)[95]		1.95
Durvalumab+MEDI0680	1	5.1	5.1 (39)[83]	NA	NR
		5.1	5.1 (39)[83]		

ADA, antidrug antibody; FDA, Food and Drug Administration; NA, not applicable; nAb, neutralizing antibody; NR, not reported; PD-1, programmed cell death protein 1.

of ADAs in their trial population (online supplemental table 1). Of these, 47 trials used electrochemiluminescence (ECL), three used enzyme-linked immunosorbent assay (ELISA), and the remaining four trials used one each of: Luminex bead-based assay, elution bridged immunoassay, a "binding assay," and a "validated assay." There was no apparent association between trial intervention and ADA assay used. The low number of trials using alternative assays to ECL precluded any consideration of links between assay type used and ADA incidence rates. Worth noting is the fact that only one out of the 31 included atezolizumab trials and only two out of the 14 included durvalumab trials reported the assay used to evaluate ADAs as compared with around 50% of trials for the other treatments.

Impact of ADAs on treatment outcomes

A total of 17 of 141 studies reported data related to the impact of ADAs on patient efficacy and safety outcomes and/or drug pharmacokinetics (table 3). Fourteen of these studies were manufacturer sponsored.

Eleven studies examined the effect of treatment-emergent ADAs on treatment efficacy. Of these, one study (not manufacturer-sponsored) reported that anti-ipilimumab ADA-positive patients reported a statistically significantly shorter median overall survival (OS) (p=0.03) and progression-free survival (PFS) (p=0.08) compared with ADA-negative patients.[38] Another study (not manufacturer sponsored) reported that ADA-positive patients following 6 months of treatment with nivolumab or pembrolizumab had earlier disease progression than ADA-negative patients

Table 3 Summary of studies reporting impact of ADAs on safety/efficacy

Author	Drug	Impact on		
		Efficacy	Safety	PK
Agrawal *et al* (2017)[20]	Nivolumab			
Antonia *et al* (2016)[21]	Durvalumab+tremelimumab			NA
Fukudo *et al* (2019)[26]	Nivolumab or pembrolizumab			NA
Hellman *et al* (2021)[31]	LY3415244	NA		
Johnson *et al* (2019)[34]	Sasanlimab		NA	
Kelley *et al* (2021)[35]	Tremelimumab+durvalumab			NA
Kverneland *et al* (2018)[38]	Ipilimumab		NA	
Lu *et al* (2021)[40]	Dostarlimab			
Ma *et al* (2021)[41]	Ipilimumab	NA		NA
Patnaik *et al* (2021)[52]	Lodapolimab	NA	NA	
Peters *et al* (2022)[44]	Atezolizumab			NA
Sasson *et al* (2021)[45]	Pembrolizumab		NA	
Shemesh *et al* (2019)[46]	Atezolizumab	NA		
van Vugt *et al* (2019)[48]	Pembrolizumab			
Wang *et al* (2019)[97]	Sintilimab	NA	NA	
Wilkins *et al* (2019)[49]	Avelumab	NA	NA	
Wu *et al* (2022)[50]	Atezolizumab			

Gray: no effect. Green: positive effect. Red: negative effect.
ADA, antidrug antibody; NA, not applicable; PK, pharmacokinetics.

(median PFS: 46 vs 119 days; log-rank p=0.0827).[26] Of the remaining nine studies that examined the association between ADAs and treatment efficacy, eight reported no measurable effect, and one study had insufficient ADA-positive patients to support correlation analyses.

Twelve of 141 studies examined the effect of treatment-emergent ADAs on safety outcomes. One study reported that all 12 patients who received LY3415244 (a PD-1 and TIM-3 inhibitor) developed treatment-emergent ADAs and two patients experienced anaphylactic reactions resulting in study termination for safety reasons.[31] A second study reported that of four patients who were ADA-positive at baseline, three experienced drug-induced fever after their initial drug infusion.[26] Of the remaining 10 studies, no impact of ADAs on treatment safety was reported in nine and one study reported having too few ADA-positive patients to conduct correlation analyses.

Thirteen studies examined the effect of treatment-emergent ADAs on pharmacokinetics. Of these, 10 studies reported that ADAs had no impact on the pharmacokinetics of the administered drug. One pembrolizumab study reported that at the first assessment time point the presence of ADAs was associated with a statistically significantly higher (p<0.05) level of circulating pembrolizumab than when ADAs were not detected.[45] One atezolizumab study reported a trend toward lower circulating atezolizumab in ADA-positive patients compared with ADA-negative patients which was even more pronounced in ADA-positive/nAb-positive patients.[50]

DISCUSSION/CONCLUSION

While the impact of immunotherapy-induced ADAs on treatment outcomes of psoriasis or rheumatoid arthritis is well characterized,[98–101] research examining the immunogenicity of ADAs in the treatment of cancer is at an early stage.

