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REVIEW

Clinical toxicity of antibody drug conjugates: a meta-analysis of payloads

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Summary *Background* Antibody drug conjugates (ADCs) utilize a monoclonal antibody to deliver a cytotoxic payload specifically to tumor cells, limiting exposure to healthy tissues. Major clinical toxicities of ADCs include hematologic, hepatic, neurologic, and ophthalmic events, which are often dose-limiting. These events may be off-target effects caused by premature release of payload in circulation. A meta-analysis was performed to summarize key clinical safety data for ADCs by payload, and data permitting, establish a dose-response model for toxicity incidence as a function of payload, dose/regimen, and cancer type. *Methods* A literature search was performed to identify and extract data from clinical ADC studies. Toxicity incidence and severity were collected by treatment arm for anemia, neutropenia, thrombocytopenia, leukopenia, hepatic toxicity, peripheral neuropathy, and ocular toxicity. Exploratory plots, descriptive summaries, and logistic regression modelling were used to explore Grade ≥ 3 (G3/4) toxicities and assess the impact of covariates, including cancer type and dose/regimen. *Results* The dataset contained 70 publications; quantitative analysis included 43 studies with G3/4 toxicity information reported for the endpoints above. G3/4 anemia, neutropenia and peripheral neuropathy were consistently reported for MMAE ADCs, thrombocytopenia and hepatic toxicity for DM1, and ocular toxicity for MMAF. Safety profiles of MMAE, DM1, and DM4 ADCs differed between solid and hematologic cancers. *Conclusions* Published ADC clinical data is limited by non-uniform reporting for toxicity and lack of dosing information, limiting the ability to develop quantitative models relating toxicity to exposure. However, the current analysis suggests that key G3/4 toxicities of ADCs in the clinic are likely off-target and related to payload.

Keywords Antibody drug conjugates (ADCs) · Oncology · Clinical trials · Safety · Toxicity · Meta-analysis

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Background

Antibody drug conjugates (ADCs) used in the treatment of cancer are designed to harness the specificity of targeted treatment and combine this with the potent cell-killing of a small molecule. ADCs have complex molecular structures, including the key components of a highly-selective monoclonal antibody (mAb) directed against a target of interest, a potent cytotoxic small molecule (payload), and a linker connecting these two species. This linker is intended to be stable in circulation and only release the payload once the ADC is

internalized into cancerous target cells. This construct was designed to provide an improvement over the narrow therapeutic indices of cytotoxic small molecule drugs, theoretically resulting in an improved safety profile of the ADC when compared to systemic administration of the traditional chemotherapy agent.

Although the concept of ADCs is theoretically simple, designing a successful ADC with an improved therapeutic index has been quite challenging, as it demands careful combination of a specific mAb, linker, and toxic payload. Although currently there are a limited number of ADCs approved for treatment of solid and hematologic malignancies, there are dozens of ADCs in all stages of clinical development. Brentuximab vedotin (Adcetris® by Seattle Genetics) and trastuzumab emtansine (T-DM1) (Kadcyla® by Genentech) have both been approved for use by the Food and Drug Administration (FDA) for several years. Brentuximab vedotin is composed of an anti-CD30 mAb connected with a cleavable peptide linker to the highly-potent tubulin inhibitor monomethyl auristatin E (MMAE), and is indicated for the treatment of relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. T-DM1 combines the anti-tumor properties of the humanized anti-human epidermal growth factor receptor 2 (HER2) antibody, trastuzumab (approved as Herceptin®), with the potent maytansinoid tubulin inhibitor, emtansine (DM1), by a stable thioether linker, used for the treatment of HER2-positive metastatic breast cancer. Gemtuzumab ozogamicin (Mylotarg®, by Wyeth, a subsidiary of Pfizer) was the first ADC approved by the FDA in 2000 as monotherapy in patients with acute myeloid leukemia (AML), but was subsequently withdrawn from the market in 2010. Gemtuzumab ozogamicin and inotuzumab ozogamicin (Besponsa® by Wyeth, a subsidiary of Pfizer) both utilize a calicheamicin-based payload and were each recently approved by the FDA for use in AML and acute lymphoblastic leukemia, respectively. Since 2013, new drug research and development interest in ADCs has been very active, with more than 60 ADCs under clinical investigation [1]. Most of these ADCs currently in clinical trials use a limited number of cytotoxic payloads, which largely belong to two major categories: tubulin inhibitors and DNA-damaging agents. The auristatins (including MMAE and monomethyl auristatin F [MMAF]) and maytansinoids (including DM1 and ravtansine [DM4]) account for the majority of cytotoxic payloads used in investigational ADCs, and both function by inhibiting microtubule assembly to cause cell cycle arrest [2]. The other remaining payloads include calicheamicins, pyrrolobenzodiazepines (PBDs), indolinobenzodiazepines, irinotecan derivatives (such as SN-38), duocarmycins, tubulysins, and doxorubicin [3]. Therefore, many of the ADCs in development share a payload or linker-payload and differ only in the mAb portion designed to target a unique cellular receptor.

For most ADCs currently in clinical development, dose-limiting toxicities (DLTs) often appear to be off-target, in other words, independent of the target of the ADC. Since the small molecule payloads typically utilize a mechanism of action (MOA) of traditional anti-cancer chemotherapy agents, once the free payload is cleaved from the mAb, it can cause the same typical chemotherapy toxicities, including hematologic and non-hematologic AEs, such as peripheral neuropathy and hepatic toxicity. Many of these off-target AEs ultimately define the DLT of the agent, which in turn often dictates the maximum tolerated dose (MTD) and subsequently the dose used in pivotal studies and eventually clinical practice. Considering that the recommended dose of an ADC is typically derived from the MTD determined by DLTs that are primarily associated with the payload, there is an opportunity to leverage the clinical experience from one ADC to inform the likelihood of observing those same DLTs in a novel ADC with the same payload or linker-payload.

The model-based meta-analysis described in this report uses statistical methods to combine and quantify the outcomes of a series of clinical trials in a single pooled analysis. The purpose of the analysis was to summarize the key clinical safety data published for ADCs by payload class, and data permitting, to establish a dose-response model for severe grade toxicity incidence as a function of payload, dose/regimen, and cancer type (solid tumor vs. hematologic cancer). Further, the authors sought to establish a methodology to complete such analyses and share this methodology for future use, including implementation in other drug classes or disease indications, with emphasis on the need for clearer, more consistent quantitative safety reporting in the clinical trial literature.

