A narrative review of the efficacy and safety FDA-approved antibody-drug conjugates in older patients

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Background and Objective: Antibody-drug conjugates (ADCs) are a class of drug consisting of an antibody, linker, and payload. However, ADCs have notable toxicity profiles that has significant implications; there have been follow-up studies focused on the older population in selecting ADCs such as gemtuzumab ozogamicin but not a general overview covering all ADCs, which is important given the unique toxicity profiles of each ADC. In our narrative review, we evaluate age subgroup analysis of older patients in trials leading to United States Food and Drug Administration (FDA) approval of ADCs and discuss toxicity profiles of ADCs.

Methods: We looked at 13 FDA-approved ADCs approved between May 17, 2000 and August 31, 2023 using a combination of searches in the English language from clinicaltrials.gov, PubMed, and the geriatric use section of FDA package inserts and looked at age subgroup analysis where available of the pivotal trials that led to FDA approval. For drugs in development, we looked at clinicaltrials.gov and noted trials for active drugs in development with results.

Key Content and Findings: Studies of ADCs reported different cutoff ages for separating older from younger patients ranging in age from 55 years in trials of inotuzumab ozogamicin to 75 years for trials involving enfortumab vendotin. The degree of benefit for ADCs compared with control arms as measured by the hazard ratio (HR) for primary efficacy endpoints was worse for patients in older cohorts in trials for brentuximab vedotin, ado-trastuzumab emtansine (TDM-1), inotuzumab ozogamicin, enfortumab vedotin, and tisotumab vedotin. Toxicity was worse in older patients with higher rates of adverse events and drug discontinuation in older patients in trials involving gemtuzumab ozogamicin, brentuximab vedotin, polatuzumab vedotin, sacituzumab govitecan, trastuzumab deruxtecan (T-DXd), and tisotumab vedotin with no trials showing a safer adverse event profile in older patients.

Conclusions: Age is a significant factor impacting the therapeutic index of ADCs. Further work is needed to understand differences in efficacy by age and ways to improve toxicity profile in elderly. Discussions with patients who are prescribed ADCs should incorporate age relevant efficacy and toxicity with an understanding that older patients could anticipate less benefit and greater risk.

Keywords: Antibody-drug conjugate (ADC); older patients; toxicity

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Introduction

Background

Chemotherapy has been the backbone of treatment for many advanced cancers over the years with varying but often limited efficacy (1). While most approved chemotherapy improve survival or prevents tumor growth it often produces substantial toxicity. Older patients and those with significant comorbidities in particular often suffer a decline in activities of daily living (ADLs) as a result of treatment toxicity (2,3). Limiting the delivery of chemotherapy to the sites of cancer using antibodies that bring the chemotherapy to sites expressing cancer antigens reduces side effects. Such antibody-chemotherapy constructs are known as antibody-drug conjugates (ADCs). These complexes contain the antibody against a tumor antigen, and a chemical linker covalently bound to a chemotherapy payload (4-6). However, while ADCs are meant to minimize toxicity, systemic chemotherapy exposure still occurs. In this review article, we will look at United States Food and Drug Administration (FDA) approved ADCs with a specific focus towards older patients, relative efficacy, and toxicity, as a key question is whether these agents are safe to use in older patients.

Rationale and knowledge gap

ADCs are an emerging class of drug in cancer treatment often used in elderly patients. In this review article, we explore the impact of these agents in from both an efficacy and a toxicity as compared with younger cohorts.

Objective

The objective of the study was to understand the changes in the risk benefit ratio for ADCs when they are used in older patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-188/rc).

Methods

For this study, we included 13 FDA-approved ADCs and their indications as of August 31, 2023 initially using PubMed and clinicaltrials.gov and extracted data on age-specific cohorts from clinical trials referenced. We then searched for the FDA package insert using the Google search engine associated with the FDA-approved ADC and added in notable information from the "geriatric use" section of the package insert that was not included in pivotal manuscript from the studies published that led to FDA approval. The search was conducted in English and all findings were either published studies found in PubMed or information that was otherwise noted in the FDA package insert (*Table 1*).

For drugs in development, we looked at clinicaltrials.gov and used the search term "antibody-drug conjugate" in intervention/treatment. We included phase 1–4 studies under study phase and filtered for results. If the drug was not one of the FDA-approved ADCs, we used the name of the drug in a search engine to determine if the ADC's development had been discontinued by the sponsor. Such drugs were omitted from this review (Table S1). Additionally for drugs in development, we did look up recent findings that had been presented at oncology conferences but had not been published as a manuscript in PubMed in which we used the Google search engine (Table S2).

ADC structure and mechanism

ADCs consist of a monoclonal immunoglobulin G, against the antigen of the tumor cell, a linker, and a cytotoxic chemotherapy payload (4-6). Targeted antigens must have significantly greater expression in cancer cells than in non-cancer cells (5-7). For example, *ERBB2*, a target that has led to the development of trastuzumab deruxtecan (T-DXd) and ado-trastuzumab emtansine (TDM-1), has 100-fold difference in cancer cells in comparison to non-cancer cells (7).

ADCs typically will bind to the antigen at the antibody-antigen complex and are internalize into the tumor cell within endosomes. These later fuse with lysosomes (4-8) where lysosomal interactions cause payload release (*Figure 1*). Some of the factors involved in internalization into the tumor cell include size of the antibody and affinity between the antibody and surface antigen. A larger size antibody may have problems with penetrating through the blood and into the tumor tissue (9). Too high of an affinity can reduce the penetration and slow down the internalization (4-9). Engineering of the antibody for smaller size can be accomplished by truncation of the Fc fragment so as to better solid tumors (6,10). However, this may affect the half-life of the ADC. Thus, multiple considerations must be made in terms of the antibody-antigen complex with regards to affinity between antibody and antigen and size of the antibody to allow for good internalization and an effective half-life.

Table 1 The search strategy summary

Items	Specification
Date of search	August 31, 2023
Databases and other sources searched	Package insert of FDA-approved drugs using Google, Clinicaltrials.gov, PubMed
Search terms used	[("FDA approved antibody drug conjugates")] OR ["gemtuzumab ozogamicin"] OR ["brentuximab vedotin"] OR ["ado-trastuzumab emtansine"] OR ["inotuzumab ozogamicin"] OR ["polatuzumab vedotin"] OR ["trastuzumab deruxtecan"] OR ["enfortumab veedotin"] OR ["sacituzumab govitecan"] OR ["loncastuximab tesirine"] OR ["tisotumab vedotin"] OR ["moxetumomab pasudotox"] OR ["mirvetuximab soravtansine"] OR ["belantamab mafodotin"] OR ["patritumab deruxtecan"] OR ["datopotomab deruxtecan"] OR ["telisotuzumab vedotin"] OR ["ARX788"] OR ["antibody drug conjugate older patients"]
Timeframe	2000–2023
Inclusion and exclusion criteria	Inclusion criteria: FDA-approved ADCs and ADCs in active development with results. For FDA-approved ADCs, inclusion criteria included study that was referenced on the package insert of the drug for the FDA indication
	Exclusion criteria: ADCs in development that have been terminated by the sponsor
Selection process	Conducted by first author with consensus by both authors

FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate.

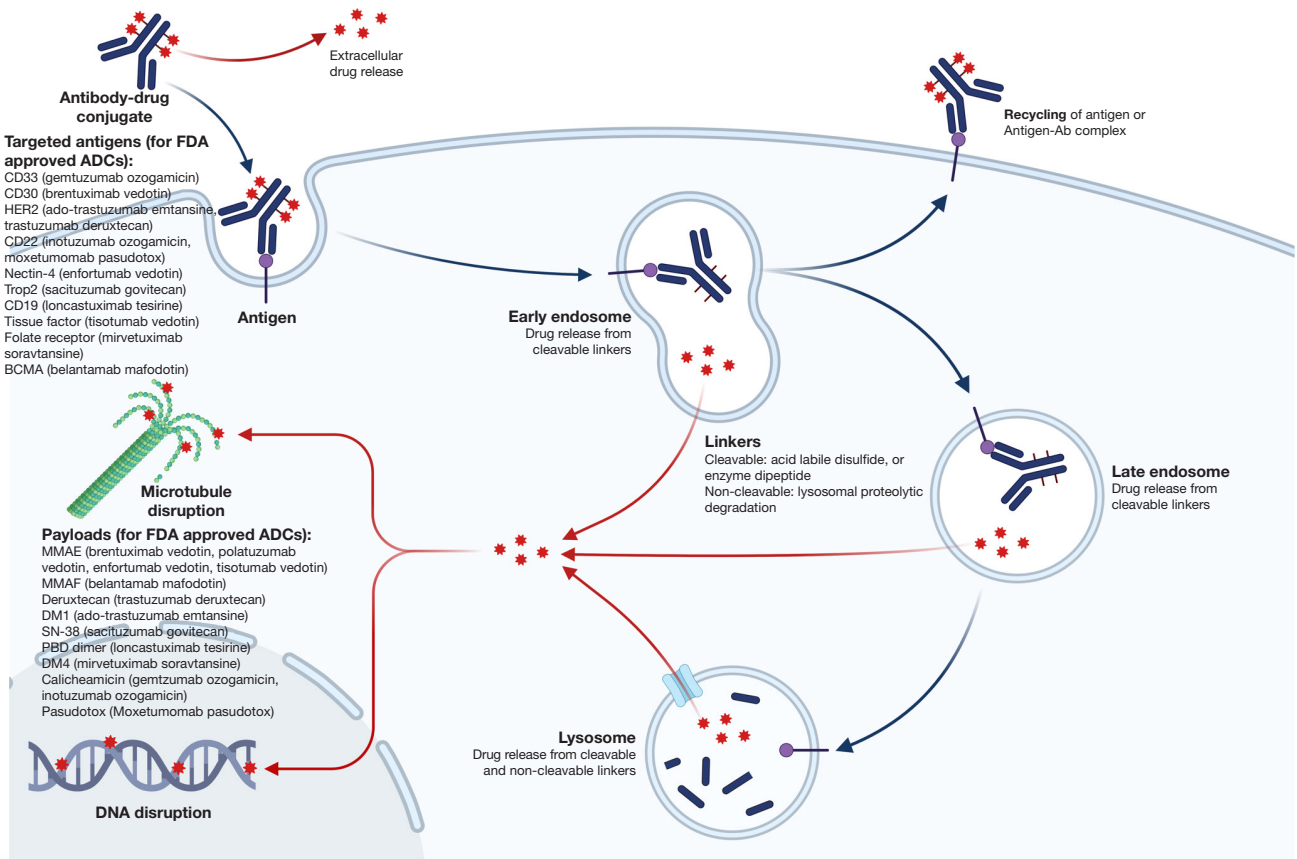

Figure 1 Mechanism of action of ADCs and list of targeted antigens, payloads, and linkers of FDA-approved ADCs. FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate; HER2, human epidermal growth factor 2; Trop2, tumor-associated calcium signal transducer 2; BCMA, B cell maturation antigen; Ab, antibody; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; PBD, pyrrolobenzodiazepine.

