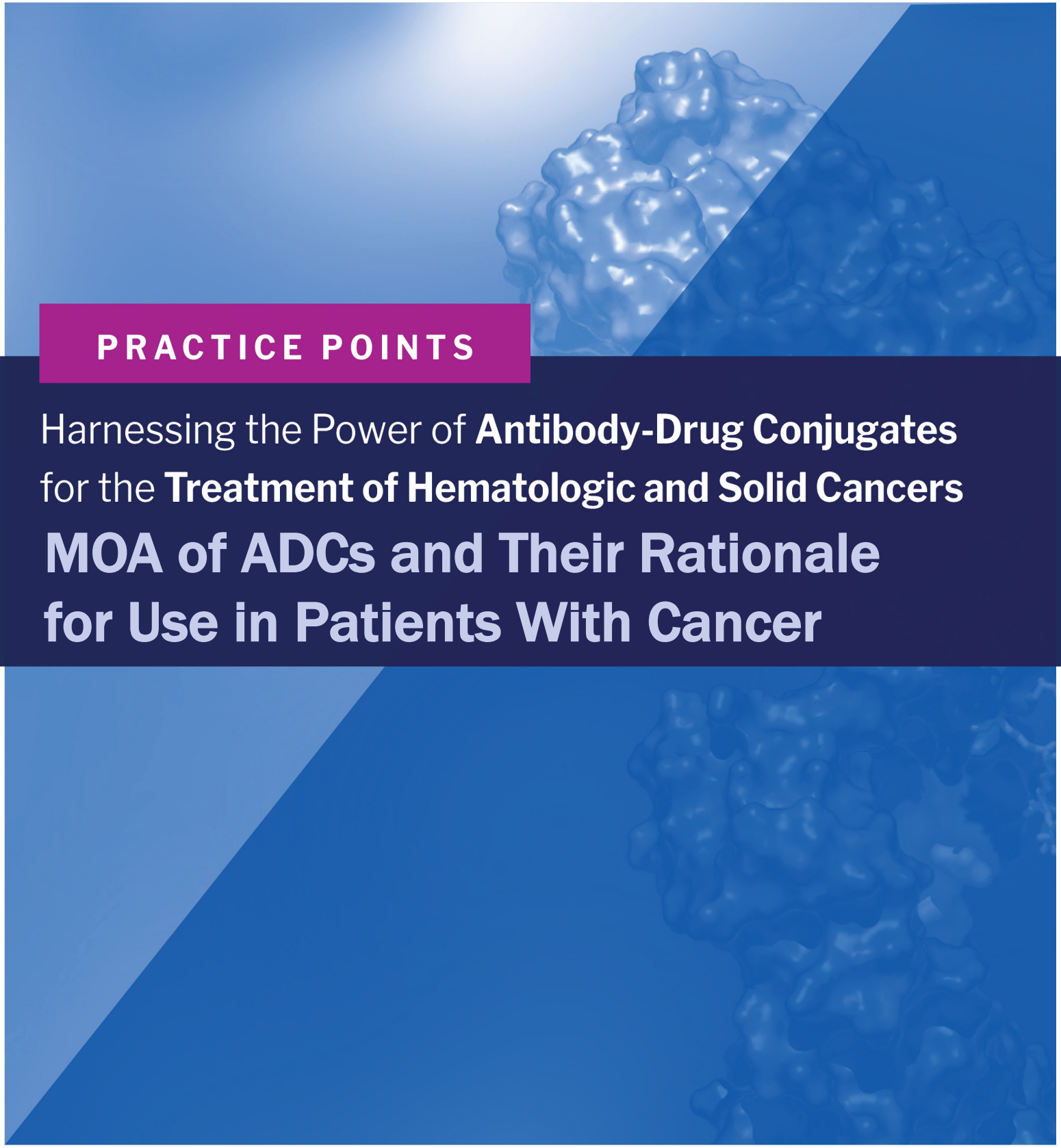

PRACTICE POINTS

Harnessing the Power of **Antibody-Drug Conjugates** for the **Treatment of Hematologic and Solid Cancers**

