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MANEJO DE LA TOXICIDAD DE LOS NUEVOS TRATAMIENTOS EN

TUMORES UROLÓGICOS

Valencia, 23 de abril de 2024

Organizado por: GUARD CONSORTIUM

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¿Por qué producen toxicidad los nuevos ADCs?

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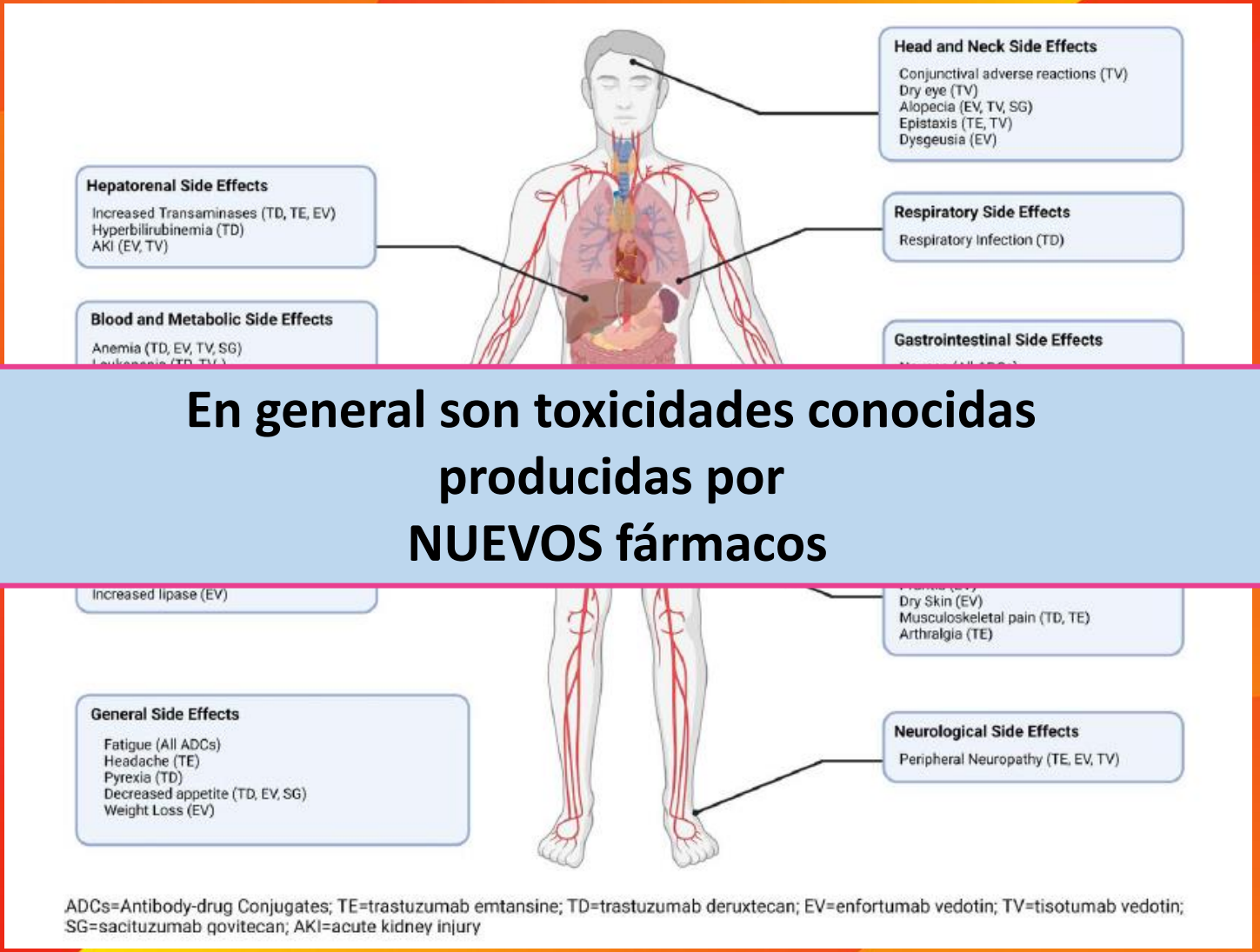
Hospital Universitario 12 de Octubre, Madrid