Linkers connect the antibody and the cytotoxic drug in the ADC (11). There are two types of linkers—cleavable and non-cleavable (*Figure 1*). Cleavable linkers break down and release the payload at the low lysosomal pH (11,12). Payload release can also be achieved by cleavage of a disulfide bond-based linker that is sensitive to reduced glutathione which is abundant inside cancer cells but not in blood (13). In addition, other non-cleavable linkers do not release payload until the antibody is degraded by lysosomal protease or beta-glucuronididases (11,14).

Cancer cell killing is accomplished by the cytotoxic payload (6) (*Figure 1*). Microtubule stability is a large part of cancer cell growth and many of the payload drugs kill cells via this mechanism. Emtansine, which is used in TDM-1 along with monomethyl auristatin E (MMAE) and F (MMAF) are tubulin inhibitors (15). Topoisomerase inhibitors interfere with DNA replication by causing DNA strand breaks; examples of this include SN-38 carried by sacituzumab govitecan and deruxtecan payload on trastuzumab (16). Additional payload mechanisms include DNA-crosslinking as seen in loncastuximab tesirine, which is used in relapsed and refractory diffuse large B-cell lymphoma (DLBCL) and DNA cleaving agents such as calicheamicin, which is used in gemtuzumab ozogamicin and inotuzumab ozogamicin (17,18). Different ADCs will carry a different number of payload chemotherapy molecules per antibody. This is termed the drug antibody ratio (DAR) and is associated with potency of the drug (19). Earlier ADCs have a DAR of 2–4 while more recently developed ADCs such as T-DXd have a DAR of nearly 8 (19).

ADC drugs

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin is an ADC targeting CD33 with a calicheamicin payload (20). It was originally approved in 2000 for newly diagnosed CD33 specifically for patients aged ≥60 years or not transplant candidates for acute myeloid leukemia (AML) (21) (*Table 2*). However, due to concerns of increased incidence of veno-occlusive disease, it was withdrawn per FDA request in 2010 (21). The ALFA-0701 trial comparing gemtuzumab ozogamicin with daunorubicin and cytarabine *vs.* daunorubicin and cytarabine showed equally significant overall survival (OS) benefit in patients aged ≥60 years and those less than age 60 years (22) (*Table 3*). Notable adverse events included grade 3 or higher infections seen in 77.9% patients and veno-occlusive disease seen in 5 cases (3.8%) (22) (*Table 4*). These results led to the re-approval of gemtuzumab ozogamicin in 2017 (21,48). It was also later approved for infants greater than 1 month old per results from the AAML0531 Children's Oncology Group trial showing superior event free survival with gemtuzumab ozogamicin (23). With regards to the elderly population, AML-19 was a study evaluating gemtuzumab ozogamicin monotherapy *vs.* best supportive care in transplant-ineligible AML patients at least 61 years old and overall showed an improved median OS 4.9 months [95% confidence interval (CI): 4.2–6.8] in the gemtuzumab ozogamicin arm *vs.* 3.6 months (95% CI: 2.6–4.2) in the best supportive care group arm (46). There was an OS benefit seen in the ages 76–80 years subgroup OS hazard ratio (HR) =0.66 (95% CI: 0.44–0.99) and the age 81 years and older subgroup OS HR =0.55 (95% CI: 0.31–0.98). The most common nonhematologic grade 3 or higher toxicity was infection (35.1%) in the gemtuzumab ozogamicin arm and there was similar percentage of deaths due to adverse events 17.1% in gemtuzumab ozogamicin and 20.2% in the best supportive care arm (46) (*Table 4*). Gemtuzumab ozogamicin has also been evaluated as a single agent in 27 patients 65 years or older and while there were no differences in effectiveness observed between these patients and younger patients, elderly patients had a higher rate of fevers and severe or greater infections (48).

Brentuximab vedotin

Brentuximab vedotin is an ADC targeting CD30 with a MMAE payload (49). It was approved originally in March 2018 based on results from the ECHELON-1 trial to receive either brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (AVD) or bleomycin plus AVD (24) (*Table 2*). It was then approved for use in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide for pediatric patients 2 years of age or older in November 2022 (25). In subgroup analysis for the ECHELON-1 trial, patients aged >60 years did not have significant OS benefit HR =0.83 (95% CI: 0.47–1.47) while patients age <60 years had a significant OS benefit HR =0.51 (95% CI: 0.29–0.89) (24) (*Table 3*). The major notable toxicity seen in brentuximab vedotin is peripheral neuropathy seen in 66.9% of patients though in 85.6% of patients there was complete resolution after systemic therapy (24) (*Table 4*). The National Comprehensive Cancer Network (NCCN) guidelines for

Table 2 List of FDA-approved ADCs with target, payload, and indication

Drug	Target	Payload	Indication
Gemtuzumab ozogamicin	CD33	Calicheamicin	Newly diagnosed CD33-positive AML in adults (22)
			Relapsed or refractory CD33-positive AML in adults and in pediatric patients 1 month and older (23)
Brentuximab vedotin	CD30	MMAE	Hodgkin lymphoma after failure of ASCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates (24)
			Previously untreated Hodgkin's lymphoma of stage IIB with bulky tumor or stage IIIB, IVA, or IVB in ages 2 years and older (25)
			Adult patients with previously untreated systemic anaplastic large cell lymphoma or other CD30 expressing PTCL including including angioimmunoblastic T cell lymphoma and PTCL not otherwise specified, in combination with CHP (26)
			Adult patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen (27)
			Adult patients with pcALCL or CD30-expressing MF who have received prior systemic therapy (28)
TDM-1	HER2	DM1	HER2-positive metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination in patient who received prior therapy for metastatic breast cancer or developed disease recurrence during or within 6 months of completing adjuvant therapy (29)
Inotuzumab ozogamicin	CD22	Calicheamicin	Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (30)
Polatuzumab vedotin	CD79	MMAE	Previously untreated DLBCL, NOS, or HGBL and who have an IPI score of 2 or greater (31)
			Relapsed or refractory DLBCL, NOS, after at least two prior treatments (32)
T-DXd	HER2	DXd	Unresectable or metastatic HER2-positive breast cancer who have received a prior anti-HER2-based regimen either in the metastatic setting or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy (33)
			Unresectable or metastatic HER2-low (IHC 1+ or 2+/ISH–) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy (34)
			Unresectable or metastatic NSCLC whose tumors are activating HER2 (*ERBB2*) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy (35)
			Locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen (36)
Enfortumab vedotin	Nectin-4	MMAE	Locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and a platinum containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting (37)

Table 2 (*continued*)

Table 2 (*continued*)

Drug	Target	Payload	Indication
Sacituzumab govitecan	Trop2	SN-38	Unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease (38)
			Locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor (39)
			Unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer whose disease progressed after the following in any setting: CDK4/6 inhibitor, endocrine therapy, taxane (40)
Loncastuximab tesirine	CD19	PBD dimer	Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, DLBCL arising from low grade lymphoma, and HGBL (41)
Tisotumab vedotin	Tissue factor	MMAE	Recurrent or metastatic cervical cancer with disease progression on or after chemotherapy (42)
Moxetumomab pasudotox[†]	CD22	Pasudotox	Relapsed or refractory hairy cell leukemia who received at least 2 prior systemic therapies including treatment with a purine nucleoside analog (43)
Mirvetuximab soravtansine	Folate receptor-alpha	DM4	Folate receptor alpha positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received 1–3 prior systemic treatment regimens (44)
Belantamab mafodotin[‡]	BCMA	MMAF	Relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent (45)

[†], manufacturer removing medication from US market as of July 2023; [‡], withdrawn per FDA request on November 22, 2022. FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate; AML, acute myeloid leukemia; MMAE, monomethyl auristatin E; ASCT, autologous stem cell transplant; PTCL, peripheral T-cell lymphomas; CHP, cyclophosphamide, doxorubicin, and prednisone; pcALCL, primary cutaneous anaplastic large cell lymphoma; MF, mycosis fungoides; TDM-1, ado-trastuzumab emtansine; HER2, human epidermal growth factor 2; DLBCL, diffuse large B-cell lymphoma; NOS, no otherwise specified; HGBL, high-grade B-cell lymphoma; IPI, international prognostic index; T-DXd, trastuzumab deruxtecan; DXd, deruxtecan; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NSCLC, non-small cell lung cancer; PD-1, programmed death receptor 1; PD-L1, programmed death-ligand 1; Trop2, tumor-associated calcium signal transducer 2; HR, hormone receptor; PBD, pyrrolobenzodiazepine; BCMA, B cell maturation antigen; MMAF, monomethyl auristatin F.

Stage III/IV Hodgkin's lymphoma do list brentuximab vedotin as one of the treatment options but state "use in caution in patients aged >60" (50). It is also approved for CD30-expressing peripheral T cell lymphoma per the ECHELON-2 study (26). While there was a similar efficacy among age subgroup analysis, among older patients 74% patients had adverse reactions grade 3 or higher compared to 62% in patients ages 65 years or younger (26,51) (*Table 4*). Older age was also a risk factor for febrile neutropenia occurring in 29% of patients who were age 65 years or older *vs.* 14% in patients less than age 65 years (51). It is also approved in patients with systemic anaplastic large cell lymphoma after failure of at least one prior multi-agent chemotherapy regimen per the AETHERA trial and approved in adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy per the ALCANZA study (27,28). In the ALCANZA study, there were no meaningful differences in safety or efficacy observed between these patients and younger patients (51).