MOA of ADCs and Their Rationale for Use in Patients With Cancer

This activity is jointly provided by University of Nebraska Medical Center and Bio Ascend™

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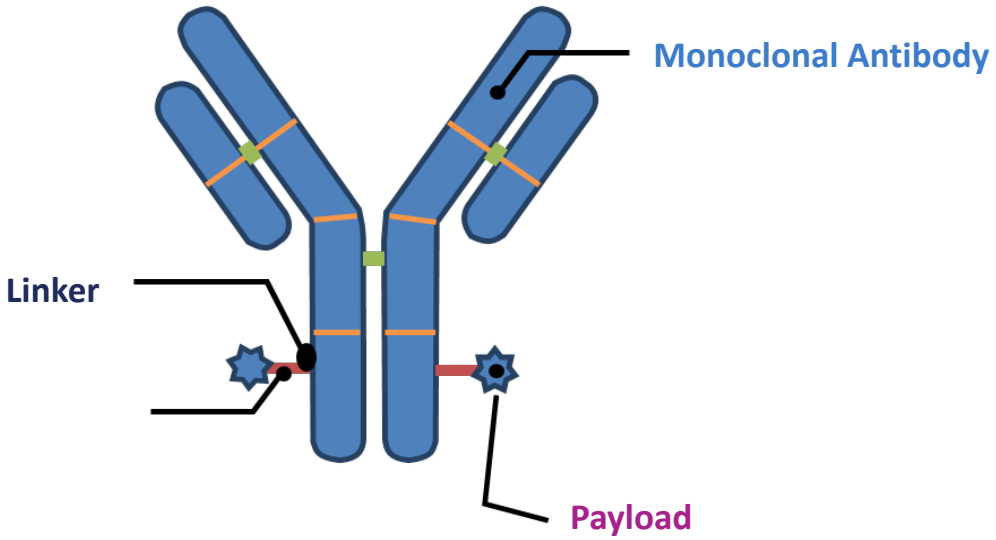
Design and Structure of ADCs



Linker

- Determines solubility, stability in systemic circulation, and overall antitumor activity
- Considered optimal when off-target interaction is minimized
- Generally categorized into cleavable and non-cleavable designs

Monoclonal Antibody

- Serve a dual purpose as they act as transporters and as targeting agents
- High specificity and affinity for the target antigen
- Favorable pharmacokinetic properties
- Minimal immunogenicity

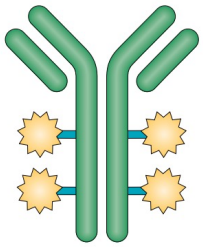
Payload

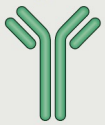
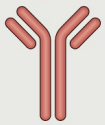
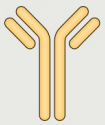
- Ultimate effector component
- Potent subnanomolar concentrations
- Generally categorized into:
  - DNA-damaging agents
  - Microtubule-disrupting agents

ADC, antibody-drug conjugate; IgG, immunoglobulin G.
Drago JZ, et al. *Nat Rev Clin Oncol*. 2021;18:327-344.

PRACTICE POINTS

ADCs: Modular Design



	IgG1	IgG2	IgG3	IgG4
Antibodies				
Serum half-life	21 days	21 days	7–21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