Methods

Systematic literature review

A literature search was performed to identify clinical ADC studies that would meet the objective of the analysis and to develop a database of safety information. The literature search, starting in the year 2000 through 17 January 2014, used the following criteria to locate the ADC studies of interest:

1. Publication databases searched: Ovid, Medline, BIOSIS Previews, Embase, and Drugs@FDA;
2. Search terms: individual ADC names (any and all known at the time to be in clinical development through ADC reviews, current literature, recent conferences and clinicaltrials.gov), payload names (any and all known to be in clinical development at the time), clinical, oncology, English language.

During the review process, papers were excluded from consideration for the following reasons: (1) non-oncology indications (2) non-ADC clinical trial, (3) non-interventional, (4) finance/business article, (5) diagnostic article, (6) nonclinical research or (7) general review articles or opinion pieces.

After an initial of review of the selected published literature, recent abstracts from the latest and/or non-indexed relevant scientific conferences (The American Society of Clinical Oncology [ASCO], The American Society of Hematology [ASH], and American Association for Cancer Research [AACR]) were searched and reviewed for inclusion into database if appropriate.

Upon further review, pediatric trials, duplicate studies, or post-hoc analyses, including reporting of sub-groups within a study or pooling of multiple studies, were removed. Lack of access to full publication text also met the exclusion criteria. Publications pertaining to ADCs with payloads of doxorubicin and calicheamicin from earlier generations were also excluded. This collection served as the literature reference database.

Data extraction to analysis dataset

The dataset for analysis was created from the literature reference database through extraction of all key data from each reference, including bibliography information, ADC name, payload/linker-payload, cellular target of ADC, cancer type and specific disease/indication, number of patients in study/arm/cohort. The endpoints of interest for this analysis (listed below) were common AEs that, when severe in grade, are often considered DLTs to determine MTD for ADCs in clinical development. The incidence and severity of the following key AEs were captured, with severity designated according to Common Terminology Criteria for Adverse Events (CTCAE) grade (when available), with further categorization as both "all grade" (CTCAE Grade 1 to Grade 4) and as "severe grade" (Grade 3 to Grade 4) AEs for each endpoint.

Anemia
Neutropenia
Thrombocytopenia
Leukopenia
Hepatic toxicity (including liver enzyme elevation)
Peripheral neuropathy
Ocular toxicity

Other key study data collected (when available) included dose, dosing regimen/frequency, patient population and demographics (including biomarker status, previous treatment, first line versus relapsed/refractory treatment, age, sex, race, etc.), reported MTD for that ADC, reported highest non-severely toxic dose (HNSTD) (from nonclinical studies), specific DLT(s) reported for that ADC, as well as multiple other study and ADC characteristics as were available in the publication.

Dataset refinement and review

The study data were extracted into a curated data file and reviewed for accuracy. If the reference did not contain quantitative safety information (i.e. AE incidence) on any of the key safety endpoints listed above graded by CTCAE, the study or arm was excluded from the analysis. If upon review, multiple references were determined to be describing the same study and presented duplicate safety information, only the most updated or most recent reference was retained in the dataset for incorporation in the analysis.

Rules and assumptions for handling the extracted data were:

If a reference reported key safety findings in multiple ways, such as report of all-cause AEs, treatment-related AEs, lab abnormalities, reports in paragraph text or in appendices, etc., which differed numerically from one another, the highest incidence reported was used for analysis for that particular safety endpoint and severity (i.e. "severe"; Grade 3 + Grade 4 [G3/4]).

If a reference provided only the incidence of graded toxicities by individual dose level, the reports were pooled to calculate the incidence of each AE in the "all patient" group, in order to facilitate comparison to other studies which only reported an overall AE incidence across all patients regardless of dose or regimen.

If a reference reported AEs by individual CTCAE grade, then Grade 1 to Grade 4 AE incidences were summed to yield "all grade" AE incidence. Likewise Grade 3 and Grade 4 AE incidences were summed to yield "severe" AE (G3/4) incidence.

If only Grade 3 incidence was reported for particular AE, it was assumed that the Grade 4 incidence for that AE was null (zero).

If Grade 4 events were reported for some key toxicity endpoints but not others, those lacking a Grade 4 value were assumed to be null (zero) when summing with a reported Grade 3 incidence, unless there was evidence in the publication suggesting otherwise. Likewise, if Grade 3 incidence was reported for most endpoints but was lacking for another endpoint with a reported Grade 4 incidence, the incidence of Grade 3 AEs for that endpoint was assumed to be null (zero), and therefore the incidence of "severe" toxicity for that AE equaled the value reported as Grade 4.

If AE incidence was only reported for an overall combination of treatment arms in a study, such as for both

treatment arm and control/standard of care (SOC) or combination arm, instead of for an individual treatment arm, this AE incidence was excluded from analysis.

Hepatic toxicity as a general endpoint included multiple variations of reporting such as liver enzyme elevation, elevated aspartate aminotransferase (AST), elevated alanine aminotransferase (ALT), transaminitis, liver dysfunction, etc. If multiple of these specific descriptions of hepatic toxicity were reported separately within a study for a certain AE grade, such as incidence of elevated AST and incidence elevated ALT, the highest incidence of any liver-related AE was used for analysis under the general endpoint of hepatic toxicity.

Ocular toxicity as a general endpoint included multiple variations of reporting such as blurry vision, corneal deposits, retinal damage, photosensitivity, etc. If multiple of these specific descriptions of ocular toxicity were reported separately within a study for a certain AE grade, the highest incidence of any ocular or vision-related AE was used for analysis under the general endpoint of ocular toxicity.

For the thrombocytopenia endpoint, reports of idiopathic thrombocytopenic purpura (ITP) were not included.

Febrile neutropenia was not included as neutropenia if it was reported separately from neutropenia.

Data analysis

The primary endpoint was defined as the percent of patients with severity Grade ≥ 3 (G3/4) for a specific toxicity in a treatment or dose group. The primary analysis was to compare G3/4 incidence for each of the toxicity endpoints across the ADC payload classes. Exploratory plots (qualitative assessment), descriptive summaries (quantitative assessment) and modeling (quantitative assessment) were used to explore G3/4 toxicities and assess the impact of covariates, such as cancer type and dose/regimen. Forest plots were used to display G3/4 toxicity incidence rates by payload class, cancer type (solid tumors vs. hematologic malignancies vs. combination of both types) and included the point estimate for the toxicity and 80% confidence intervals using the Agresti-Coull method [4]. A qualitative assessment of all grade toxicity by payload class was also performed.

Statistical modeling was done using mixed-effects logistic meta-regression with payload class as the main structural variable. Treatment, dose, cancer type, regimen (frequency of administration) were considered as potential covariates for assessing the variability of the G3/4 toxicity endpoints. Individual ADCs were not analyzed by modeling due to limited information; ADCs were grouped according to payload class for analysis purposes. Estimates of the G3/4 toxicities and their confidence limits were computed by payload class from the model. These estimates were back-transformed and reported as incidence of G3/4 toxicity for each payload class by AE endpoint.