TDM-1

TDM-1 is an ADC targeting human epidermal growth factor 2 (HER2) with a DM-1 payload (15). It is approved in HER2-positive metastatic breast cancer patients previously receiving trastuzumab and a taxane separately or in combination in patients who received prior therapy for metastatic breast cancer or developed disease recurrence

Table 3 Evaluation of age group OS HR unless otherwise indicated and median OS in ADC trials

Drug	Trial	Treatment	OS HR (95% CI)†	Median OS (95% CI)†	Efficacy†
GO	ALFA-0701 (NCT00927498) (22)	GO + daunorubicin + cytarabine *vs.* daunorubicin + cytarabine	≥60 years (n=97 GO + daunorubicin + cytarabine, n=84 daunorubicin + cytarabine): 0.56 (0.39–0.80) <60 years (n=38 GO + daunorubicin + cytarabine, n=52 daunorubicin + cytarabine): 0.52 (0.29–0.92)	Not reported	Not reported
GO	AML-19 (NCT00091234) (46)	GO *vs.* BSC	61–75 years (n=41 GO, n=44 BSC): 0.82 (0.53–1.26) 76–80 years (n=49 GO, n=52 BSC): 0.66 (0.44–0.99) ≥81 years (n=28 GO, n=23 BSC): 0.55 (0.31–0.98)	Not reported	Best response: CR 30 (27%), CRi 17 (15.3%), PR 6 (5.4%), SD 43 (38.7%), PD 16 (14.4%), induction death 8 (7.2%)
Brentuximab vedotin	ECHELON-1 (NCT01712490) (24)	A + AVD *vs.* ABVD	≥60 years (n=84 A + AVD, n=102 ABVD): 0.83 (0.47–1.47) <60 years (n=580 A + AVD, n=568 ABVD): 0.51 (0.29–0.89) ≥45 years (n=213 A + AVD, n=247 ABVD: 0.75 (0.47–1.18) <45 years (n=451 A + AVD, n=423 ABVD): 0.44 (0.20–0.99)	Not reported	% deaths: ≥60 years: A + AVD 20/84 (24%) *vs.* ABVD 29/102 (28.4%) <60 years: A + AVD 19/580 (3.3%) *vs.* ABVD 35/568 (6.2%) ≥45 years: A + AVD 30/213 (14.1%) *vs.* ABVD 46/247 (18.6%) <45 years: A + AVD 9/451 (2.0%) *vs.* ABVD 18/423 (4.3%)
Brentuximab vedotin	ECHELON-2 (NCT01578499) (26)	A + CHP *vs.* CHOP	≥65 years (n=69 A + CHP, n=70 CHOP): 0.64 (0.39–1.06) <65 years (n=157 A + CHP, n=156 CHOP): 0.64 (0.38–1.08)	Not reported	% deaths: ≥65 years: A + CHP 25/69 (36.2%) *vs.* CHOP 36/70 (51.4%) <65 years: A + CHP 26/157 (16.6%) *vs.* CHOP 37/156 (23.7%)
TDM-1	EMILIA (NCT00829166) (29)	TDM-1 *vs.* C + L	Final OS HR: ≥75 years (n=25 total at start): 2.79 (0.99–7.88) 65–74 years (n=113 total at start): 0.89 (0.56–1.43) <65 years (n=853 total at start): 0.73 (0.47–0.87)	Not reported	Number of deaths: ≥75 years (n=25 total): TDM-1 8 *vs.* C + L 8 65–74 years (n=113 total): TDM-1 35 *vs.* C + L 35 <65 years (n=853 total): TDM-1 290 *vs.* C + L 260
TDM-1	KATHERINE (NCT01772472) (7)	TDM-1 *vs.* T	Invasive free HR: ≥65 years (n=58 TDM-1, n=68 T): 0.55 (0.22–1.34) 40–64 years (n=542 TDM-1, n=522 T): 0.49 (0.36–0.67) <40 years (n=143 TDM-1, n=153 T): 0.50 (0.29–0.86)	3 years invasive free survival: ≥65 years: TDM-1 87.4% *vs.* T 81.1% 40–64 years: TDM-1 88.8% *vs.* T 77.1% <40 years: TDM-1 86.5% *vs.* T 74.9%	% with invasive disease: ≥65 years: TDM-1 7/58 (12.1%) *vs.* T 15/68 (22.1%) 40–64 years: TDM-1 64/542 (11.8%) *vs.* T 113/522 (21.6%) <40 years: TDM-1 20/143 (14.0%) *vs.* T 37/153 (24.2%)
Inotuzumab ozogamicin	INO-VATE (NCT01564874) (47)	Ino *vs.* SOC	≥55 years (n=60 Ino, n=59 SOC): 0.89 (0.57–1.37) <55 years (n=104 Ino, n=103 SOC): 0.67 (0.47–0.95)	≥55 years: Ino 5.6 *vs.* SOC 5.3 months <55 years: Ino 8.6 *vs.* SOC 8.0 months	CR/CRi rate: ≥55 years: Ino 71.7% *vs.* SOC 35.6% (P<0.001) <55 years: Ino 75.0% *vs.* SOC 28.2% (P<0.001)
Polatuzumab vedotin	GO29365 (NCT02257567) (32)	Pola + BR *vs.* BR	≥65 years (n=23 Pola + BR, n=26 BR): 0.39 (0.19–0.79) <65 years (n=17 Pola + BR, n=14 BR): 0.47 (0.19–1.19)	Not reported	% deaths: ≥65 years: Pola + BR 13/23 (56.5%) *vs.* BR 19/26 (73.1%) <65 years: Pola + BR 10/17 (58.8%) *vs.* BR 9/14 (64.3%)
Polatuzumab vedotin	POLARIX (NCT03274492) (31)	Pola + R-CHP *vs.* R-CHOP	PFS HR: >60 years (n=300 Pola + R-CHP, n=308 R-CHOP): 0.7 (0.5–0.9) ≤60 years (n=140 Pola + R-CHP, n=131 R-CHOP): 0.9 (0.6–1.5)	2-year PFS: >60 years (n=608): 77.9% (300/440) *vs.* 69.5% (308/439) ≤60 years (n=271): HR 0.9 (0.6–1.5)	Not reported
T-DXd	DESTINY-Breast04 (NCT03734029) (34)	T-Dxd *vs.* IC	Hormone receptor-positive cohort (PFS HR): ≥65 years (n=71 T-DXd, n=43 IC): 0.47 (0.29–0.77) <65 years (n=260 T-DXd, n=120 IC): 0.51 (0.39–0.67)	Hormone receptor-positive cohort (median PFS): ≥65 years: 12.0 (9.5–14.7) *vs.* 5.6 (4.3–10.8) months <65 years: 9.8 (8.4–11.3) *vs.* 5.4 (4.1–7.8) months	% events: ≥65 years: T-DXd 41/71 (57.7%) *vs.* IC 31/43 (72.1%) <65 years: T-DXd 170/260 (65.4%) *vs.* IC 79/120 (65.8%)

Table 3 (*continued*)

Table 3 (*continued*)

Drug	Trial	Treatment	OS HR (95% CI)[†]	Median OS (95% CI)[†]	Efficacy[†]
T-DXd	DESTINY-Gastric01 (NCT03329690) (36)	T-DXd *vs.* IC	≥65 years (n=67 T-DXd, n=34 IC): 0.44 (0.26–0.76) <65 years (n=82): 0.82 (0.44–1.53)	Not reported	ORR: ≥65 years: T-DXd 46.3% (n=98) *vs.* IC 20.6% (n=41) <65 years: T-DXd 57.7% (n=52) *vs.* IC 4.5% (n=23)
EV	EV-301 (NCT03474107) (37)	EV *vs.* IC	≥65 years (n=193 EV, n=196 IC): 0.75 (0.56–1.00) <65 years (n=108 EV, n=111 IC): 0.68 (0.47–0.99) ≥75 years (n=52 EV, n=68 IC): 0.91 (0.55–1.51) <75 years (n=249 EV, n=239 IC): 0.69 (0.53–0.89)	Not reported	% deaths: ≥65 years: EV 85/193 (44.0%) *vs.* IC 101/196 (51.5%) <65 years: EV 49/108 (45.37%) *vs.* IC 66/111 (59.5%) ≥75 years: EV 25/52 (48.1%) *vs.* IC 39/68 (57.4%) <75 years: EV 109/249 (43.8%) *vs.* IC 128/239 (53.6%)
SG	ASCENT (NCT02574455) (38)	SG *vs.* chemo	PFS HR: ≥65 years (n=90): 0.22 (0.12–0.40) <65 years (n=378): 0.46 (0.35–0.59)	PFS: ≥65 years: SG 7.1 (5.8–8.9) *vs.* chemo 2.4 (1.4–2.9) months <65 years: SG 4.6 (3.7–5.7) *vs.* chemo 1.7 (1.5–2.5) months	Not reported
SG	TROPHY-U-01 (NCT03547973) (39)	SG	Not reported	Not reported	ORR: ≥65 years (n=60): 14/60 (23.3%; 95% CI: 13.38–36.04%) 50–64 years (n=45): 15/45 (33.3%; 95% CI: 20–48.95%) <50 years (n=8): 2/8 (25.0%; 95% CI: 3.19–65.09%)
SG	TROPicS-02 (NCT03901339) (40)	SG *vs.* chemo	≥65 years (n=140): 0.80 (0.54–1.19) <65 years (n=403): 0.81 (0.64–1.02)	≥65 years: 14.9 (12.0–17.5) *vs.* 10.1 (7.6–14.2) months <65 years: 14.1 (12.7–16.4) *vs.* 11.5 (10.3–13.3) months	Not reported
Loncastuximab tesirine	LOTIS-2 (NCT03589469) (41)	Loncastuximab tesirine	DOR: ≥75 years (n=11): 13.37 months (5.98–not reached) 65–74 years (n=27): 10.25 months (3.84–not reached) <65 years (n=32): 9.63 months (3.22–not reached)	Not reported	ORR: ≥75 years (n=21): 52.4% (95% CI: 29.8–74.3%) 65–74 years (n=59): 45.8% (95% CI: 32.7–59.2%) <65 years (n=65): 49.2% (95% CI: 36.6–61.9%)
Belantamab mafodotin	DREAMM-2 (NCT03525678) (45)	Belantamab mafodotin (2 arm study—2.5 mg/kg and 3.4 mg/kg cohort)	Not reported	Not reported	ORR: ≥75 years: 2.5 mg/kg dose (n=13) 7.7% (95% CI: 0.2–36.0%), 3.4 mg/kg dose (n=17) 35.3% (95% CI: 14.2–61.7%) 65–74 years: 2.5 mg/kg dose (n=39) 43.6% (95% CI: 27.8–60.4%), 3.4 mg/kg dose (n=46) 32.6% (95% CI: 19.5–48.0%) 18–64 years: 2.5 mg/kg dose (n=45) 26.7% (95% CI: 14.6–41.9%), 3.4 mg/kg dose (n=36) 36.1% (95% CI: 20.8–53.8%)