Organizado por: GUARD CONSORTIUM

Common adverse effects of FDA-approved ADCs



En general son toxicidades conocidas producidas por NUEVOS fármacos

ADCs=Antibody-drug Conjugates; TE=trastuzumab emtansine; TD=trastuzumab deruxtecan; EV=enfortumab vedotin; TV=tisotumab vedotin; SG=sacituzumab govitecan; AKI=acute kidney injury

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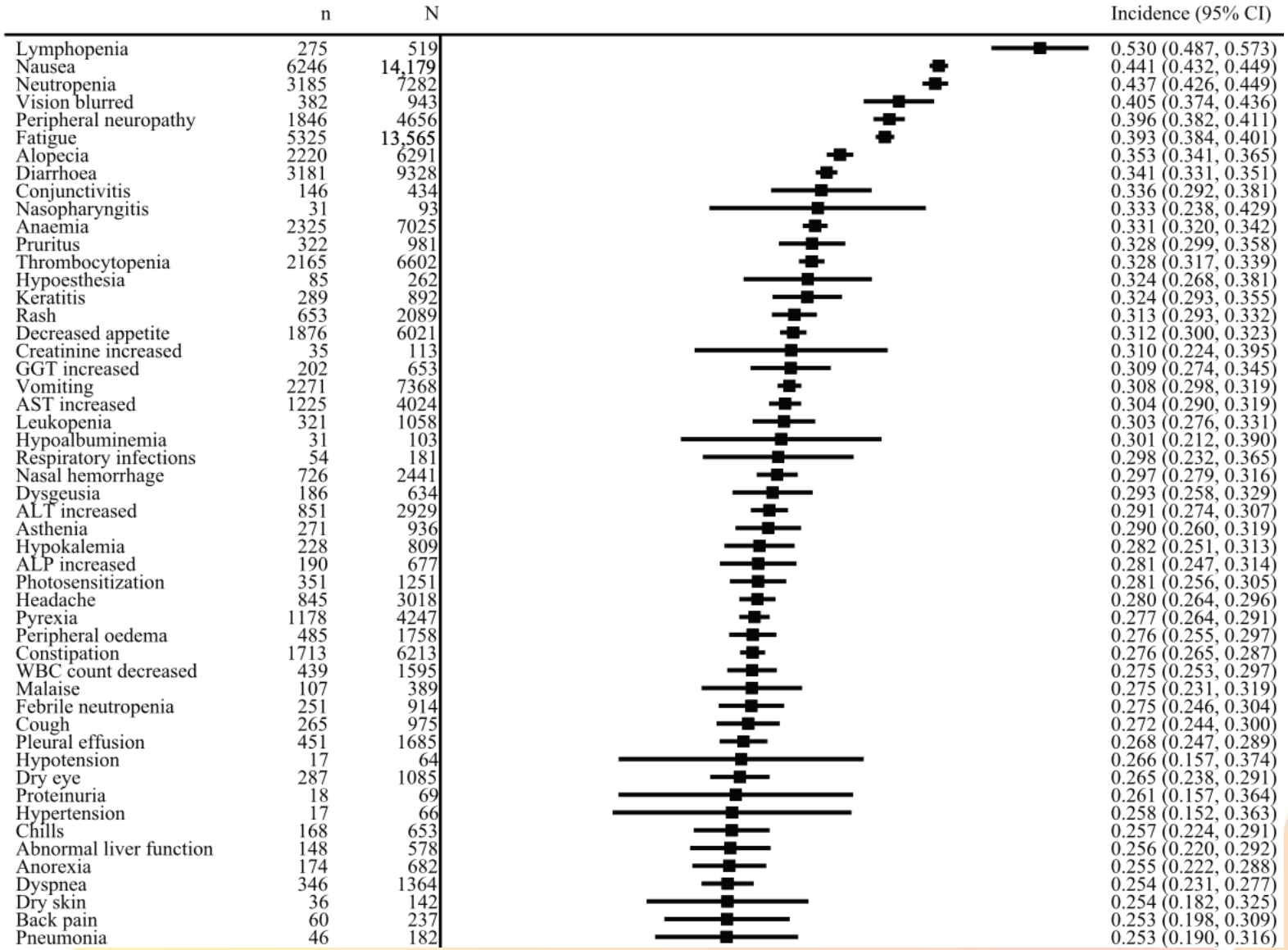
Mohamed A. Gouda et al Cancer J 2022;28: 496–507)