Studies with treatment arms of the same ADC but different dosing schedules were combined for the purpose of analysis for reason described above. All plots, descriptive summaries, and logistic regression modeling were done using the R package (version 3.22).

Results

Figure 1 presents a flow chart of the publication selection process. The initial selection process yielded 642 publications, including conference abstracts, published posters, and manuscripts. In parallel to the review process for inclusion/exclusion, an additional 18 abstracts containing clinical data from ADC studies from the most recent relevant scientific congresses (ASCO, ASH, and AACR) were included for a total of 660 publications reviewed for this analysis. After multiple rounds of review of publications according to the specified inclusion/exclusion criteria detailed previously, 73 publications remained in the final literature reference database for data extraction. Three additional publications were excluded during dataset review, since they reported only endpoints from combination therapy (ADC with concomitant anti-cancer agents), yielding a total of 70 publications in the dataset available for performing qualitative and quantitative analyses.

Of the 70 studies, 50 reported Grade 3 and/or Grade 4 toxicity information for at least one of the safety endpoints of interest in at least 1 dose group. Forty-three studies out of 50 (86%) reported incidence under an “all patients” group where the rates for each toxicity were combined across dose or treatment groups, or reported rates in every dose group to allow for post-hoc calculation of incidence across all patients. The bibliographic information for the 43 publications used in the quantitative analysis is listed in the Appendix.

Table 1 displays the payload classes, specific ADC agents within each payload class, and the number of studies and treatment arms. Four payload classes were present in the dataset for the 43 studies, including DM1, DM4, MMAE and MMAF. The majority of studies were conducted with ADCs utilizing DM1 and MMAE payloads, the payloads utilized in the only 2 currently-approved ADCs.

Key data extracted verbatim into the dataset were categorized as needed in order to have uniformity for appropriate descriptions and analyses. Various styles and terms were used to describe the ADC agents and payloads, diseases, AEs, and descriptions of frequency of administration. For example several ADCs have multiple names used throughout the literature

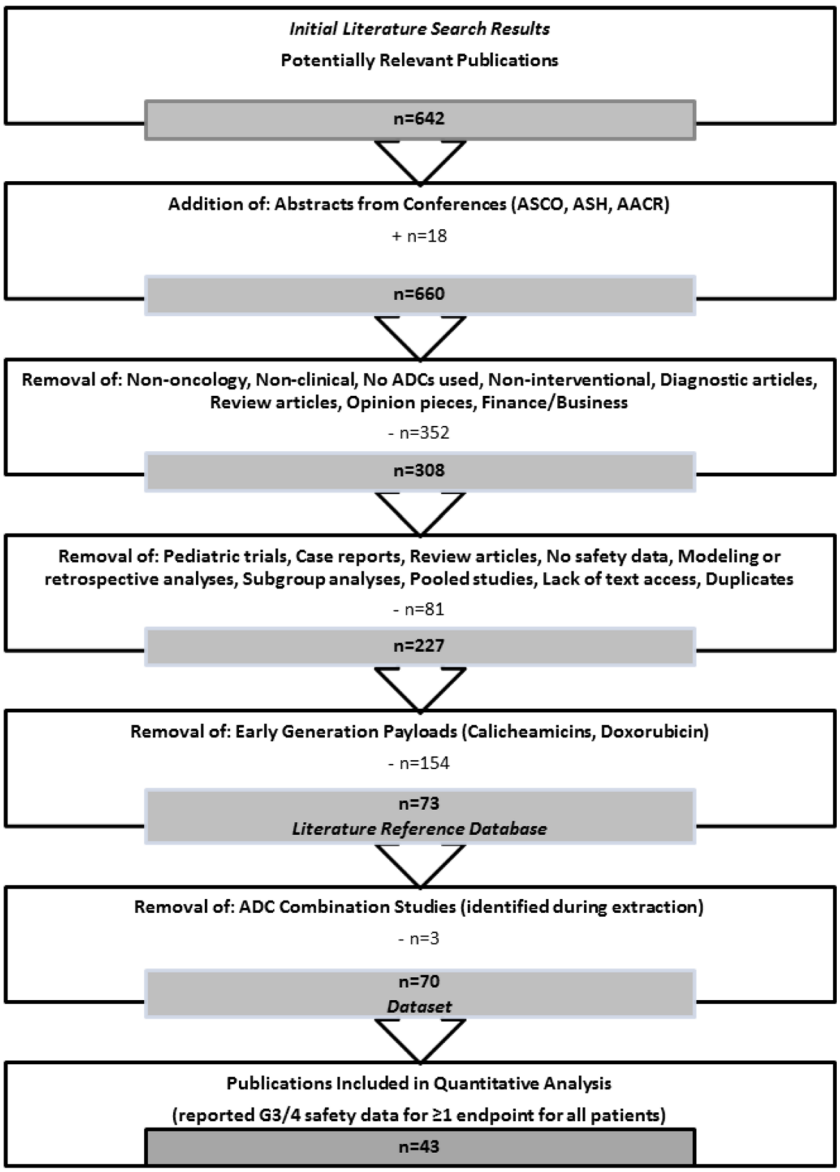

Fig. 1 Flowchart of publication selection process. Quantitative analyses included 43 publications reporting G3/4 safety information on at least 1 of the key endpoints across the study (reported in total for the all patient group or reported separately for each and every dose/regimen administered in the study)

and thus needed to be identified all under a single name. Several of the key AEs were presented using various terminologies that were interpreted and re-classified, such as "low platelets" versus "thrombocytopenia", or "liver toxicity" versus "hepatic dysfunction" or "transaminitis". Similarly, dosing frequencies were re-classified into common categories, such as

Table 1 Summary of ADCs included in the dataset for quantitative analyses

Payload class	ADCs (# agents)	# Studies [1]	# Arms [2]
DM1	bivatuzumab mertansine, cantuzumab mertansine, IMGN529, MLN2704, trastuzumab emtansine (5)	16	56
DM4	IMGN388, SAR-566658, SAR3419 (3)	5	22
MMAE	ASG-5ME, brentuximab vedotin, DNIB0600A, glembatumumab vedotin, MLN0264, pinatuzumab vedotin, polatuzumab vedotin, PSMA ADC (8)	20	41
MMAF	ABT-414, vorsetuzumab mafodotin (2)	2	7

[1] Out of 43 studies with AE Grade ≥ 3 information for these payloads

[2] Includes combined all patient arms and individual dose groups across all toxicities. Logistic regression analyzed the all patients group where dose levels within a study were combined giving 1 arm/study for the analysis of each safety endpoint

combining "bimonthly", "every other week (QOW)" and "every 2 weeks (Q2W)" under one common term.