Tistoumab vedotin, moxetumomab pasudotox, and mirvetuximab soravtansine did not report age-specific survival or efficacy numbers in their studies. [†], unless noted otherwise. OS, overall survival; HR, hazard ratio; ADC, antibody-drug conjugate; CI, confidence interval; GO, gemtuzumab ozogamicin; BSC, best supportive care; CR, complete response; CRi, complete response with incomplete blood count recovery; PR, partial response; SD, stable disease; PD, progressive disease; A + AVD, brentuximab vedotin + doxorubicin + vinblastine + dacarbazine; ABVD, bleomycin + doxorubicin + vinblastine + dacarbazine; A + CHP, brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; TDM-1, ado-trastuzumab emtansine; C + L, capecitabine + lapatinib; T, trastuzumab; Ino, inotuzumab ozogamcin; SOC, standard of care; Pola + BR, polatuzumab vedotin + bendamustine+ rituximab; BR, bendamustine + rituximab; Pola + R-CHP, polaztuzumb vedotin+ rituximab + cyclophosphamide + doxorubicin + prednisone; R-CHOP, rituximab + cyclophosphamide + doxorubicin + prednisone; T-DXd, trastuzumab deruxtecan; IC, investigator's choice; EV, enfortumab vedotin; SG, sacituzumab govitecan; chemo, chemotherapy.

Table 4 Notable toxicities for studies associated with FDA-approved ADCs

Drug	Trial	Treatment	Notable adverse events†	Grade 3 or higher†
GO	ALFA-0701 (NCT00927498) (22)	GO + daunorubicin + cytarabine *vs.* daunorubicin + cytarabine (control)	GO arm: any SAE 88/131 (67.2%), thrombocytopenia 34/131 (26.0%), bronchopulmonary aspergillosis 14/131 (10.7%), septic shock 12/131 (9.2%), febrile bone marrow aplasia 12/131 (9.2%), bacterial sepsis 7/131 (5.3%)	GO arm (n=131): infections 102 (77.9%), hemorrhage 30 (22.9%), VOD 5 (3.8%)
GO	AML-19 (NCT0091234) (46)	GO *vs.* BSC	Death due to any AE: 19/111 (17.1%) in GO arm *vs.* 23/114 (20.2%) in BSC arm	Non-hematologic adverse events GO arm (n=111): overall incidence 68 (61.2%), infection 39 (35.1%), febrile neutropenia 20 (18%), bleeding 14 (12.6%), fatigue 13 (11.7%), liver 8 (7.2%), cardiac 7 (6.3%), metabolic 4 (3.6%), renal 4 (3.6%)
Brentuximab vedotin	ECHELON-1 (NCT01712490) (24)	A + AVD *vs.* ABVD	443/662 in A + AVD arm (66.9%) with peripheral neuropathy; 379/443 (85.6%) with complete resolution	Peripheral neuropathy: grade 3+ 16/662 (2.5%) A + AVD arm; death 39/662 (5.9%) of any cause in A + AVD, including 32 cases from Hodgkin's lymphoma or complication
Brentuximab vedotin	ECHELON-2 (NCT01578499) (26)	A + CHP *vs.* CHOP	Among older patients (30% of A-CHP arm ≥ age 65 years): 74% patients had adverse reactions grade 3 or higher compared to 62% in patients ages 65 years or younger	A + CHP arm (n=223): neutropenia 77 (35%), anemia 30 (13%), diarrhea 13 (6%), peripheral sensory neuropathy 8 (4%)
TDM-1	EMILIA (NCT00829166) (29)	TDM-1 *vs.* C + L	9 patients died from adverse events; 3 from TDM-1 group (n=490) (metabolic encephalopathy, neutropenic sepsis, AML)	TDM-1 arm (n=490): thrombocytopenia 70 (14%), increased aspartate aminotransferase levels 22 (5%), anemia 19 (4%)
TDM-1	KATHERINE (NCT01772472) (7)	TDM-1 *vs.* T	138/740 (18.6%) with peripheral neuropathy of any grade in TDM-1 arm, 19/740 (2.6%) pneumonitis	TDM-1 arm (n=740): any grade ≥3 adverse event 190 (25.7%), decreased platelet count 42 (5.7%), hypertension 15 (2.0%), radiation-related skin injury 10 (1.4%), peripheral sensory neuropathy 10 (1.4%), decreased neutrophil count 9 (1.2%), hypokalemia 9 (1.2%), fatigue 8 (1.1%), anemia 8 (1.1%)
Ino	INO-VATE (NCT01564784) (47)	Ino *vs.* SOC	131/164 (79.9%) in Ino arm *vs.* 126/143 (88.1%) in standard of care arm died with ALL being most common cause 80/164 (48.8%) in Ino arm *vs.* 100/143 (69.9%) in standard of care arm). Fatal toxicity from 8 inotozumab ozogamcin arm patients included 5 from VOD, 1 from multiorgan failure concomitant with VOD, 1 due to respiratory distress, 1 due to pneumonia	Ino arm (n=164): any toxicity 80 (48.8%), febrile neutropenia 19 (11.6%), veno-occlusive liver disease 19 (11.6%), sepsis 4 (2.4%), disease progression 8 (4.9%), pneumonia 9 (5.5%), respiratory failure 2 (1.2%), pyrexia 2 (1.2%), neutropenic sepsis 3 (1.8%), septic shock 3 (1.8%)
Polatuzumab vedotin	GO29365 (NCT02257567) (32)	Pola + BR *vs.* BR	Peripheral neuropathy of any grade seen in 17/39 (43.6%) cases in Pola + BR arm, 0 cases grade 3–4 in Pola + BR arm	Pola + BR arm (n=39): neutropenia 18 (46.2%), thrombocytopenia 16 (41.0%), anemia 11 (28.2%), lymphopenia 5 (12.8%), febrile neutropenia 4 (10.3%)
Polatuzumab vedotin	POLARIX (NCT03274492) (31)	Pola + R-CHP *vs.* R-CHOP	Peripheral neuropathy of any grade of 230/435 (52.9%) in Pola + R-CHP including 13.8% grade 2 or higher	Pola + R-CHP arm (n=435): neutropenia 123 (28.3%), febrile neutropenia, 60 (13.8%), anemia 52 (12.0%), diarrhea 17 (3.9%), peripheral neuropathy 7 (1.6%), asthenia 7 (1.6%)
T-DXd	DESTINY-Breast04 (NCT03734029) (34)	T-DXd *vs.* IC	Drug-related ILD or pneumonitis seen in 45/371 (12.1%) patients—13 (3.5%) grade 1, 24 (6.5%) grade 2, 5 (1.3%) grade 3, and 3 (0.8%) with grade 5 event	T-DXd arm (n=371): neutropenia 51 (13.7%), anemia 30 (8.1%), thrombocytopenia 19 (5.1%), leukopenia 24 (6.5%), nausea 17 (4.6%), vomiting 17 (9.9%), diarrhea 31 (18.0%), constipation 22 (12.8%)
T-DXd	DESTINY-Breast03 (NCT03529110) (33)	T-DXd *vs.* TDM-1	Drug-related ILD or pneumonitis seen in 39/257 (15%) patients treated with T-DXd compared to 8/261 (3%) treated with TDM-1	T-DXd arm (n=257): anemia 24 (9%), platelet count decreased 20 (8%), nausea 18 (7%), white blood cell count decreased 16 (6%)
T-DXd	DESTINY-LUNG01 (NCT03505710) (35)	T-DXd	Drug-related ILD occurred in 24/91 (26%) patients—grade 1 in 3 patients, grade 2 in 15 patients, grade 3 in 4 patients, grade 5 in 2 patients	T-DXd (n=91): any adverse event 42 (46%), nausea 8 (9%), fatigue 6 (7%), neutropenia 17 (18%), anemia 9 (10%), leukopenia 4 (4%), diarrhea 3 (3%)
T-DXd	DESTINY-Gastric01 (NCT03329690) (36)	T-DXd *vs.* IC	12/125 (10%) of patients in T-DXd group had drug-related ILD or pneumonitis—3 events of grade 1, 6 events of grade 2, 2 events of grade 3, 1 event of grade 4, 1 death associated with T-DXd therapy (pneumonia)	T-DXd arm (n=125): neutrophil count decreased 64 (51%), anemia 47 (38%), white cell count decreased 26 (21%), decreased appetite 21 (17%), platelet count decreased 14 (12%), lymphocyte count decreased 14 (11%), fatigue 9 (7%), nausea 6 (5%)
EV	EV-301 (NCT03474107) (37)	EV *vs.* IC	Treatment-related rash in 130/301 (43.9%) of patients including 43/301 (14.5%) with grade 3+ rash 55/301 (18.6%) patients with ocular disorders including 47/301 (15.9%) with dry eye, 12/301 (4.1%) with blurred vision, and 2/301 (0.7%) with corneal disorders Peripheral neuropathy in 137/301 (46.3%) patients with 15/301 (5.1%) with grade 3 peripheral neuropathy	EV arm (n=301): any adverse event 152 (51.4%)—macropapular rash 22 (7.4%), fatigue 19 (6.4%), decreased neutrophil count 18 (6.1%), neutropenia 14 (4.7%), diarrhea 10 (3.4%), peripheral sensory neuropathy 9 (3.0%), decreased appetite 9 (3.0%), anemia 8 (2.7%)
SG	ASCENT (NCT02574455) (38)	SG *vs.* chemo	Three deaths owing to adverse events but no deaths were considered to be related to SG	SG arm (n=235): any treatment-related adverse event 165 (64%), neutropenia 132 (51%), anemia (8%), leukopenia 26 (10%), thrombocytopenia 4 (2%), febrile neutropenia 15 (6%), diarrhea 27 (10%), nausea 7 (2%), vomiting 3 (1%), abdominal pain 3 (1%), fatigue 8 (3%)
SG	TROPHY-U-01 (NCT03547973) (39)	SG	1 case of grade 2 ILD and 1 treatment-related death because of sepsis due to febrile neutropenia	SG (n=113): neutropenia 39 (35%), leukopenia 20 (18%), anemia 16 (14%), diarrhea 11 (10%), febrile neutropenia 11 (10%)