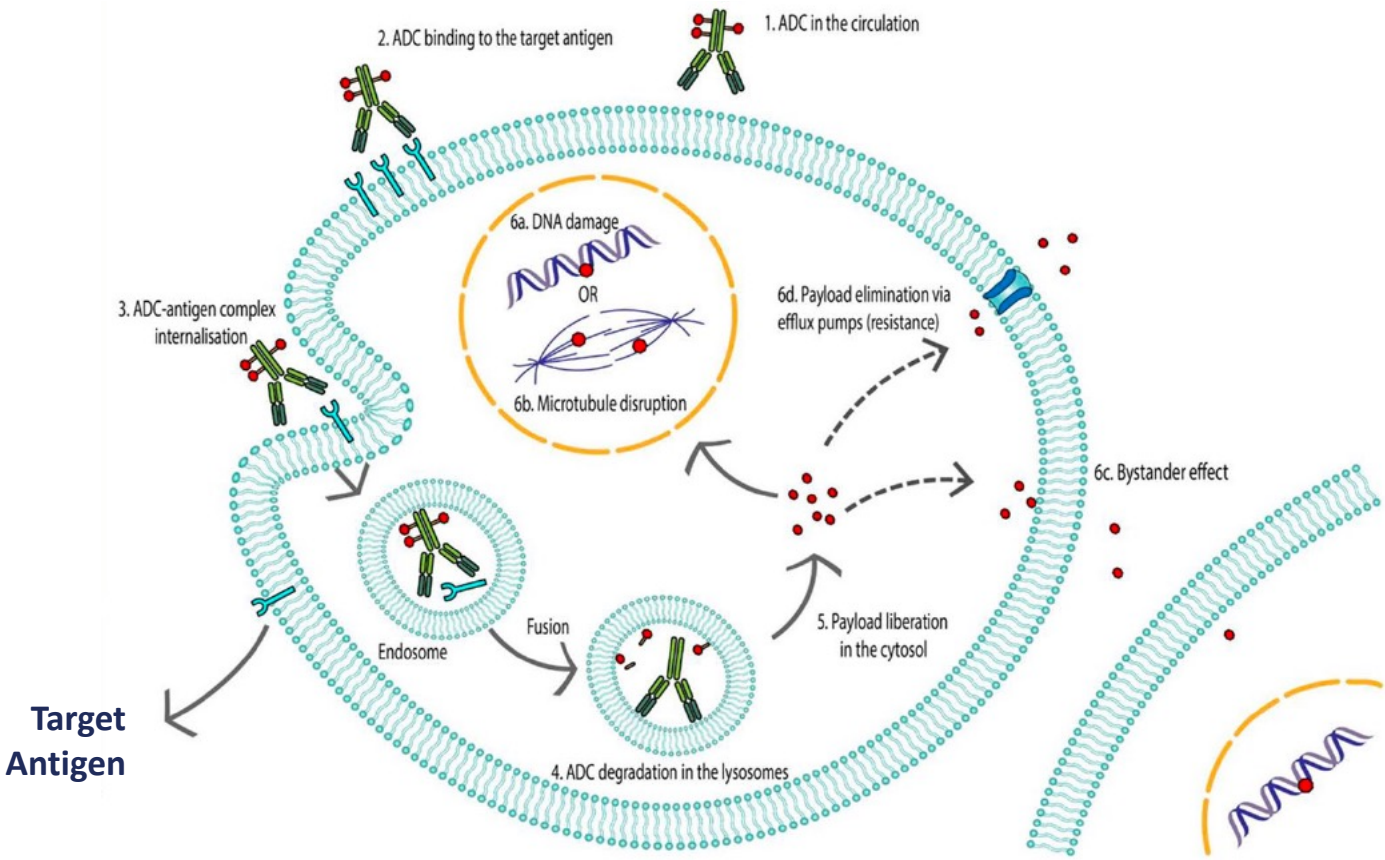
	Cleavable			Non-cleavable
Linkers	Hydrazone	Disulfide	Dipeptide	MC* MCC*
	Acid cleavable	Reducible	Protease cleavable	

Payloads				
	Auristatins	Maytansinoids	Calicheamicins	Camptothecins
	Anti-microtubule	Anti-microtubule	DNA cleavage	Topoisomerase 1 inhibition

The selection of all 3 components for ADCs is important and has significant impact on efficacy, pharmacokinetic/pharmacodynamic profiles, and therapeutic index

ADC, antibody-drug conjugate; IgG, immunoglobulin G.
Drago JZ, et al. *Nat Rev Clin Oncol*. 2021;18:327-344.