Figures 2, 3, 4, 5 and 6 display forest plots of the most frequent G3/4 toxicities by payload class and according to cancer type. In general there were certain payloads associated with particular key AEs at a severe grade (G3/4). Severe anemia was consistently reported for MMAE ADCs (Fig. 2), neutropenia reported with MMAE (Fig. 3) and thrombocytopenia for DM1 (Fig. 4). For severe non-hematologic AEs, hepatic toxicity (mostly manifesting as AST and/or ALT elevation) was consistently reported with DM1 ADCs (Fig. 5) and peripheral neuropathy with MMAE agents (Fig. 6). Ocular toxicity was more frequently reported for MMAF ADCs but the data for this endpoint was limited at the time of data collection and analysis (data not shown). Safety trends for MMAE, DM1, and DM4 ADCs appeared to differ between solid and hematologic cancer indications for some AE endpoints.

Information on dosing, and on the incidence and grade of specific AEs according to dose level, were not reported in most publications. Thus, a dose-response analysis, as intended, was not feasible, and therefore safety data was presented by ADC as a treatment, but not further delineated by dose level and/or frequency of administration.

The results of logistic regression analyses are presented in Table 2, as the estimated incidence of G3/4 AE by toxicity and by payload class, including the 90% confidence limits. Payload class was the primary covariate for modeling. As mentioned, dose, dose regimen/frequency, and cancer type data were not robust enough (i.e. convergence issues) to include in the model. Since dose could not be included as a covariate in the model, each study was modeled as an "all patients" group with G3/4 rates combined for each safety endpoint if these were reported separately by dose. Not every publication reported information for each of the endpoints, therefore the number of studies modeled differed for each safety endpoint, and was fewer than the total of 43 studies in the analysis dataset. As demonstrated in Table 2, ADCs with MMAE or DM4 as the payload consistently report Grade 3 or greater hematologic toxicities (≥5% for each toxicity) whereas in the remaining payload classes, these types of toxicities are not as frequent (<5% for most of the hematologic toxicities). However, thrombocytopenia specifically is reported with an incidence of ≥5% across all payload classes. Severe hepatic toxicity is most common with DM1 ADCs (7.2%) but quite low in ADCs with the remaining payloads. The G3/4 toxicity rate for peripheral neuropathy is low across all ADCs, but is most frequent in ADCs with an MMAE payload (6.5%). Ocular toxicities were most frequent with ADCs containing MMAF payloads, but occurred at a lower frequency with DM4 and DM1 as well.

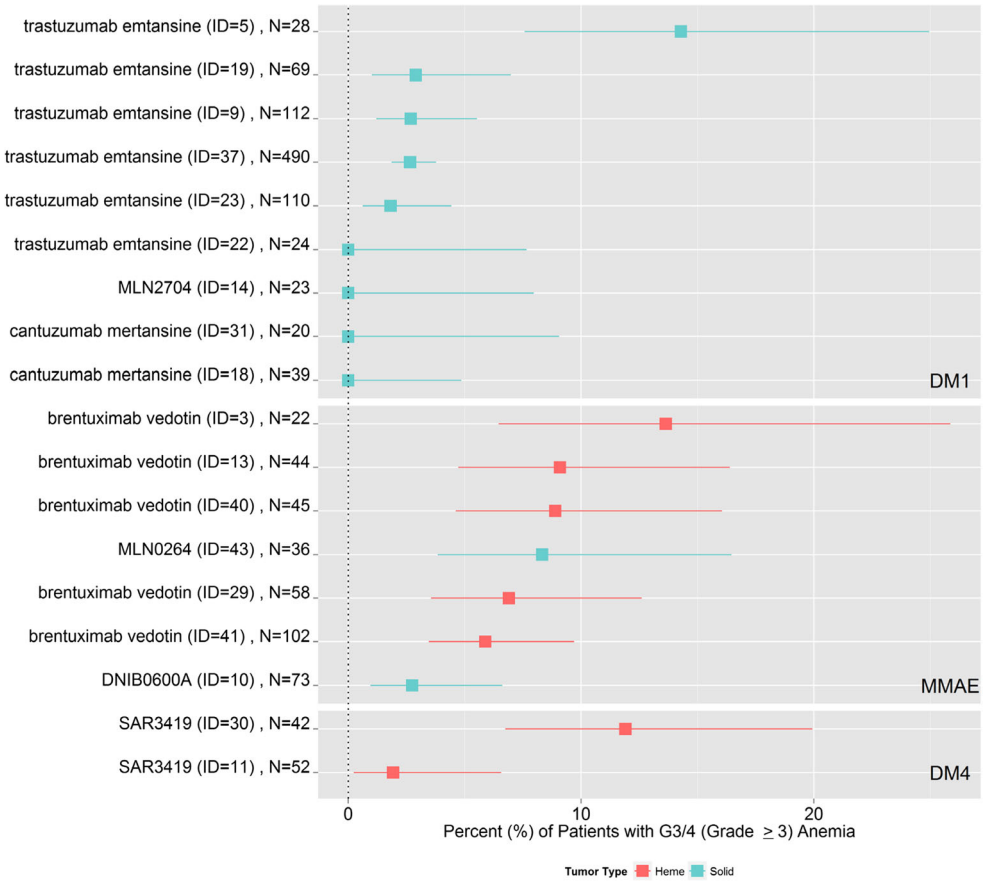

Fig. 2 Forest plots displaying percent of G3/4 toxicity for anemia reported for individual study treatment arms (ID) and sample size (N), grouped by payload. Points represent mean, error bars represent 80% confidence interval, cancer type is represented by color (red for hematologic malignancies and blue for solid tumors)