Table 4 (*continued*)

Table 4 (*continued*)

Drug	Trial	Treatment	Notable adverse events[†]	Grade 3 or higher[†]
SG	TROPicS-02 (NCT03901339) (40)	SG *vs.* chemo	1 fatal adverse event (septic shock caused by neutropenic colitis) determined to be related to SG	SG arm (n=272): any treatment-emergent adverse event 198 (74%), neutropenia 136 (51%), anemia 17 (6%), leukopenia 23 (9%), lymphopenia 10 (4%), febrile neutropenia 14 (5%), diarrhea 25 (9%), fatigue 15 (6%), asthenia 5 (2%), neuropathy 3 (1%)
Loncastuximab tesirine	LOTIS-2 (NCT03589469) (41)	Loncastuximab tesirine	Treatment-emergent adverse events with fatal outcome observed in 8 (6%) of 145 patients, none were related to loncastuximab tesirine	Loncastuximab tesirine n=145: any treatment related adverse event 105 (73%), neutropenia 37 (26%), thrombocytopenia 26 (18%), increased gamma-glutamyl transferase 24 (17%)
Tisotumab vedotin	innovaTV 204/GOG 3023/ ENGOT-cx6 (NCT03438396) (42)	Tisotumab vedotin	One death due to septic shock related to therapy with three additional deaths that were not related	Tisotumab vedotin (n=101): any treatment related adverse event 28 (28%) including neutropenia 3 (3%), fatigue 2 (2%), ulcerative keratitis 2 (2%), peripheral neuropathies 2 (2%)
Moxetumomab pasudotox	Study 1053 (NCT01829711) (43)	Moxetumomab pasudotox	No treatment-related deaths noted; 2 cases of capillary leak syndrome and 4 cases of hemolytic uremic syndrome	Moxetumomab pasudotox (n=80): lymphocyte count decreased 6 (8%), hemolytic uremic syndrome 4 (5%), capillary leak syndrome 2 (3%), nausea 2 (3%), anemia 2 (3%), platelet count decreased 2 (3%), hypertension 2 (3%), acute kidney injury 2 (3%), neutropenia 2 (3%), white blood cell count decreased 2 (3%)
Mirvetuximab soravtansine	SORAYA (NCT04296890) (44)	Mirvetuximab soravtansine	Six patients died while on study, four due to disease progression and two due to unrelated adverse events	Mirvetuximab soravtansine (n=106): any treatment related event 31 (29%), blurred vision 6 (6%), keratopathy 9 (9%), dry eye 2 (2%), neutropenia 2 (2%), diarrhea 2 (2%)
Belantamab mafodotin	DREAMM-2 (NCT03525678) (45)	Belantamab mafodotin	Two deaths were potentially treatment related (one case of sepsis in 2.5 mg/kg cohort and one case of hemophagocytic lymphohistiocytosis in 3.4 mg/kg cohort)	Belantamab mafodotin 2.5 mg/kg (n=95) and 3.4 mg/kg (n=99): keratopathy 26 (27%) in 2.5 mg/kg cohort and 21 (22%) in 3.4 mg/kg cohort, thrombocytopenia 19 (20%) in 2.5 mg/kg cohort and 33 (33%) in 3.4 mg/kg cohort, anemia 19 (20%) in 2.5 mg/kg cohort and 25 (25%) in 3.4 mg/kg cohort

[†], data are presented as n (%) unless otherwise noted. FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate; GO, gemtuzumab ozogamicin; SAE, severe adverse event; VOD, veno-occlusive disease; BSC, best supportive care; A + AVD, brentuximab vedotin + doxorubicin + vinblastine + dacarbazine; ABVD, bleomycin + doxorubicin + vinblastine + dacarbazine; A + CHP, brentuximab vedotin + cyclophosphamide + doxorubicin + prednisone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; TDM-1, ado-trastuzumab emtansine; C + L, capecitabine + lapatinib; AML, acute myeloid leukemia; T, trastuzumab; Ino, inotuzumab ozogamcin; SOC, standard of care; ALL, acute lymphoblastic leukemia; Pola + BR, polatuzumab vedotin + bendamustine+ rituximab; BR, bendamustine + rituximab; Pola + R-CHP, polaztuzumb vedotin+ rituximab + cyclophosphamide + doxorubicin + prednisone; R-CHOP, rituximab + cyclophosphamide + doxorubicin + prednisone; T-DXd, trastuzumab deruxtecan; IC, investigator's choice; ILD, interstitial lung disease; EV, enfortumab vedotin; SG, sacituzumab govitecan; chemo, chemotherapy.

during or within 6 months of completing adjuvant therapy (29) (*Table 2*). It is also approved for use in adjuvant disease in HER2-positive breast cancer patients who have residual invasive disease after neoadjuvant taxane-based chemotherapy and trastuzumab-based treatment. The EMILIA trial compared TDM-1 with capecitabine and lapatinib and OS HR age subgroup analysis showed a significant benefit of TDM-1 in patients ages <65 years while in patients ages 75 years or older though a small sample size of 25 patients, the OS HR was 2.79 (95% CI: 0.99–7.88) (29). In the KATHERINE trial, which evaluated adjuvant TDM-1 therapy in patients who had residual invasive disease after neoadjuvant therapy, TDM-1 had a clear benefit in patients ages <40 years and ages 40–64 years but this benefit was less clear in patients ages ≥65 years OS HR =0.55 (95% CI: 0.22–1.34) (7) (*Table 3*). Furthermore, there was a smaller absolute 3-year invasive disease-free survival difference in patients ≥65 years: 87.4% *vs.* 81.1% compared with patients <40 years: 86.5% *vs.* 74.9%. In terms of toxicity, thrombocytopenia/decreased platelet count was the most common grade 3 or higher toxicity in both trials. Three patients died in the EMILIA trial secondary to TDM-1, one thought to be from metabolic encephalopathy, another from neutropenic sepsis, and a third from AML (29). In the KATHERINE trial, 18.6% of patients had peripheral neuropathy of any grade and there were 19 cases (2.6%) of pneumonitis seen (7) (*Table 4*). However, despite these noted age subgroup differences, population pharmacokinetic analysis suggests that age does not have a clinically meaningful effect on the pharmacokinetics of TDM-1 (52).

Inotuzumab ozogamicin

Inotuzumab ozogamicin is an ADC targeting CD22 with a calicheamicin payload that is approved in patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (30,47) (*Table 2*). The INO-VATE trial compared patients to receive either inotuzumab ozogamicin with standard intensive chemotherapy and in subgroup analysis patients aged greater than 55 years did not have a significant OS HR =0.89 (95% CI: 0.57–1.37) with a median OS of 5.6 *vs.* 5.3 months while patients aged <55 years had a significant OS benefit (8.6 *vs.* 8.0 months with OS HR =0.67 (95% CI: 0.47–0.95) (30) (*Table 3*). In terms of notable toxicity, eight patients from the inotuzumab ozogamicin arm died, including five from veno-occlusive disease. Veno-occlusive and febrile neutropenia (both 11.6%) were the most common grade 3 or higher toxicities seen in the trial (47) (*Table 4*). Based on population pharmacokinetic analysis in 765 patients, no adjustment to starting dose is required based on age (53).

Polatuzumab vedotin

Polatuzumab vedotin is a CD79b targeted ADC with a MMAE payload that has been FDA-approved in relapsed or refractory DLBCL after at least two prior treatments and previously untreated DLBCL who have an international prognostic index (IPI) score of 2 or greater (31,32) (*Table 2*). In the GO29365 study, polatuzumab vedotin with bendamustine and rituximab (pola-BR) was compared with bendamustine with rituximab (BR) in transplant ineligible patients and there was a significant OS benefit in patients age ≥65 years HR =0.39 (95% CI: 0.19–0.79) (32). Of note, patients aged ≥65 years (64%) had numerically higher incidence of serious adverse events compared to patients aged >65 years (53%) (54). The POLARIX trial compared untreated intermediate or high-risk DLBCL patients receiving polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) compared with rituximab, cyclophosphamide, doxorubicin, and vincristine (R-CHOP) and in older patients aged greater than 60 years, there was a significant OS benefit HR =0.7 (95% CI: 0.5–0.9) but not seen in patients age ≤60 years HR =0.9 (95% CI: 0.6–1.5) (31) (*Table 3*). The most common grade 3 or higher toxicity seen in both trials was neutropenia, which was seen in 46.2% of patients receiving pola-BR and in 28% of patients receiving pola-R-CHP (31) (*Table 4*).

T-DXd

T-DXd is an ADC targeting HER2 with a deruxtecan payload (19) (*Table 2*). It was initially FDA-approved in patients with unresectable or metastatic HER2-positive breast cancer who had received a prior anti-HER2-based regimen in the metastatic or had disease recurrence during or within 6 months of neoadjuvant or adjuvant therapy (33). It was then approved for unresectable or metastatic HER2 low [immunohistochemistry (IHC) 1+ or 2+/fluorescence in situ hybridization (FISH)–] breast cancer who had received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of neoadjuvant or adjuvant therapy from results in the DESTINY-Breast04 trial (34).

It also has been approved in non-small cell lung cancer (NSCLC) for unresectable or metastatic NSCLC HER2-positive for patients who have received previous systemic therapy from results in the DESTINY-LUNG01 trial (35). In locally advanced or metastatic gastric and gastroesophageal junction adenocarcinoma, it is approved in patients who had received a prior trastuzumab-based regimen from results in the DESTINY-Gastric01 trial (36). In the studies comparing subgroups by age, patients age ≥65 years had significant progression-free survival (PFS) benefit in the hormone receptor cohort HR =0.47 (95% CI: 0.29–0.77) while patients age <65 years did not have significant PFS benefit 0.51 (95% CI: 0.39–0.67) in the DESTINY-Breast04 trial while in the DESTINY-Gastric01 trial patients age ≥65 years had a significant overall response rate (ORR) HR =0.44 (95% CI: 0.26–0.76) while patients <65 years had ORR HR of 0.82 (95% CI: 0.44–1.53) (34,36) (*Table 3*). A pooled analysis of DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast 03 showed a similar PFS and ORR between patients age <65 and those 65 years and older (55). Drug-related interstitial lung disease (ILD) was a notable adverse event—in the DESTINY-Breast04 trial, drug-related ILD was seen in 12.1% cases, in the DESTINY-Breast03 trial, drug-related ILD was seen in 15% of cases, in the DESTINY-Gastric01 trial 10% of cases, and in the DESTINY-LUNG01 trial drug-related ILD was seen in 26% of cases including 6.5% cases with grade 3 or higher (33-36) (*Table 4*). Other adverse events seen across the trials include neutropenia, anemia, thrombocytopenia, and diarrhea (33-36). Meanwhile, an age-pooled analysis of T-DXd of patients from DESTINY-Breast01, DESTINY-Breast02, and DESTINY-Breast03 showed an increased drug discontinuation percentage in patients age ≥65 years of 25.4% compared to 18.7% in patients age <65 years and incidence of adjudicated drug-related ILD to be 17.5% in patients age ≥65 years *vs.* 11.8% in patients age <65 years (55). Furthermore, of the 883 breast cancer patients treated with T-DXd 5.4 mg/kg in clinical trials, there was a higher incidence of grade 3–4 adverse events observed in patients aged 65 years or older (60%) compared to younger patients (48%) (56). In the DESTINY-LUNG01 trial and the DESTINY-Gastric01 trials, no differences were seen in safety in patients ≥65 years compared to younger patients (56).