Of the 141 trials captured in this review, covering a total of 15 treatment options across 16 different tumor types, only the PD-L1 inhibitor atezolizumab returned robust data on the incidence of ADAs in cancer immunotherapy, corroborated by multiple phase 3 RCTs conducted in several hundred patients across multiple cancer types. This is an important consideration because the immunostimulatory mechanism of action of checkpoint inhibitors may lead to higher ADA rates than other cancer immunotherapies. Previous evidence on treatment-emergent ADAs across 81 trials testing a wide variety of immunotherapies for cancer revealed that the highest frequency (10%) of ADAs was seen with nivolumab monotherapy, with this rate increasing to 21.9% with nivolumab ipilimumab combination therapy.[15]

While not all ADAs have drug-neutralizing potential, data on treatment-emergent nAb in cancer immunotherapy are even more scarce. A 2020 review by Chen *et al* confirmed the poor correlation between ADA and nAb incidence. When considering forerunner PD-1/PD-L1 inhibitors such as nivolumab, durvalumab, and pembrolizumab, ADA incidence rates of 12.9%, 3.1% and 1.8%, respectively, were mirrored by nAb incidence rates

of 0.7% for nivolumab and 0.4% for durvalumab and pembrolizumab, highlighting the difficulty in drawing conclusions as to the functional meaning of ADAs.[102]

The data identified in this systematic review suggest that, of the various treatments considered, and when focusing only on those studies with a larger sample size, atezolizumab is associated with the highest incidence of treatment-emergent ADAs (29.6%), followed by nivolumab (11.2%). While there was no obvious correlation between ADA and nAb rates across the included trials, atezolizumab was also associated with the highest incidence of nAbs, although it was not possible to determine if there was a dose-dependent effect due to the small number of studies included. The higher immunogenicity of atezolizumab relative to other treatments could be due to the isotype structure of the antibody—atezolizumab has a humanized fragment crystallizable (fc) region that other PD-L1 inhibitors do not have.[103] However, higher ADA incidence could also be the result of the more extensive evidence base for atezolizumab compared with other immunotherapies.

Our study presents compelling evidence to suggest that emergence of ADA is not exclusively dependent on the characteristics of the therapeutic antibody but may be a function of immunologic synergy between coinhibitory pathway blockade. Although the data were suggestive of increased ADA with PD-L1 inhibitors compared with other drug classes, it was not clear if this was a true effect or an artifact due to the large number of studies that included atezolizumab as an intervention. However, combination treatment with PD-1, PD-L1, or CTLA-4 inhibitors appeared to be associated with an increased incidence of treatment-emergent ADAs compared with monotherapy. Durvalumab plus tremelimumab, for instance, was associated with an ADA incidence of up to 18.5%,[93] and combination therapy with ipilimumab plus nivolumab, a rate of 27.3%.[95] In contrast, use of any of these agents as monotherapy was associated with lower ADA incidence rates ranging from 0% with durvalumab[104] to 12.7% with nivolumab.[20] A recently published phase 3 trial of durvalumab plus tremelimumab versus durvalumab in hepatocellular carcinoma reinforces this view through evidence from randomized cohorts of a higher incidence of antidurvalumab antibodies (4.6%) when durvalumab was coadministered with tremelimumab compared with only 2.5% in the durvalumab monotherapy arm.[105] While crucial in regulating T cell exhaustion, a cardinal feature underlying the progression of malignancy, the PD-1 and CTLA-4 pathways have been identified as regulators of B cell biology, being involved in the downregulation of B cell proliferation and antibody production.[1 106] It is, therefore, plausible that concomitant inhibition of both pathways might lead to increased ADA production through selective enhancement of antibody production.

We found no apparent trend for increased ADAs in trials in which PD-1, PD-L1, or CTLA-4 inhibitors were administered in combination with other chemotherapy drugs, suggesting that combination with cytotoxics does not modulate ADA production through inhibition of humoral immunity.

Another important finding of our review is the lack of apparent correlation between the type of cancer treated and the incidence of treatment-emergent ADAs, including no evidence of a difference between solid and liquid tumors.