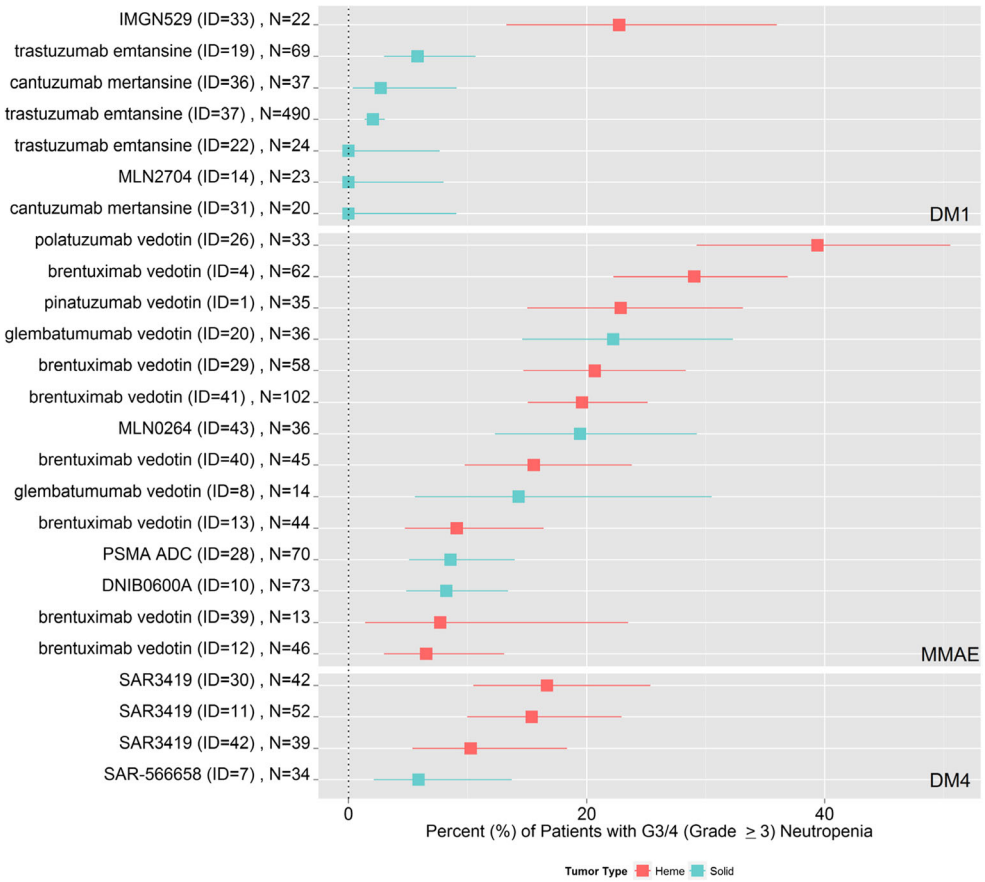

Fig. 3 Forest plots displaying percent of G3/4 toxicity for neutropenia reported for individual study treatment arms (ID) and sample size (N), grouped by payload. Points represent mean, error bars represent 80% confidence interval, cancer type is represented by color (red for hematologic malignancies and blue for solid tumors)

A qualitative representation of G3/4 toxicities observed in the dataset presented by cancer type is shown in Table 3; the data is an observational collection, and does not include any statistical analysis nor does it account for dose, target, linker, number of studies, or other factors. Nevertheless, this compilation of observations allows for a rapid, simple qualitative assessment and comparison of the G3/4 toxicities for solid versus hematologic malignancies by payload reported in at least 10% of patients of at least 1 clinical study in the dataset. The information provided in the table suggests that the toxicity profile within a given payload may differ based on the patient population for some payloads more than others. For example, this comparison suggests that the hematologic toxicities for MMAE-containing ADCs are more common in patients with hematologic malignancies, while patients with solid tumors appear to have less frequent hematologic toxicities. However, for DM4, the opposite trend is observed in which hematologic toxicities are actually more frequent in patients with solid tumors compared to hematologic cancers. However, data was quite limited for DM4 ADCs at the time of this analysis. In other cases, toxicity does not appear to differ by cancer type. For example, peripheral neuropathy is observed frequently with MMAE ADCs regardless of cancer type, and ocular toxicity appears most often with MMAF or DM4 ADCs, across cancer types, although MMAF studies included a mixture of solid tumor and hematologic malignancies and safety was not differentiated based on patient population. It should be noted that this is based on the observed data across all study arms in this analysis, and cannot be extrapolated to predicting patient-level outcomes.

Discussion

The majority of the study results included in the final analysis were described in meeting abstracts, instead of complete manuscripts or posters, which immediately limited the amount of data and detail presented and therefore available for extraction and use in modeling. In most cases within abstracts, multiple dose levels or treatment cohorts were combined for safety reporting, and often only a few toxicities were reported quantitatively. Whether the incidence of the toxicities varied by dose level, dosing frequency, or by treatment cohort, remained unknown. Also the abstracts often represented interim, immature data, which may have evolved as the study matured or further doses were explored after abstract publication. In this analysis we did not stipulate that only final study manuscripts be included, as this would have severely limited the number of studies available for the database. Despite this limitation, the authors felt there was still substantial value in including