ADC Mechanism of Action



Target Antigen

- Key to site-selective delivery
- Tumor-specific and homogeneous expression profile
- High levels of expression
- Rapid internalization
- Minimal shedding

- ADCs are designed for internalization and are processed via the endocytic pathway resulting in the release of the payload and cytotoxic effect

ADC, antibody-drug conjugate.
Theocharapoulos C, et al. *Ther Adv Med Oncol.* 2020;12:1758835920962997.

Target Expression in Hematologic Malignancies

Target	HL	B-NHL	T-NHL	MM	CLL	Myeloid Leukemia
CD3			■			
CD19		■			■	
CD22		■			■	
CD30	■	■	■			
CD33						■
CD56				■		
CD74				■		
CD138				■		
CD79b		■		■		
CD98				■		■
BCMA				■		

BCMA, B-cell maturation antigen; B-NHL , B-cell non-Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; T-NHL, T-cell non-Hodgkin lymphoma.
Leslie LA, et al. *Am Soc Clin Oncol Educ Book*. 2013;33:e108-e113; Dean AQ, et al. *Mabs*. 2021;13:1951427.

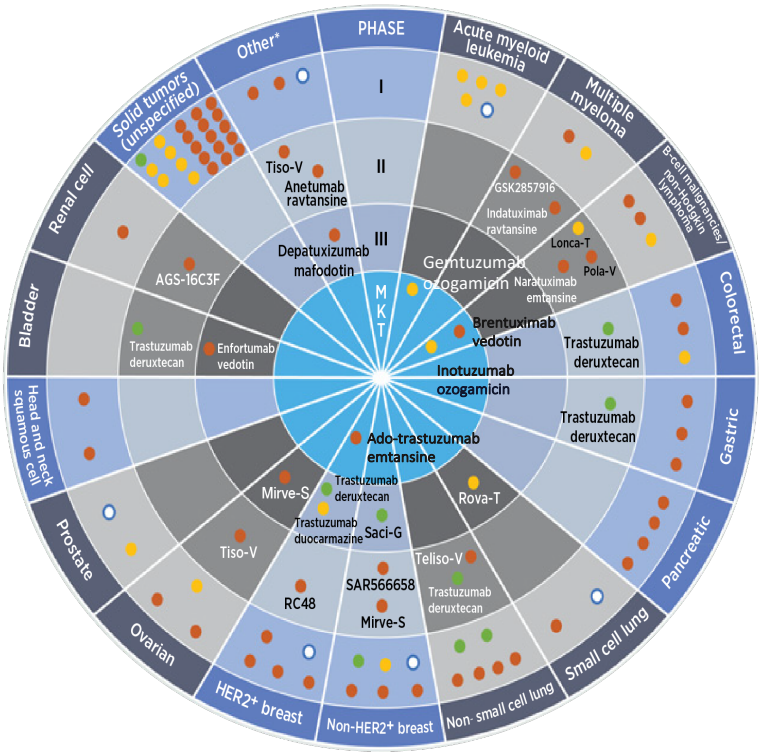
Target Expression in Solid Tumors

Target	Breast Cancer	Bladder Cancer	Ovarian Cancer	CRC	Pancreatic Cancer	Esophageal/ GEJ Cancer	Lung Cancer
HER2	■	■	■	■	■	■	
HER3	■			■			■
TROP2	■		■	■	■		■
LIV-1	■					■	■
Nectin 4	■	■			■		■
GPNMB	■						
CEACAM5				■			■
Folate receptor-α	■		■				
Mesothelin			■		■		