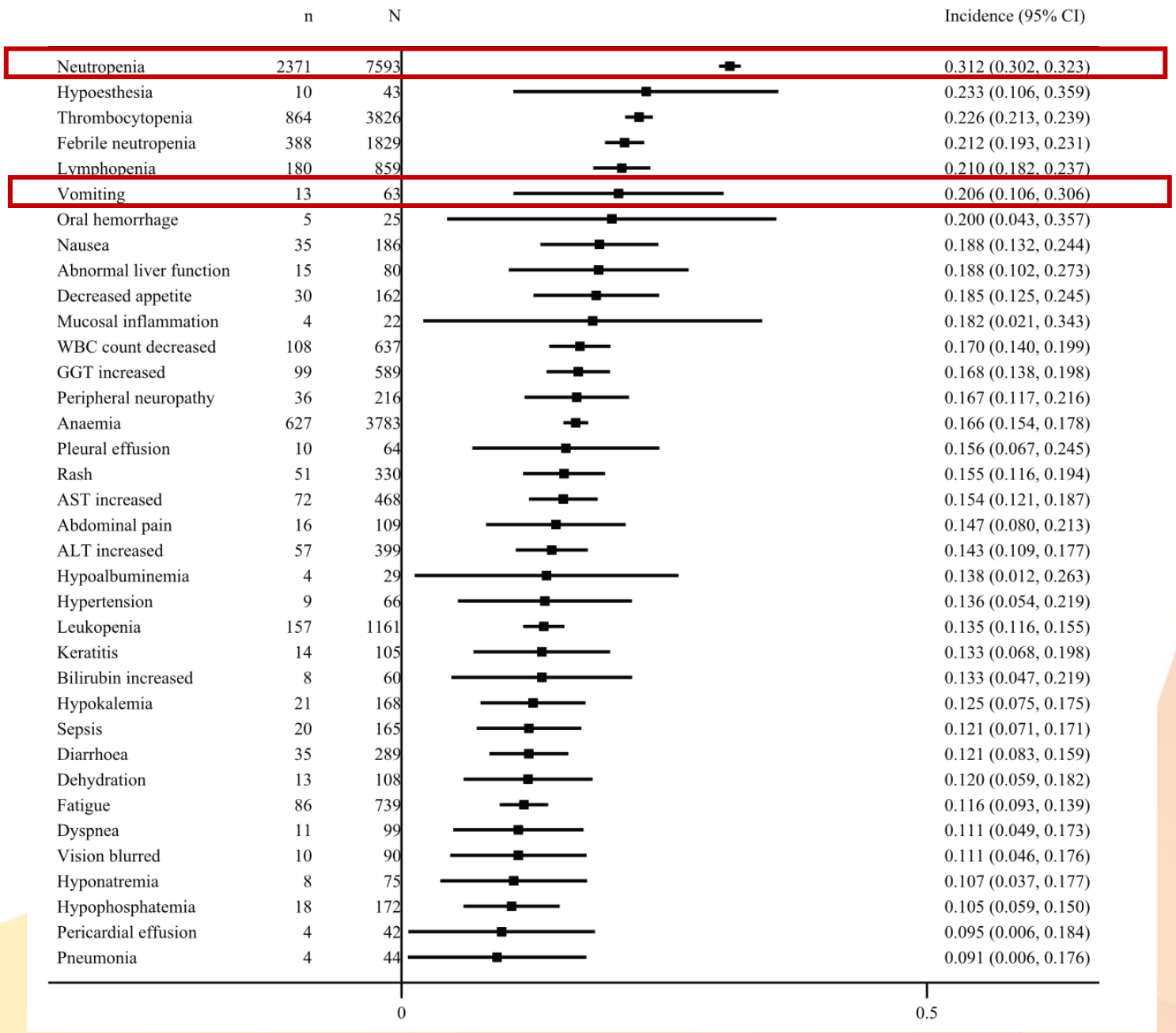


	n	N	Incidence (95% CI)
Lymphopenia	275	519	0.530 (0.487, 0.573)
Nausea	6246	14,179	0.441 (0.432, 0.449)
Neutropenia	3185	7282	0.437 (0.426, 0.449)
Vision blurred	382	943	0.405 (0.374, 0.436)
Peripheral neuropathy	1846	4656	0.396 (0.382, 0.411)
Fatigue	5325	13,565	0.393 (0.384, 0.401)
Alopecia	2220	6291	0.353 (0.341, 0.365)
Diarrhoea	3181	9328	0.341 (0.331, 0.351)
Conjunctivitis	146	434	0.336 (0.292, 0.381)
Nasopharyngitis	31	93	0.333 (0.238, 0.429)
Anaemia	2325	7025	0.331 (0.320, 0.342)
Pruritus	322	981	0.328 (0.299, 0.358)
Thrombocytopenia	2165	6602	0.328 (0.317, 0.339)
Hypoesthesia	85	262	0.324 (0.268, 0.381)
Keratitis	289	892	0.324 (0.293, 0.355)
Rash	653	2089	0.313 (0.293, 0.332)
Decreased appetite	1876	6021	0.312 (0.300, 0.323)
Creatinine increased	35	113	0.310 (0.224, 0.395)
GGT increased	202	653	0.309 (0.274, 0.345)
Vomiting	2271	7368	0.308 (0.298, 0.319)
AST increased	1225	4024	0.304 (0.290, 0.319)
Leukopenia	321	1058	0.303 (0.276, 0.331)
Hypoalbuminemia	31	103	0.301 (0.212, 0.390)
Respiratory infections	54	181	0.298 (0.232, 0.365)