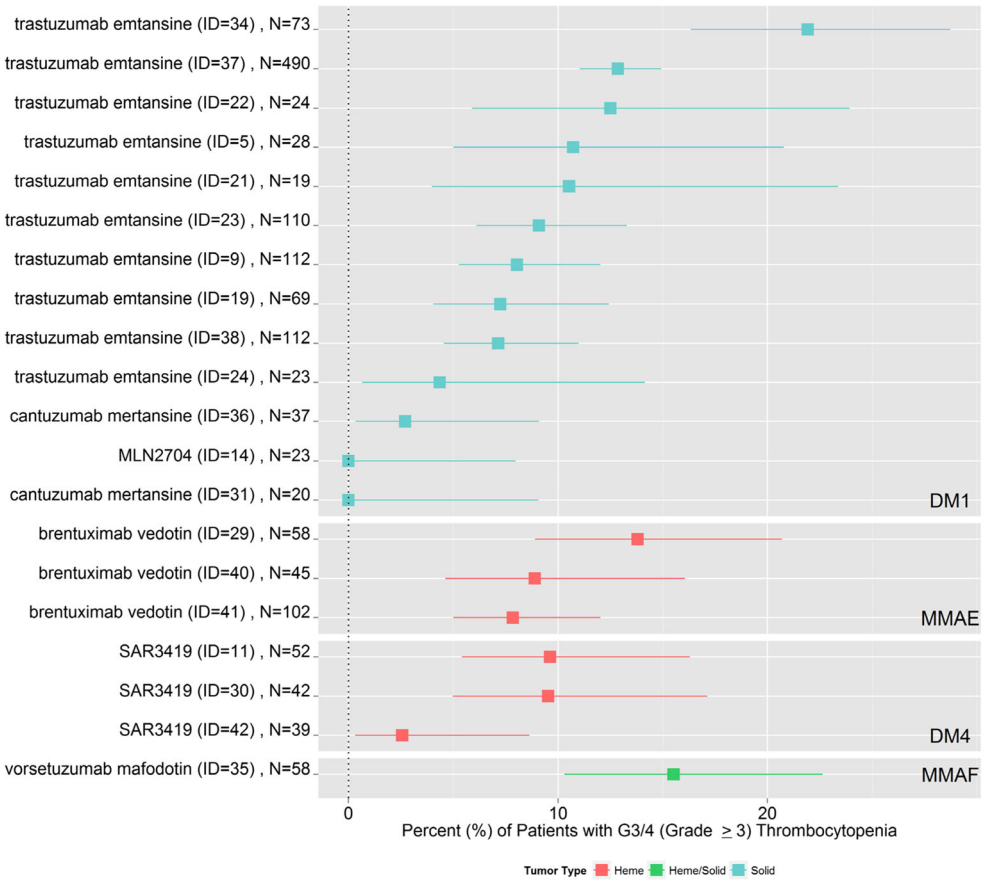

Fig. 4 Forest plots displaying percent of G3/4 toxicity for thrombocytopenia reported for individual study treatment arms (ID) and sample size (N), grouped by payload. Points represent mean, error bars represent 80% confidence interval, cancer type is represented by color (red for hematologic malignancies, blue for solid tumors and green for both indications)

abstracts with limited safety data, and other publications of ongoing studies, as the ADC field itself is still relatively young.

Another limitation of this analysis is due again to the available data, which was heavily weighted towards the 2 approved ADCs: trastuzumab emtansine (DM1) and brentuximab vedotin (MMAE). Many of the studies/arms included in the analysis were from these two agents alone, simply because they had the most studies completed, particularly large late phase studies, as compared to the many ADCs still in investigational status, particularly Phase 1. The majority of the full manuscripts with rich safety data reporting were from these two ADCs, while others had primarily abstracts with less detailed reporting. Therefore, although in the analysis dataset there were 4 other DM1-based ADCs and 7 other MMAE-based ADCs, the trends in toxicity of these agents may be driven disproportionately by the specific safety findings with trastuzumab emtansine for the DM1 class and brentuximab vedotin for the MMAE class. Once more mature data is available on multiple ADCs with each of the payload classes, presented in full manuscripts, this potential bias of disproportionate representation could be minimized.

The original intention of this model-based meta-analysis included development of a dose-response model, if not by individual ADC, then by payload class (or payload-linker combination, if possible), for the key toxicities. While the critical lack of dosing information for safety endpoints in the published studies prevented establishing this model, there is still much value in observing the trends within and between payloads. Better understanding of which toxicities are likely to be DLTs and ultimately drive MTD at the early drug design stage will improve planning from the start of clinical strategy. Based on the intended population and known symptoms, comorbidities, or complications of that disease, one can work to mitigate overlapping toxicities or alter dosing regimens to avoid severe adverse events. Identifying trends in AEs and DLTs for specific payload classes becomes even more critical for combination treatment strategies, which are ever-increasing in oncology. Since even early in development many investigational cancer therapies are intended as part of combination therapy with standard of care, often including traditional chemotherapy, researchers can plan for minimizing overlapping toxicity, both in the type (such as thrombocytopenia or peripheral neuropathy), and in the time course (such as the onset, nadir, and recovery of neutropenia). Including an MMAE-based ADC as part of a treatment regimen with agents such as paclitaxel or vinka alkaloids which also have notable peripheral neuropathy, may prompt reconsideration of the payload or at least the relative timing of dosing of both agents.

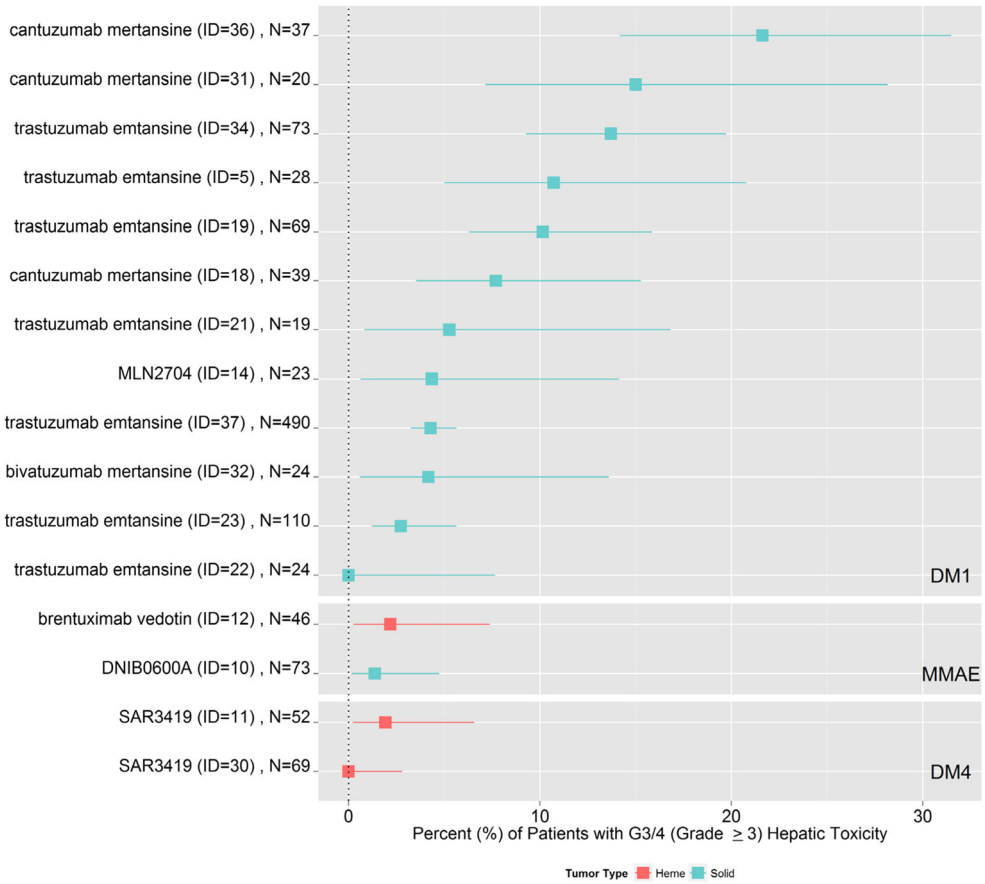

Fig. 5 Forest plots displaying percent of G3/4 hepatic toxicity reported for individual study treatment arms (ID) and sample size (N), grouped by payload. Points represent mean, error bars represent 80% confidence interval, cancer type is represented by color (red for hematologic malignancies and blue for solid tumors)