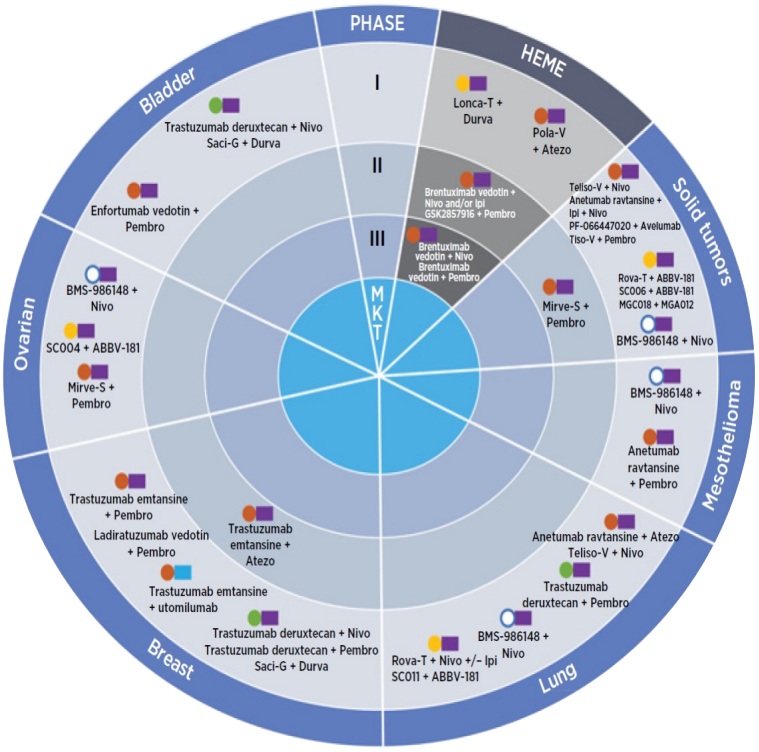
CRC, colorectal cancer; GEJ, gastroesophageal junction; HER, human epidermal growth factor receptor; TROP2, trophoblast cell surface antigen 2.
Criscitiello C, et al. *J Hemat Oncol*. 2021;14:20; Nikolaos D, et al. *Br J Cancer*. 2016;1-6.

ADCs in Clinical Development

ADCs in Clinical Development



ADCs in Combination With Checkpoint Inhibitors



DNA damaging

Topoisomerase inhibitor

Costimulation agonist

Microtubule inhibitor

Checkpoint inhibitor

Mechanism unknown

*Includes neuroendocrine, esophageal, glioblastoma multiforme, cervical, mesothelioma, and melanoma.
ADC, antibody-drug conjugate; Atezo, atezolizumab; Durva, durvalumab; HER, human epidermal growth factor; Ipi, ipilimumab; Lonca-T, loncastuximab tesirine; MKT, market; Mirve-S, mirvetuximab soravtansine; Nivo, nivolumab; Pembro, pembrolizumab; Pola-V, polatuzumab vedotin; Rova-T, rovalpituzumab tesirine; Saci-G, sacituzumab govitecan; Teliso-V, telisotuzumab vedotin; Tiso-V, tisotumab vedotin.
Coats S, et al. *Clin Cancer Res*. 2019;25:5441-5448.

PRACTICE POINTS

FDA-Approved ADCs in Hematologic Malignancies

Drug/Study		Target Antigen	FDA-Approved Indication	Clinical Efficacy	Safety
Loncastuximab tesirine-lpyl LOTIS-2 trial		CD19	R/R DLBCL	48.3% ORR; 24.1% CR	Edema and effusion, myelosuppression, infections, cutaneous reactions
Polatuzumab vedotin-piiq GO29365		CD79	R/R DLBCL	Pola+BR: 40% CR	Cytopenias, anemias, PN, IRR, myelosuppression
Belantamab mafodotin DREAMM-2		CD69 (BCMA)	R/R MM	31% ORR	Ocular effects, anemia, neutropenia
Gemtuzumab ozogamicin	ALFA-0701	CD33	Newly diagnosed CD33+ AML	GO + chemo mEFS: 17.3 mo GO vs BSC: mOS 4.9 mo vs 3.6 mo	IRR, cytopenias, liver toxicity, VOD
	AML-19		R/R CD33+ AML	GO vs BSC: mOS 4.9 mo vs 3.6 mo	
Inotuzumab ozogamicin INO-VATE ALL		CD22	R/R B-cell ALL	2-yr OS: 22%	IRR, cytopenias, VOD
Moxetumomab pasudotox-tdfk Study 1053		CD22	R/R HCL	ORR 75%; CR 41%,	Capillary leak syndrome, hemolytic uremic syndrome
Brentuximab vedotin	ECHELON-2	CD30	cHL, sALCL or CD30+ PTCL	BV+CHP vs CHP mPFS: 48.2 mo vs 20.8 mo	Neutropenia, GI symptoms fatigue, PN
	ALCANZA		R/R pALCL or CD30+ MF	BV vs chemo ORR4: 56.3% vs 12.5%	