Enfortumab vedotin

Enfortumab vedotin is an ADC targeting nectin-4 with a MMAE payload (57). It has been FDA-approved for locally advanced or metastatic urothelial cancer who previously received a programmed death receptor 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a platinum containing chemotherapy (37) (*Table 2*). The EV-301 trial showed a significant OS benefit in younger patients but not so in patients age ≥75 years old HR =0.91 (95% CI: 0.55–1.51) (37) (*Table 3*). Treatment-related rash was seen in 43.9% of patients including 14.5% with grade 3 or higher rash. Ocular disorders were seen in 18.6% of patients including 15.9% with dry eye, 4.1% with blurred, and 0.7% with corneal disorders (37). Peripheral neuropathy was seen in 46.3% of patients including 5.1% with grade 3 peripheral neuropathy (37) (*Table 4*). In previous earlier phase studies for enfortumab vedotin, there were not differences in safety though between patients ages 65 years or older *vs.* younger patients (58).

Sacituzumab govitecan

Sacituzumab govitecan is an ADC targeting tumor-associated calcium signal transducer 2 (Trop2) with a SN-38 topoisomerase inhibitor payload (59) (*Table 2*). It was first FDA-approved for unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies based on data from the ASCENT trial; later after results from the TROPicS-2 trial, sacituzumab govitecan was approved for unresectable locally advanced or metastatic hormone receptor-positive/HER2-negative breast cancer whose cancer has progressed after CDK4/6 inhibitor, endocrine therapy, or taxane (38,40). It was also approved from results in the TROPHY-U-01 for locally advanced or metastatic urothelial cancer who have previously a platinum-containing chemotherapy and either a PD-1 or PD-L1 inhibitor (39). In the ASCENT trial, patients ages ≥65 years had a significant PFS benefit HR =0.22 (95% CI: 0.12–0.40) with those receiving sacituzumab govitecan having a PFS of 7.1 months (95% CI: 5.8–8.9) compared to 2.4 months (95% CI: 1.4–2.9) in the chemotherapy arm (38). In the TROPicS-02 trial, patients ages ≥65 years had an OS of 14.9 months (95% CI: 12.0–17.5) in the sacituzumab govitecan arm compared

to 10.1 months in the chemotherapy arm with HR of 0.80 (95% CI: 0.54–1.19) while similar results were seen in patients ages <65 years 14.1 months (95% CI: 12.7–16.4) *vs.* 11.5 months (95% CI: 10.3–11.3) HR 0.81 (95% CI: 0.64–1.02) (40). In the TROPHY-U-01 trial, patients ages ≥65 years had an ORR of 23.3% (95% CI: 13.38–36.04%) while those ages 50–64 years had a 33.3% ORR (95% CI: 20–48.5%) (39) (*Table 3*). Across the three trials, the most common grade 3 or higher adverse events were neutropenia, anemia, and leukopenia. In the TROPicS-02 trial, there was one drug-related fatal event from septic shock caused by neutropenic colitis and in the TROPHY-U-01 trial, one case of treatment-related death because of sepsis due to febrile neutropenia (39,40) (*Table 4*). In the ASCENT trial, there was a subgroup analysis performed for patients age ≥65 years showed similar rates of dose reduction between sacituzumab govitecan *vs.* standard of care (35% *vs.* 33%) though a higher percentage than those <65 years (35% *vs.* 19%) with febrile neutropenia 14%, fatigue 10%, and diarrhea 6% being the most common culprits of dose reduction (38,60) (*Table 4*). No significant differences in safety were seen in other trials involving sacituzumab govitecan in elderly compared to younger patients (61).

Loncastuximab tesirine

Loncastuximab tesirine is a CD19-targeted ADC with a pyrrolobenzodiazepine (PBD) dimer payload (17) (*Table 2*). It is FDA-approved for relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, not otherwise specified, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma based on findings from the LOTIS-2 trial (41). Duration of response in the LOTIS-2 trial was similar in the age ≥75 years subgroup 13.37 months (95% CI: 5.98–not reached) compared to the 65–74 years subgroup 10.25 months (95% CI: 3.84–not reached), and the age <65 years subgroup 9.63 months (95% CI: 3.22–not reached) (41) (*Table 3*). The most common grade 3 or higher treatment adverse events were neutropenia (26%), thrombocytopenia (18%), and increased gamma-glutamyl transferase levels (17%) (41). There were eight treatment-emergent adverse events with fatal outcome in 8 (6%) of the 145 patients, but none were thought to be secondary to loncastuximab tesirine (41) (*Table 4*). Of the 145 patients who have received loncastuximab tesirine in clinical trials, 14% were 75 years or older and there have not reported differences in safety or effectiveness (62).

Tisotumab vedotin

Tisotumab vedotin is an ADC targeting tissue factor, a transmembrane protein whose primary role is to initiate the coagulation cascade, with a MMAE payload (63) (*Table 2*). It received FDA approval for recurrent or metastatic cervical cancer with disease progression on or after chemotherapy per findings from the innovaTV 204/GOG 3023/ENGOT-cx6 trial (42). The ORR of the study was 24% (95% CI: 16–33%) with 7 (7%) complete responses though no age-related survival data was reported (42) (*Table 3*). Most common grade 3 or higher toxicities included neutropenia 3%, fatigue 2%, and ulcerative keratitis 2% (42) (*Table 4*). Among the 101 patients in the innovaTV 204/GOG 3023/ENGOT-cx6 trial, 13% were age ≥65 years and grade ≥3 adverse reactions occurred in 69% patients age ≥65 years and 59% patients age <65 years (64). No patients age ≥65 years experienced a tumor response (64).

Moxetumomab pasudotox

Moxetumomab pasudotox is a CD22 targeted ADC with a pasudotox payload that received FDA approval for relapsed or refractory hairy cell leukemia in patients who had received at least two prior systemic therapies including treatment with a purine nucleoside analog per findings from Study 1053 (43) (*Table 2*). No age subgroup data was available; the median age of subjects in this study was 60.0 years with a range of 34–84 years including 31% of the patients being 65 years or older and 8% being 75 years or older (43,65). At median follow-up of 24.6 months, the overall complete response rate was 41% with 34% of all patients being minimal residual disease (MRD) negative (43). There were no treatment-related deaths in the study but 2 cases (3%) of capillary leak syndrome and 4 cases (5%) of hemolytic uremic syndrome. Exploratory analysis showed a higher incidence of adverse reactions leading to drug discontinuation in 23% *vs.* 7% and renal toxicity in 40% *vs.* 20% in older patients (65) (*Table 4*). Recently, this medication is being discontinued from future use in the US as of July 2023 due to low clinical uptake since FDA approval (66).

Mirvetuximab soravtansine

Mirvetuximab soravtansine is a folate-receptor alpha directed ADC with a DM4 payload that is FDA-approved for folate receptor alpha, platinum-resistant epithelial

ovarian, fallopian tube, or primary peritoneal cancer patients who have received 1–3 prior systemic treatment regimens per results from the SORAYA trial (44) (*Table 2*). No age subgroup analysis was available but the median age of patients on the trial was 62 years with a range of 35–85 years with 44% of patients being 65 years or older (44,67). The median duration of response was 6.9 months (95% CI: 5.6–9.7), and ORR was 38.0% (95% CI: 24.7–52.8%) (44) (*Table 3*). Keratopathy (9%) and blurred vision (6%) were the most common adverse grade 3 or higher events (44) (*Table 4*). Adverse reactions occurred in 49% of patients age ≥65 years and 51% patients age <65 years (67).

Belantamab mafodotin

Belantamab mafodotin is an ADC targeting BCMA with a MMAF payload (68) (*Table 2*). It was originally FDA-approved for relapsed or refractory multiple myeloma patients who had received at least four prior therapies include an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent from results from the DREAMM-2 trial (45). In this two-arm study, patients age ≥75 years old had an ORR of 7.7% (95% CI: 0.2–36.0%) in the 2.5 mg/kg cohort which was lower than other age groups but a 35.3% (95% CI: 14.2–61.7%) ORR in the 3.4 mg/kg cohort which was similar to other age groups (45) (*Table 3*). Keratopathy was the most common grade 3 or higher toxicity (27% in the 2.5 mg/kg cohort and 22% in the 3.4 mg/kg cohort); among the patients who received the 2.5 mg/kg dose, keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older (45,69). Two deaths were potentially related to treatment (one case of sepsis in the 2.5 mg/kg cohort and one case of hemophagocytic lymphohistiocytosis in the 3.4 mg/kg cohort) (45) (*Table 4*). Belantamab mafodotin however was withdrawn from use per FDA request on November 22, 2022 following results from the DREAMM-3 study comparing belanatamab mafodotin compared to pomalidomide plus dexamethasone (Pd) in patients with relapse/refractory multiple myeloma in which belanatmab mafodotin did not have superior PFS to Pd (70).

Notable ADCs in development

There are multiple ADCs in development with notable results with a few of the ADCs in further development are in NSCLC (*Table 5*).