The process of extracting safety data in this meta-analysis brought attention to a much broader concern, beyond ADCs. There were major inconsistencies and in many cases lack of clarity in reporting adverse events, including identifying which severe toxicities were actually observed in a study. It's acknowledged that within any clinical trial, safety findings are defined in multiple forms, such as all-cause, treatment-emergent, treatment-related, and graded lab abnormalities. However, at minimum the incidence of Grade 3 and Grade 4 toxicities should be clearly presented and easily identifiable to readers. The lack of reporting consistency from study to study may be a result of different required presentation styles and formatting preferences or limitations from various journals. Nevertheless, this does not fully account for the difficulty in interpreting the specific toxicities, both type and frequency, reported in a clinical study. For instance, as most manuscripts report safety in a table format, the text description and discussion of safety should match numerically with the safety table. However, often the text is describing a different aspect or subset of the safety data and it is difficult to delineate if the data in the text and table overlap or represent additional data. Further, various thresholds for incidence reporting of AEs were used, such as reporting only those AEs occurring in >10% of patients in one study, while another reported those >2% and yet another included a 0% if the AE did not occur. However, if a threshold of 15% occurrence was utilized in one study for reporting, a Grade 3 or 4 AE occurring in 12% of patients would not be reported and therefore not included in this analysis, while another study reporting a 3% incidence would inform the regression model. If each study can continue reporting safety findings, particularly severe AEs, without having any agreed-upon standards, then the medical and research community will have a difficult time reliably comparing tolerability of one patient population to the next, monotherapy versus combination therapy, or one agent or drug class versus another. Here, we created rules for interpretation out of necessity, including assumptions of taking the highest reported incidence of a particular severe grade AE, regardless if it was noted as related to the ADC or not, and assuming a 0% incidence if no Grade 3 or 4 AE was reported for a particular toxicity. Since many studies reported different selections of causality (all-cause versus treatment-related, for example), we felt this data handling rule was the most appropriate option in order to maintain ability to capture the AE data in the most studies. Also in this case we simply excluded combination treatment arms. As meta-analyses such as this become a valuable tool in assessing clinical endpoints across therapies or populations, a lack of certainty and clarity in the extracted data from the primary literature source introduces limitations, potential bias, and possible error. While flexibility in reporting

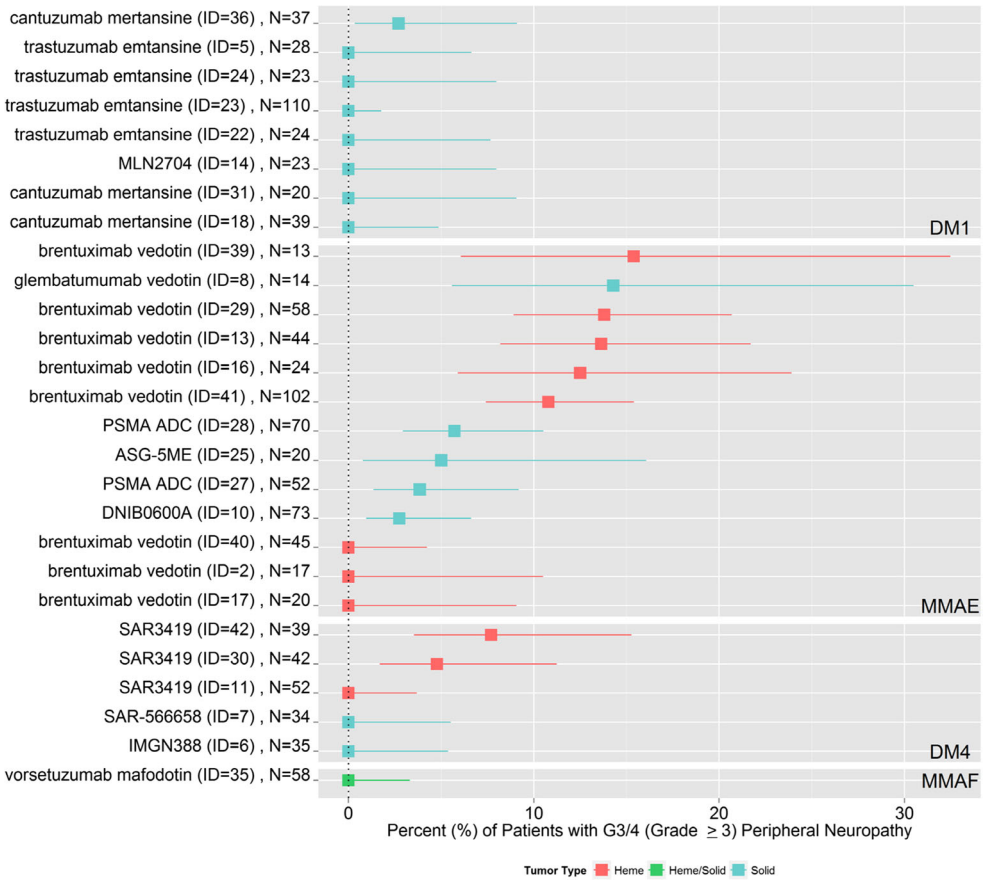

Fig. 6 Forest plots displaying percent of G3/4 toxicity for peripheral neuropathy reported for individual study treatment arms (ID) and sample size (N), grouped by payload. Points represent mean, error bars represent 80% confidence interval, cancer type is represented by color (red for hematologic malignancies, blue for solid tumors and green for both indications)

clinical trials is important, some standards and uniformity of safety reporting, particularly in oncology, would be advantageous, specifically in efforts to compare drugs in development.

In this analysis, the early generation doxorubicin and calicheamicin-based ADCs with available clinical safety data were excluded, as these payloads were not of principal interest at the time this work was conducted. As most ADCs in development had moved on to newer-generation payloads, namely the auristatins and maytansinoids, understanding and comparing the safety profiles of these categories of emerging payloads was the primary focus here. For comparing all ADCs that have reached clinical development in the past few decades, a wider meta-analysis could be conducted in the future including study-level safety data for the ADCs containing doxorubicin, calicheamicin (including gemtuzumab ozogamicin, inotuzumab ozogamicin, and other calicheamicin ADCs), and more recently-introduced payloads such as SN-38 and PBD.