ADC, antibody-drug conjugate; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen; BSC, best supportive care; BV, brentuximab vedotin; cHL, classical Hodgkin lymphoma; CHP, cyclophosphamide-doxorubicin-prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FDA, US Food and Drug Administration; GI, gastrointestinal; GO, gemtuzumab ozogamicin; HCL, hairy cell leukemia; IRR, infusion-related reaction; mEFS, median event-free survival; MF, myelofibrosis; MM, multiple myeloma; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; ORR4, objective response rate ≥4 months; OS, overall survival; pALCL, peripheral anaplastic large cell lymphoma; Pola+BR, polatuzumab vedotin + bendamustine/rituximab; PN, peripheral neuropathy; PTCL, peripheral T-cell lymphoma; sALCL, systemic anaplastic large cell lymphoma; VOD, veno-occlusive disease.

Food and Drug Administration. Oncology (cancer)/hematologic malignancies approval notifications. Accessed March 14, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

PRACTICE POINTS

FDA-Approved ADCs in Solid Tumors

Drug/Study		Target Antigen	FDA-Approved Indication	Clinical Efficacy	Safety
Ado-trastuzumab emtansine (T-DM1)	KATHERINE	HER2	HER2-positive early BCa	HR 0.5 (95% CI: 0.39-0.64)	Fatigue, nausea, increased transaminases, musculoskeletal pain
	EMILIA		HER2-positive metastatic BCa	Median PFS: 9.6 mo	
Fam-trastuzumab deruxtecan	DESTINY-Gastric01	HER2	Advanced or metastatic gastric or GEJ adenocarcinoma	OS: 12.5 months; 40.5% ORR	Anemia, cytopenia, nausea, decreased appetite
	DESTINY-Breast01		Metastatic HER2-positive BCa	60.3% ORR 4.3% CR	Nausea, fatigue, vomiting, alopecia, constipation, decreased appetite
Sacituzumab govitecan	IMMU-132-01	TROP2	Metastatic TNBC (≥3L)	33.3% ORR; median DOR: 7.7 mo	Nausea, neutropenia, diarrhea, fatigue
	ASCENT		Metastatic TNBC (unresectable locally advanced ≥3L)	Median PFS: 4.8 mo; median OS: 11.8 mo	
	TROPHY		Metastatic UC	27.7% ORR; 5.4% CR	
Enfortumab vedotin Trial EV-301		Nectin 4	Metastatic UC	51% ORR; 22% CR; median DOR 13.8 mo	Rash, aspartate aminotransferase increased, glucose increased, creatinine increase, fatigue

3L, third line; ADC, antibody-drug conjugate; BCa, breast cancer; CR, complete response; DOR, duration of response; FDA, US Food and Drug Administration; GEJ; gastroesophageal junction; HER, human epidermal growth factor receptor; HR; hazard ration;
ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen 2; UC, urothelial cancer.

Food and Drug Administration. Oncology (cancer)/hematologic malignancies approval notifications. Accessed March 14, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

PRACTICE POINTS

Safety of ADCs in Cancer

ADCs exhibit both on-target and off-target toxicities

Most toxicities seem to be related to the nature of the payload

Off-target toxicities can be attributable to payload release in the circulation, in nontumor tissues, or in the tumor microenvironment

Moderate to high levels of neutropenia, alopecia, and gastrointestinal side effects have been observed in clinical trials of many novel ADCs

ADC, antibody-drug conjugate.