Patritumab deruxtecan

Patritumab deruxtecan is an ADC targeting HER3, which is expressed in over 80% of NSCLC, and an analysis on the metastatic epidermal growth factor receptor (*EGFR*) mutant NSCLC patients who had progressed on *EGFR* tyrosine kinase inhibitor (TKI) showed an ORR of 39% (95% CI: 26.0–52.4%) with a median PFS of 8.2 months (95% CI: 4.4–8.3) (71). At the 5.6 mg/kg dosing, the median age was 66.0 years with a range of 40–80 years. The most common grade 3 or higher adverse events were platelet count decrease/thrombocytopenia (30%), neutrophil count decrease/neutropenia (19%), and fatigue (14%). Adjudicated treatment related ILD was seen in 7% of cases (71). More recently, the HERTHENA-Lung01 study, a phase II trial on *EGFR* mutant NSCLC patients who had progressed on both an *EGFR* TKI and a platinum-based chemotherapy showed an ORR of 29.8% (95% CI: 23.9–36.2%) with a median PFS of 5.5 months and a median OS of 11.9 months (72).

Datopotomab deruxtecan (Dato-DXd)

Dato-DXd is an ADC targeting Trop2 with a deruxtecan payload. In the phase 1 trial analyzing the NSCLC cohort, the ORR was 26% (95% CI: 14.6–40.3%) with a median PFS of 6.9 months (95% CI: 2.7–8.8) and a median OS of 11.4 months (95% CI: 7.1–20.6) (73). In the TROPION-Lung02 trial looking at Dato-DXd plus pembrolizumab with or without platinum chemotherapy as first-line therapy in metastatic NSCLC without actionable mutations, there was an ORR of 58% in those who received Dato-DXd and pembrolizumab doublet therapy and ORR of 75% in those who received Dato-DXd, pembrolizumab, and platinum chemotherapy triplet therapy (74). Of note, 17% of patients receiving the doublet therapy in this study had ILD, with 3% having grade 3 and higher and 43% of patients receiving triplet therapy having ILD with 6% having grade 3 and higher (74). In addition, 16% patients in the doublet therapy cohort had ocular surface toxicity and 24% patients in the triplet therapy cohort (74).

Telisotuzumab vedotin (Teliso-V)

Teliso-V targets c-Met with a MMAE payload; in the first in human study 18.8% cases of c-Met NSCLC were found to have response to Teliso-V and on a further study focused on c-Met over-expressing advanced NSCLC, ORR was

Table 5 Key ADCs in active development

Drug	Target	Payload	Study/indication	Efficacy	Grade 3 or higher[†]
Patritumab deruxtecan	HER3	DXd	Phase 1 study on safety/efficacy of patritumab deruxtecan in metastatic *EGFR* mutant NSCLC after disease progression on *EGFR* TKI (NCT03260491) (71)	ORR: 22/57 (39%; 95% CI: 26.0–52.4%) and median PFS 8.2 months (95% CI: 4.4–8.3)	At 5.6 mg/kg dosing (n=57): Any treatment emergent adverse events 42 (74%), platelet count decrease/thrombocytopenia 17 (30%), neutrophil count decrease/neutropenia 11 (19%), fatigue 8 (14%), anemia/hemoglobin decrease 5 (9%), dyspnea 5 (9%), febrile neutropenia 5 (9%), hypoxia 4 (7%), white blood count decrease/leukopenia 4 (7%), hypokalemia 3 (5%), lymphocyte count decrease/lymphopenia 3 (5%); adjudicated ILD 5 (9%), treatment related ILD 4 (7%)
Patritumab deruxtecan	HER3	DXd	Phase II trial of patritumab deruxtecan (HER3-DXd) in *EGFR*-mutated NSCLC after *EGFR* TKI therapy and platinum-based chemotherapy (NCT05338970) (72)	ORR 67/225 (29.8%; 95% CI: 23.9–36.2%), median PFS 5.5 months, median OS 11.9 months	Patritumab deruxtecan (n=225): any treatment emergent adverse events 64.8%, thrombocytopenia 21%, neutropenia 19%, anemia 14%, fatigue 6%, ILD 5.3%
Dato-DXd	Trop2	DXd	First-in-human, phase 1 dose-escalation and dose expansion of Trop2 directed ADC datopotamab deruxtecan in NSCLC: TROPION-PanTumor01 (NCT03401385) (73)	ORR: 13/50 (26%; 95% CI: 14.6–40.3%), median PFS 6.9 months (95% CI: 2.7–8.8), median OS 11.4 months (95% CI: 7.1–20.6) Potential ILD 7/50 (14%) at 6 mg/kg dose with 4/50 (8%) being grade 3+	At 6 mg/kg dose (n=50): any treatment emergent adverse events 27 (54%), drug-related treatment emergent adverse events 13 (26%), potential ILD 4 (8%), interstitial adjudicated as drug-related 1 (2%), nausea 2 (4%), anemia 2 (4%)
Dato-DXd	Trop2	DXd	TROPION-Lung02: Dato-DXd plus pembrolizumab with or without platinum chemotherapy in advanced NSCLC (NCT04526691) (74)	ORR: 58% (37/64) in first-line doublet therapy and 75% (54/72) in first-line triplet therapy Median duration of response not reached in either arm	Doublet therapy (n=64)/triplet therapy (n=72): 34 (53%) grade 3+ treatment emergent adverse event with 20 (31%) being study treatment related in doublet therapy—8% stomatitis, 6% increased amylase, 5% decreased appetite, 3% fatigue, 2% anemia, 2% nausea, 2% diarrhea. 55 (76%) grade 3+ treatment emergent adverse event with 42 (58%) being study treatment related in doublet therapy—14% decreased neutrophil count, 13% neutropenia, 13% anemia, 8% fatigue, 8% increased amylase, 7% platelet count decreased, 6% stomatitis. 11 (17%) ILD all grades with 2 (3%) as grade 3+ in doublet therapy and 31 (43%) ILD all grades with 4 (6%) as grade 3+ in triplet therapy. 10 (16%) ocular surface toxicity all grades with 1 (2%) as grade 3+ in doublet therapy and 17 (24%) ocular surface toxicity all grades with 2 (3%) as grade 3+ in triplet therapy
Teliso-V	c-Met	MMAE	First-in human phase I study evaluating safety of Teliso-V (NCT02099058) (75)	ORR: 3/48 (6.3%) in all patients, 3/16 (18.8%) patients with c-Met NSCLC	Total patients n=48: 23 (48%) reported grade 3+ treatment related adverse events including anemia 5 (10.4%), pneumonia 5 (10.4%), hyponatremia 4 (8.3%)
Teliso-V	c-Met	MMAE	Monotherapy in patients with previously treated c-Met-overexpressing advanced NSCLC (NCT03539536) (76)	ORR was 19/52 (36.5%) in the NSQ *EGFR* WT cohort (12/23 (52.2%) in c-Met high group and 7/29 (24.1%) in c-Met intermediate group) and 5/43 (11.6%) in *EGFR* mutant cohort	Most common any-grade AEs were peripheral sensory neuropathy (25.0%), nausea (22.1%), and hypoalbuminemia (20.6%). Grade 5 AEs considered possibly related to Teliso-V occurred in two patients (sudden death and pneumonitis in 1 pt each in the SQ cohort)
ARX788	HER2	AS269	Phase 1 dose expansion study of ARX788 as monotherapy in HER2-positive advanced gastric and gastroesophageal junction adenocarcinoma (77)	ORR: 37.9% (95% CI: 20.7–57.7%) and DCR: 55.2% (95% CI: 35.7–73.6%) Median PFS 4.1 months (95% CI: 1.4–6.4) and OS 10.7 months (95% CI: 4.8–not reached)	4 (13.3%) experienced drug-related AEs grade 3 or higher including one case with pneumonitis and one case with blurred vision ILD seen in 5 (16.7%) of cases

[†], data are presented as n (%) unless otherwise noted. ADC, antibody-drug conjugate; HER3, human epidermal growth factor 3; DXd, deruxtecan; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; ORR, overall response rate; CI, confidence interval; PFS, progression-free survival; ILD, interstitial lung disease; OS, overall survival; Dato-DXd, datopotomab deruxtecan; Trop2, tumor-associated calcium signal transducer 2; Teliso-V, telisotuzumab vedotin; MMAE, monomethyl auristatin E; NSQ, non-squamous; WT, wild-type; AE, adverse event; HER2, human epidermal growth factor 2; DCR, disease control rate.

36.5% (75,76). The most common adverse event in the study was peripheral sensory neuropathy (25%); two deaths in the study were considered possibly related to Teliso-V including pneumonitis in one patient (76).

Another notable ADC that has been studied in gastric and breast cancer is ARX788. ARX788 is an ADC targeting HER2 with a AS269 payload (78). In the Phase 1 dose expansion study of ARX788 monotherapy in HER2-positive gastric and gastroesophageal cancer, there was an ORR of 37.9% (95% CI: 20.7–57.7%) with a median PFS of 4.1 months (95% CI: 1.4–6.4) and an OS of 10.7 months (95% CI: 4.8–not reached) (77). ILD was seen in 16.7% of cases (77).

ADCs in combination with other agents

Another consideration moving forward is the combination of ADC with other agents (*Table 6*). One notable example is enfortumab vedotin in combination with pembrolizumab in front-line cisplatin-ineligible patients with locally advanced/metastatic urothelial cancer (79). There was an ORR of 73.3% (95% CI: 58.1–85.4%) with 15.6% complete response (79). The most common grade 3 or higher adverse event was increased lipase seen in 17.8% of patients and fatigue and macropapular rash seen in 11.1% of patients each (79). Sacituzumab govitecan and pembrolizumab combination have been recently studied in NSCLC and urothelial cancer with the most common grade 3 or higher toxicities being diarrhea and anemia similar in toxicity profile to sacituzumab govitecan monotherapy (81). Finally, Teliso-V and *EGFR* TKI combination are being studied with initial analysis showing ORR of 58% in Teliso-V and osimertinib and median PFS of 5.9 months (95% CI: 2.8–not reached) and ORR of 32.1% in *EGFR* mutated patients in Teliso-V and erlotinib (82,83). Notable grade 3 or higher toxicities seen in these trials were peripheral sensory neuropathy and in the Teliso-V and erlotinib study there was 14% grade 3 or higher pulmonary embolism toxicity (82,83).