Not unexpectedly, this meta-analysis shows that specific severe-grade key toxicities were consistently reported with certain payload classes, supporting the theory of the small

Table 2 Estimates (±90% confidence limits) from logistic regression of the incidence of G3/4 response by toxicity and payload class. NA = not applicable; NR = not reported

Endpoint	DM1	DM4	MMAE	MMAF	# Studies	# Patients
Anemia	2.6 (1.9, 3.6)	6.4 (3.3, 12.0)	6.8 (5.0, 9.3)	NR	18	1389
Neutropenia	3.5 (2.0, 6.0)	11.7 (6.9, 19.0)	16.4 (12.7, 21.0)	NR	25	1519
Thrombocytopenia	9.3 (7.3, 11.9)	7.3 (4.1,12.6)	9.7 (6.3, 14.8)	15.3 (7.8, 27.8)	20	1536
Leukopenia	0.6 (0.1, 3.1)	9.5 (4.3, 20.0)	10.3 (5.8, 17.4)	NR	8	284
Hepatic toxicity	7.2 (5.1, 10.2)	0.7 (0.1, 4.2)	1.5 (0.4, 5.6)	NR	16	1196
Peripheral neuropathy	0.3 (0.1 1.7)	2.1 (0.9, 5.0)	6.5 (4.4, 9.4)	0.0 (NA, NA)	27	1116
Ocular toxicity	3.3 (0.8, 12.0)	5.3 (2.4, 11.0)	NR	16.0 (6.9, 33.0)	8	272

Table 3 Qualitative comparison of toxicities within and across select payloads and cancer types. Y = yes, N = no

	MMAE		MMAF[a]		DM1		DM4	
	Solid	Heme	Solid	Heme	Solid	Heme	Solid	Heme
AE: Grade ≥ 3 (≥ 10% reported)								
Anemia	N	Y	N	N	Y	N	N	Y
Neutropenia	Y	Y	N	N	N	Y	N	Y
Thrombocytopenia	N	Y	Y	Y	Y	N	N	N
Leukopenia	N	Y	N	N	N	N	N	N
Hepatic toxicity	N	N	N	N	Y	N	N	N
AE: any Grade / Grade ≥ 3 (≥ 10% reported)								
Peripheral neuropathy	Y/Y	Y/Y	Y/N	Y/N	Y/N	N	Y/N	Y/N
Ocular toxicity	N	N	Y/Y	Y/Y	Y/N	N	Y/N	Y/Y

[a] MMAF reported safety included mix of solid tumor and hematologic malignancy patients, therefore these cannot be differentiated

molecule payload as a main driver for AEs. These results further suggest that despite the core intent of ADCs widening the narrow therapeutic index of small molecule cytotoxic chemotherapy, off-target toxicity from the payload is still largely driving tolerability and ultimately the recommended dose. This is likely due at least in part to linker instability, which presents an opportunity for enhanced chemical design and implementation with future ADCs to improve upon this concern of non-selective, off-target toxicity. Based on limitations of data maturity for ADCs described previously, in this analysis there was no ability to isolate the payload molecule from the linker (including cleavable versus non-cleavable linker); at the time of literature search and analysis, examples of quantitative clinical safety data were not available for a single payload combined with multiple linker types in different ADCs. However, the differences in safety profiles between 2 payloads of the same general class (auristatin or maytansinoid) suggest that the linker is also indeed a contributing factor to toxicity, in particular off-target AEs, as seen with the respective comparison of MMAF and DM1 ADCs with non-cleavable linkers versus MMAE and DM4 ADCs with cleavable linkers. The degree to which payload molecule or linker type individually contributes to off-target AEs is yet to be elucidated, but as more ADCs enter the clinic with various combinations of payloads and linkers, investigations should continue to further inform key drivers of toxicity for ADCs.

In discussing clinical safety, great attention must be paid of course to the intended molecular target, which through the interaction with the mAb confers the desired specificity of the ADC concept. The impact of the molecular target could not be assessed in this analysis, as the current data is unfortunately not rich enough to include this as a covariate. Expectedly, many of the ADCs in clinic utilize different targets, and therefore in our dataset there were rare instances of 2 ADCs sharing the same target. Beyond simply the individual target itself, even a binary classification of the array of cellular targets as tumor-specific versus tumor-associated would be a valuable covariate in the regression model, in order to determine any difference in safety profile based on this target characteristic. Similarly, the impact of the level of expression and the biodistribution of the target would be of interest in providing a more complete picture regarding drivers of clinical toxicity of ADCs. For example, a highly potent and toxic payload may be a preferred choice for a tumor-specific target ("clean" target), but may be an unwise option for "dirtier" target present in healthy tissues, due to difficulties of mitigating the inevitable target-related toxicities. Despite these limitations in the data and analysis, and a clear need to incorporate target information in more comprehensive future models of ADC safety for understanding target-driven AEs, the results of this analysis still suggest that the non-selective payload remains a principal driver for safety and DLTs, based the available clinical data.

Many of the ADCs included in the analysis had reported safety for both solid tumors and hematologic malignancies, allowing for a comparison of the AEs for a given ADC in both indications. There was not sufficient data to run a quantitative analysis to determine statistical differences in the AE rates in solid versus hematologic tumors, however qualitatively there were some noteworthy findings. For MMAE, DM1, and DM4, there appeared to be a notable difference in the safety profile of severe key AEs between cancer types. The reason for this difference could be complex, including the expression and distribution of the target in that disease, the accessibility of the ADC to the tumor, and the impact of comorbid conditions or complications caused by the disease itself on the tolerability response to the ADC. This observation warrants further investigation, as this may contribute to the selection of payloads during early ADC design and development for an intended solid versus hematologic cancer indication.

Conclusion

This work demonstrates the current lack of consistent reporting of safety data in oncology drug development, and supports the argument for increased uniformity in AE reporting to facilitate improved interpretation of toxicity. Improved reporting would also more effectively facilitate future meta-analyses of toxicity during clinical development, for ADCs or any other drug class. As the published clinical data for ADCs increases in quantity and quality, the driver(s) of ADC toxicity must be studied further, whether it is primarily the payload exacting off-target AEs, or a combination of drug and disease factors contributing target-dependent and independent toxicity. Improved understanding of payload-related toxicities is crucial for ADC research and development, as this analysis suggests many common DLTs to be off-target effects. Payload-driven toxicity is unarguably a key factor when designing an ADC, and this insight should be combined thoughtfully with increasing knowledge of linker technology, cancer type, molecular target including expression and distribution in the body, and profiles of probable concomitant anticancer or supportive therapies, in order to select the optimal ADC dose and administration regimen for the intended patient population. Furthermore, this a priori understanding of the clinical profile of the payload will drive strategy in clinical trial design for ADCs, particularly in the early development phase, including more tailored clinically-relevant DLT assessment plan for determination of recommended dose.

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Compliance with ethical standards

Conflict of interest Joanna C. Masters, Dana Nickens, Dawei Xuan, and Michael Amantea are employees of Pfizer and hold Pfizer stock. Ronald L. Shazer is an employee of Inspyr Therapeutics, Inc. and was a former employee of Pfizer, Inc. at the time of this analysis and holds Pfizer stock.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Supplement of References Used in the Analysis

Bracketed [] numbers match ID number in forest plots

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