Nasal hemorrhage	726	2441	0.297 (0.279, 0.316)
Dysgeusia	186	634	0.293 (0.258, 0.329)
ALT increased	851	2929	0.291 (0.274, 0.307)
Asthenia	271	936	0.290 (0.260, 0.319)
Hypokalemia	228	809	0.282 (0.251, 0.313)
ALP increased	190	677	0.281 (0.247, 0.314)
Photosensitization	351	1251	0.281 (0.256, 0.305)
Headache	845	3018	0.280 (0.264, 0.296)
Pyrexia	1178	4247	0.277 (0.264, 0.291)
Peripheral oedema	485	1758	0.276 (0.255, 0.297)
Constipation	1713	6213	0.276 (0.265, 0.287)
WBC count decreased	439	1595	0.275 (0.253, 0.297)
Malaise	107	389	0.275 (0.231, 0.319)
Febrile neutropenia	251	914	0.275 (0.246, 0.304)
Cough	265	975	0.272 (0.244, 0.300)
Pleural effusion	451	1685	0.268 (0.247, 0.289)
Hypotension	17	64	0.266 (0.157, 0.374)
Dry eye	287	1085	0.265 (0.238, 0.291)
Proteinuria	18	69	0.261 (0.157, 0.364)
Hypertension	17	66	0.258 (0.152, 0.363)
Chills	168	653	0.257 (0.224, 0.291)
Abnormal liver function	148	578	0.256 (0.220, 0.292)
Anorexia	174	682	0.255 (0.222, 0.288)
Dyspnea	346	1364	0.254 (0.231, 0.277)
Dry skin	36	142	0.254 (0.182, 0.325)
Back pain	60	237	0.253 (0.198, 0.309)
Pneumonia	46	182	0.253 (0.190, 0.316)