The effect of treatment-emergent ADAs on cancer patient treatment outcomes remains unclear. A recent publication, not identified in the current review as the data were presented at a congress held after this review's search date, showed that high levels of ADAs were independently associated with shorter progression-free survival and overall survival in patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab.[107] Of the seventeen studies this review identified that reported on the impact of the presence of ADAs on efficacy, safety, or pharmacokinetics, only two reported a significant or numerically negative effect of the presence of ADAs on progression-free survival and overall survival,[26 38] and only two studies reported a negative impact of ADAs on safety outcomes.[26 31] A further two studies reported conflicting effects of ADAs on drug pharmacokinetics.[45 50]

The type of assay used to detect treatment-emergent ADAs was poorly reported across trials. No clear relationship between ADA assay type and reported ADA incidence was identified; however, firm conclusions could not be drawn because assay-type data were missing from a large number of studies. It is interesting to note that very few trials of atezolizumab and durvalumab treatments reported the ADA assay type (n=1/31 and 2/14, respectively).

As ADAs are increasingly recognized as putative modulators of efficacy in cancer therapy, lack of harmonization in ADA assay type and in reporting of ADA data is concerning, as it might constitute an unmeasured source of bias in the interpretation of pharmacokinetic and efficacy data in clinical trials.

There are several limitations to this systematic review. First, only studies that reported ADAs were included, meaning that the list of included studies could be subject to reporting bias. Robust assessment of treatment-emergent ADAs/nAbs and any relationship to PD-1, PD-L1, or CTLA-4 checkpoint inhibitors were hampered by the often small sample sizes of the included trials. There was also considerable heterogeneity between studies in terms of their patient population characteristics, line of therapy, tumor type, treatment dosages, study follow-up time points, and assay used for detecting ADAs; this may explain the wide variation in ADA incidence that was reported even between studies of the same drug. We did not restrict the literature searches by clinical trial phase, and a future analysis could be conducted to assess the impact of trial phase on ADA production (eg, from phase 1/2 to observational studies).

Since the time points at which the levels of ADAs were assessed were not consistent between trials, inter-study comparisons were challenging. Many trials did

not even report the time point at which ADAs were tested for and this has implications for measuring the effect of ADAs on efficacy outcomes. The definitions of treatment-emergent ADAs and nAbs also varied across studies, with some reporting detailed methodology of the definition, time points at which ADAs were measured, and the assay employed, while others simply presented results without indicating how the data were measured or defined. There may also be inherent differences between the assays employed to measure ADAs; the development of a standardized assay to measure ADAs may be beneficial for routine clinical practice.

Despite these limitations, this systematic review highlights some important trends such as the increased incidence of treatment-emergent ADAs with atezolizumab and nivolumab when compared with other PD-1, PD-L1, or CTLA-4 checkpoint inhibitors, as well as the increased incidence of ADAs with combination therapy versus monotherapy. The full impact of ADAs and nAbs on the long-term efficacy and safety of these immunotherapies warrants further exploration in larger studies enrolling sufficient patients with ADAs to permit robust statistical analyses. The findings also have wider implications for other immunotherapeutic agents, including bispecific antibodies or antibodies targeting novel checkpoints (eg, LAG-3, TIM, TIGIT, BTLA)[108] as they may be subject to the development of ADAs and nAbs.

Another issue this systematic review highlights is the lack of consistency in the reporting of cancer immunotherapy clinical trials, particularly in terms of how ADAs are defined, and at which time point(s), and by what assay method, they are tested for. There is a need for an ad hoc committee that would issue recommendations for better consistency in cancer immunotherapy clinical trial reporting. Along with larger clinical trials, standardized reporting of ADAs in clinical trials is certainly necessary to advance our understanding of the relationship between PD-1, PD-L1, or CTLA-4 checkpoint inhibitors, treatment-emergent ADAs, and treatment outcomes. We recommend that ADAs are reported from phase 1 to phase 3 of the drug development process to achieve these goals. This will aid understanding of whether other therapies, such as corticosteroids, may be introduced to mitigate the effects of ADAs. The potential production of ADAs is pertinent not only to the drug development process but also to clinical decision-making (eg, treatment sequencing) now that multiple immune checkpoint inhibitor regimens are available; this further emphasizes the need for standardized ADA assays that can be used in clinical practice.

Immune checkpoint inhibitors are a therapeutic advance in the treatment of cancer, but they are potentially undermined by treatment-emergent ADAs. Whereas the impact of immunotherapy-induced ADAs on treatment outcomes in non-oncological indications is well characterized, the impact of treatment-emergent ADAs on cancer patient treatment outcomes is poorly understood. This systematic review, the largest such review of ADA incidence rates in checkpoint inhibitors to date, suggests agents such as atezolizumab and nivolumab are associated with an increased incidence of treatment-emergent ADAs and nAbs. Immunotherapy but not immuno-chemotherapy combinations are associated with higher ADA levels, suggesting emergence of ADAs to be a true immune-mediated effect from treatment. Larger clinical trials investigating the immunogenicity of PD-1, PD-L1, or CTLA-4 inhibitors for the treatment of cancer, and more consistency in clinical trial reporting, specifically in relation to ADAs, is required.

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