Discussion on efficacy and toxicity of ADCs in elderly

In age subgroup analysis, we showed differing efficacy HRs in brentuximab vedotin [OS: age ≥60 years, HR =0.83 (95% CI: 0.47–1.47) *vs.* age <60 years, HR =0.51 (95% CI: 0.29–0.89) in the ECHELON-1 trial], TDM-1 [OS: age ≥75 years, HR =2.79 (95% CI: 0.99–7.88) *vs.* age 65–74 years, HR =0.89 (95% CI: 0.56–1.43) *vs.* age <65 years, HR =0.73 (95% CI: 0.47–0.87) in the EMILIA trial], inotuzumab ozogamicin [OS: age ≥55 years, HR =0.89 (95% CI: 0.57–1.37) *vs.* age <55 years, HR =0.67 (95% CI: 0.47–0.95) in the INO-VATE trial], enfortumab vedotin [OS: age ≥75 years, HR =0.91 (95% CI: 0.55–1.51) *vs.* age <75 years, HR =0.69 (95% CI: 0.53–0.89) in the EV-301 trial], polatuzumab vedotin [PFS: age ≥60 years, HR =0.7 (95% CI: 0.5–0.9) *vs.* age <60 years, HR =0.9 (95% CI: 0.6–1.5) in the POLARIX trial], and T-DXd [PFS: age ≥65 years, HR =0.7 (95% CI: 0.5–0.9) *vs.* age <65 years, HR =0.9 (95% CI: 0.6–1.5) in the DESTINY-Breast04; and ORR: age ≥65 years, HR =0.44 (95% CI: 0.26–0.76) *vs.* age <65 years, HR =0.82 (95% CI: 0.44–1.53) in the DESTINY-Gastric01 trial] in older patients compared to younger (24,29-31,34,36,37) (*Table 3*). On review of toxicity data across trials by age groups, we saw higher rates of febrile neutropenia in older subjects in the ECHELON-2 trial for brentuximab vedotin and in the ASCENT trial for sacitizumab vedotin, higher rates of severe adverse events in the innovaTV 204/GOG 3023/ENGOT-cx6 trial for tistoumab vedotin and POLARIX trial for polatuzumab vedotin (51,54,60,64). We also saw higher incidences of drug discontinuation in moxetumomab pasudotox in older patients and age-pooled analysis of T-DXd trials (55,65). Meanwhile, the most common grade 3 or higher toxicities were predominantly related to hematotoxicity—anemia and neutropenia which can be debilitating to patients from a fatigue standpoint and put them at increased risk for severe infections which did lead to deaths in sacitizumab govitecan, gemtuzumab ozogamicin, and TDM-1 trials (7,22,29,38,39,46,60). Specifically in hematologic malignancies, veno-occlusive disease is a serious and potentially fatal complication. Meanwhile, in solid tumors, ILD is seen in some of the trials particularly ones in NSCLC such as the DESTINY-Lung 01 trial (26%), TROPION-PanTumor01 (14%, including 8% with grade 3 or higher), and the phase 1 patritumab deruxtecan trial (7%) (35,71,73). In addition, ocular toxicities are another notable adverse event; keratopathy was seen in over 20% of patients in the belantamab mafodotin DREAMM-2 study, 16 and 9% of patients in the mirvetuximab soravtansine while 16% of patients in the Dato-DXd TROPION-Lung02 had ocular surface toxicities (44,45,74).

Thus, the combination of worse outcomes in primary efficacy in some of the ADCs, increased toxicity in older patients in multiple trials, and the implications of some of the most common side effects such as anemia, ILD, and

Table 6 Notable combinations with ADCs

Drug	ADC target	Payload	Study/indication	Efficacy	Notable adverse events[†]
EV + P	Nectin-4	MMAE	Phase Ib/II first-line cisplatin-ineligible patients with locally advanced/metastatic urothelial cancer (NCT04223856) (79)	ORR 33/45 (73.3%; 95% CI: 58.1–85.4%) with 7/45 (15.6%) with a complete response and 26/45 (57.8%) received a partial response	EV + P (n=45): 29 (64.4%) had grade 3+ treatment related adverse event including increased lipase (17.8%), fatigue 5 (11.1%), macropapular rash 5 (11.1%), increased amylase 4 (8.9%), hyperglycemia 4 (8.9%), neutropenia 4 (8.9%)
SG + P	Trop2	SN-38	Phase II previously untreated or metastatic NSCLC (NCT05186974) (80)	PD-L1 TPS ≥50% (n=29): ORR 69%; PD-L1 TPS <50% (n=32): ORR 44%	Most common any-grade treatment emergent adverse events diarrhea 54%, anemia 48%, asthenia 38%. One treatment related death observed due to sepsis
SG + P	Trop2	SN-38	Phase II cohort 3 study on patients with metastatic urothelial cancer who have progressed after platinum-based regimens (NCT03547973) (81)	ORR 14/41 (34%; 95% CI: 20.1–50.6%) with 6-month PFS rate of 47%	SG + P (n=41): treatment related adverse events grade 3 or higher occurred in 59% of patients including diarrhea (24%), anemia (20%), febrile neutropenia (10%), fatigue (7%), and asthenia (5%)
Teliso-V + Osi	c-Met	MMAE	Phase 1/1b study of Teliso-V + Osi after failure of prior Osi in patients with advanced, c-Met overexpressing, *EGFR*-mutated NSCLC (NCT0209058) (82)	ORR 11/19 (58%) [including 8/12 (67%) at 1.9 mg/kg dose]	Teliso-V + Osi (n=25): most common all grade toxicity were peripheral sensory neuropathy (36%), nausea and peripheral edema (20%). Most common grade 3 or higher toxicities are anemia (12%), and peripheral motor neuropathy (8%)
Teliso-V + E	c-Met	MMAE	Phase 1b study of Teliso-V in combination with erlotinib in patients with c-Met protein-expressing NSCLC (83)	ORR (n=28) 32.1% in *EGFR* mutated patients and 52.6% in *EGFR* mutated patients with high c-Met expression (n=15)	Teliso-V + E (n=42): treatment related adverse events grade 3 or higher occurred in 64% of patients, including pulmonary embolism 14%, hypokalemia 10%, hypophosphatemia 7%, peripheral sensory neuropathy 7%, diarrhea 7%

[†], data are presented as n (%) unless otherwise noted. ADC, antibody-drug conjugate; EV + P, enfortumab vedotin + pembrolizumab; MMAE, monomethyl auristatin E; ORR, overall response rate; CI, confidence interval; SG + P, sacituzumab govitecan+ pembrolizumab; Trop2, tumor-associated calcium signal transducer 2; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TPS, tumor proportion score; PFS, progression-free survival; Teliso-V + Osi, telisotuzumab vedotin + osimertinib; *EGFR*, epidermal growth factor receptor; Teliso-V + E, telisotuzumab vedotin + erlotinib.

ocular toxicities merits closer investigation particularly as ADCs become more potent with higher DAR such as trastsuzumab deruxtecan (19).

The strength of this study was that the investigators for most of these studies did include some sort of survival subgroup analysis and that the FDA package inserts for each approved ADC had a specific section for "geriatric use" which provided important information that would be easily accessible to the healthcare professional. However, the limitation of the study, likely due to either sample size or length of follow up, was that these publications lacked uniform information on age group survival analysis, as studies used OS, PFS, or ORR, and the age cutoffs were not uniform. More importantly, there was not disclosure of adverse events stratified by age unless there was a study specific to the elderly population such as the EORTC-GIMEMA AML-19 trial (46). Thus, disclosure of adverse events stratified by age in ADC studies would be a good start to better inform providers and their patients along with more detailed efficacy and safety data in the "geriatric use" section of the FDA package insert to better inform the provider. This will become even more paramount as new studies incorporate combination regimens which may include other chemotherapies and immune checkpoint inhibitors.

Conclusions

Despite the goal of avoiding traditional chemotherapy effects, ADCs are associated with considerable systemic toxicity related to the chemotherapy payload carried by each. Like traditional chemotherapy these are particularly problematic for elderly patients who also experience less benefit in terms of efficacy relative to younger patients. This reduction in the therapeutic index occurs across all ADCs regardless of payload or linker, though the toxicity profile varies according to these features. Studies on older patients in T-DXd and moxetumomab pasudotox showed increased rates of drug discontinuation while there were higher percentages of adverse events in elderly in trials involving brentuximab vedotin, polatuzumab vedotin, sacituzumab govitecan, and tistoumab vedotin. Overall adverse events of ADCs demonstrate grade 3 or higher toxicities to be most commonly hematotoxicity with notable toxicities of veno-occlusive disease in hematologic malignancies, peripheral neuropathies, ocular toxicities, and ILD. These findings merit further consideration of patient age and comorbidities when counseling patients on the risks and benefits when using these agents.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-188/rc

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Supplementary

Table S1 The search strategy summary for clinicaltrials.gov

Items	Specification
Date of search	August 31, 2023
Databases and other sources searched	Clinicaltrials.gov
Search terms used	"Antibody-drug conjugate (under the treatment/intervention)", "phase 1–4 (under study phase)", "with results (under study results)"
Timeframe	Up to August 31, 2023
Inclusion and exclusion criteria	Inclusion criteria: ADCs that were either FDA-approved or still being actively studied by the sponsor
	Exclusion criteria: ADCs that had been discontinued for further development by the sponsor
Selection process	Conducted by first author, consensus by both authors

FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate.

Table S2 The search strategy summary for additional studies in drugs in development

Items	Specification
Date of search	August 31, 2023
Databases and other sources searched	Google.com
Search terms used	[("FDA approved antibody drug conjugates")] OR[" gemtuzumab ozogamicin"] OR [" brentuximab vedotin"] OR ["ado-trastuzumab emtansine"] OR ["inotuzumab ozogamicin"] OR ["polatuzumab vedotin"] OR [" trastuzumab deruxtecan"] OR ["enfortumab veedotin"] OR ["sacituzumab govitecan"]OR[" loncastuximab tesirine"] OR [" tisotumab vedotin"] OR ["moxetumomab pasudotox"] OR ["mirvetuximab soravtansine"] OR[" belantamab mafodotin"] OR [" patritumab deruxtecan"] OR ["datopotomab deruxtecan"] OR[" telisotuzumab vedotin"] OR ["ARX788"] OR ["antibody drug conjugate older patients"]
Timeframe	Up to August 31, 2023
Inclusion and exclusion criteria	Inclusion criteria: ADCs that were either FDA-approved or still being actively studied by the sponsor. Abstracts regarding the ADC from previous oncology conferences (i.e., American Society of Clinical Oncology Annual Meeting)
	Exclusion criteria: ADCs that had been discontinued for further development by the sponsor. Findings already found in previous search
Selection process	Conducted by first author, consensus by both authors

FDA, United States Food and Drug Administration; ADC, antibody-drug conjugate.

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