Incidencia de AEs (todos los grados) en >25% de pacientes

Zhu et al. Cancer. 2023;129:283–295

Incidencia de AEs grado ≥3



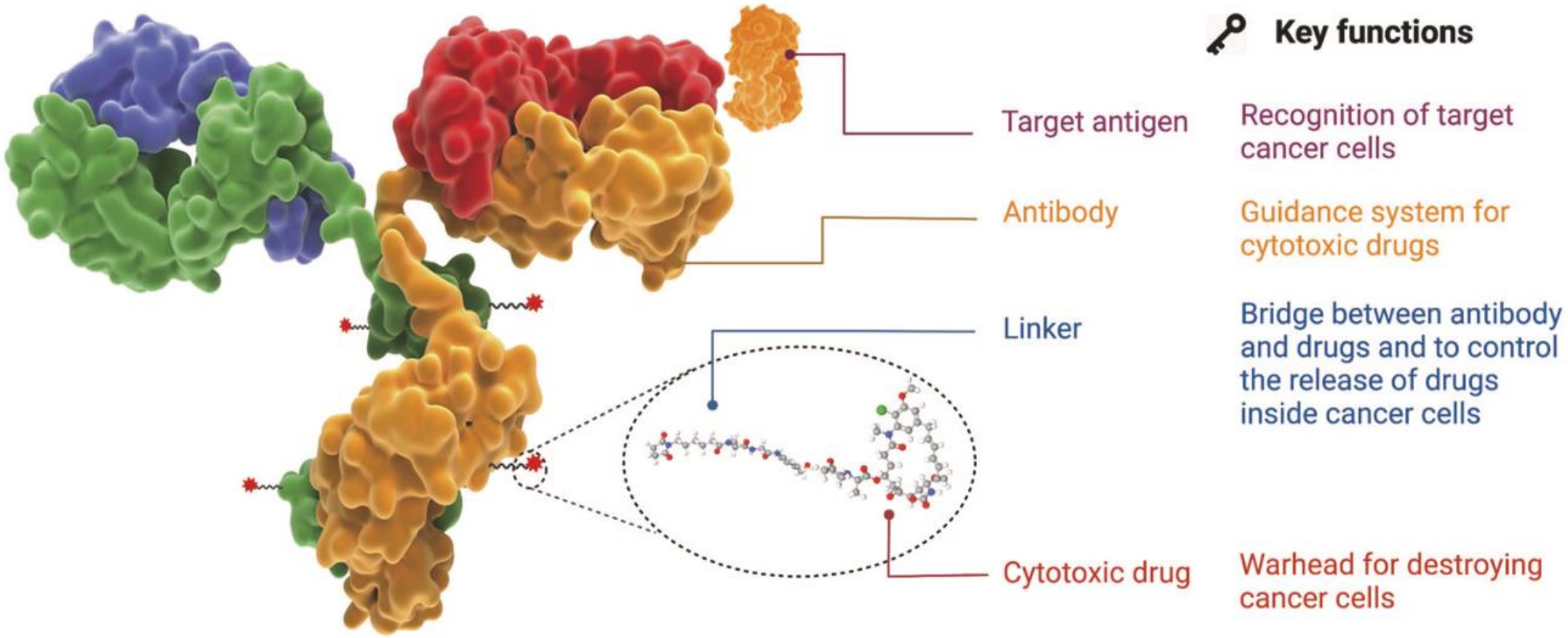
Zhu et al. Cancer. 2023;129:283–295

Some negative DATA

The delta-like protein 3 (DLL3)-targeted ADC rovalpituzumab Tesirin - SCLC less tolerable and to provide inferior overall survival compared to topotecan

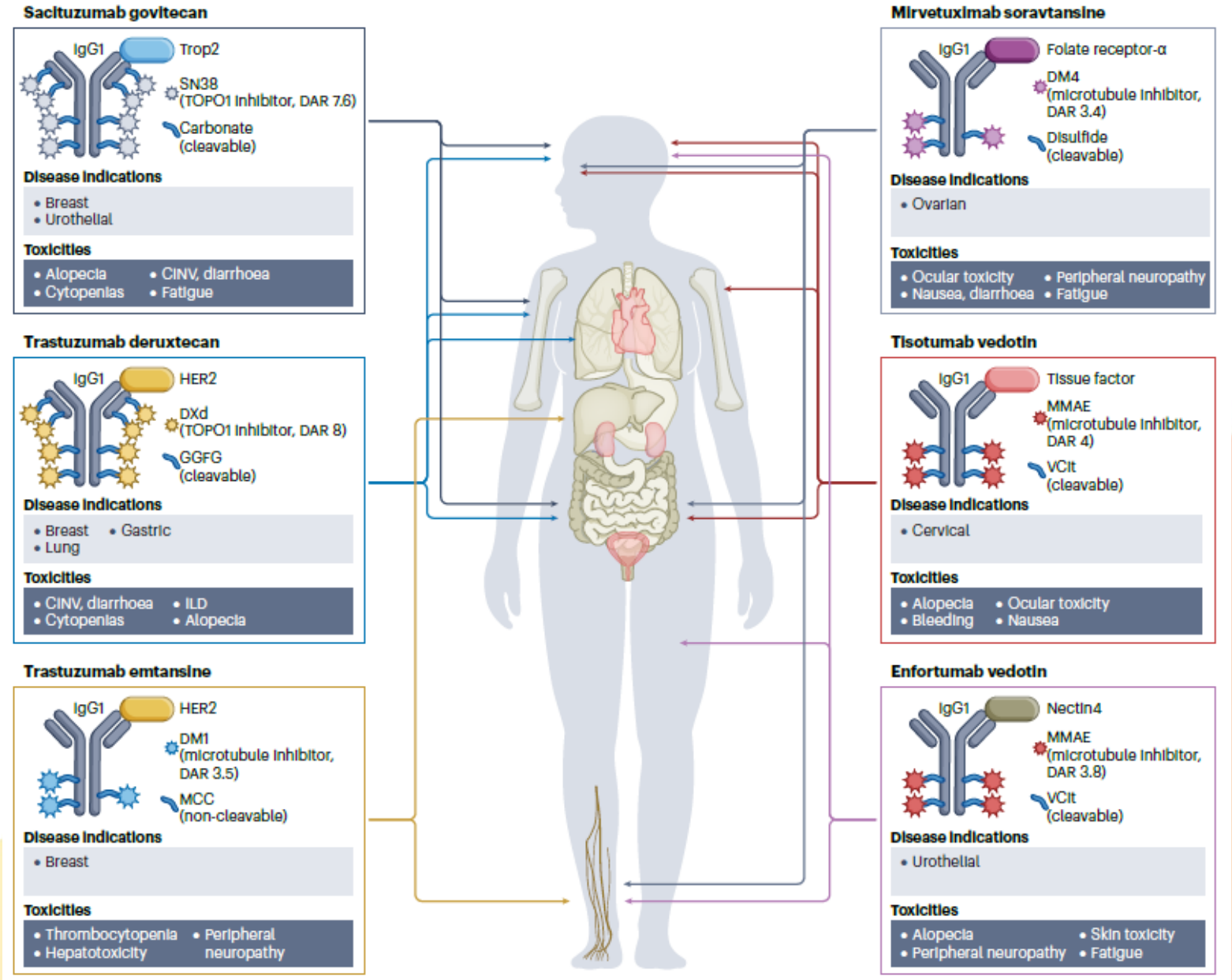
The EGFR-targeted construct depatuxizumab mafodotin was discontinued after the emergence of relevant toxicities plus no improvement in overall survival in glioblastoma

Estructura ADC



Z Fu. Signal Transduction and Targeted Therapy (2022)

Structure and main toxicities of ADCs currently approved for patients with solid tumours

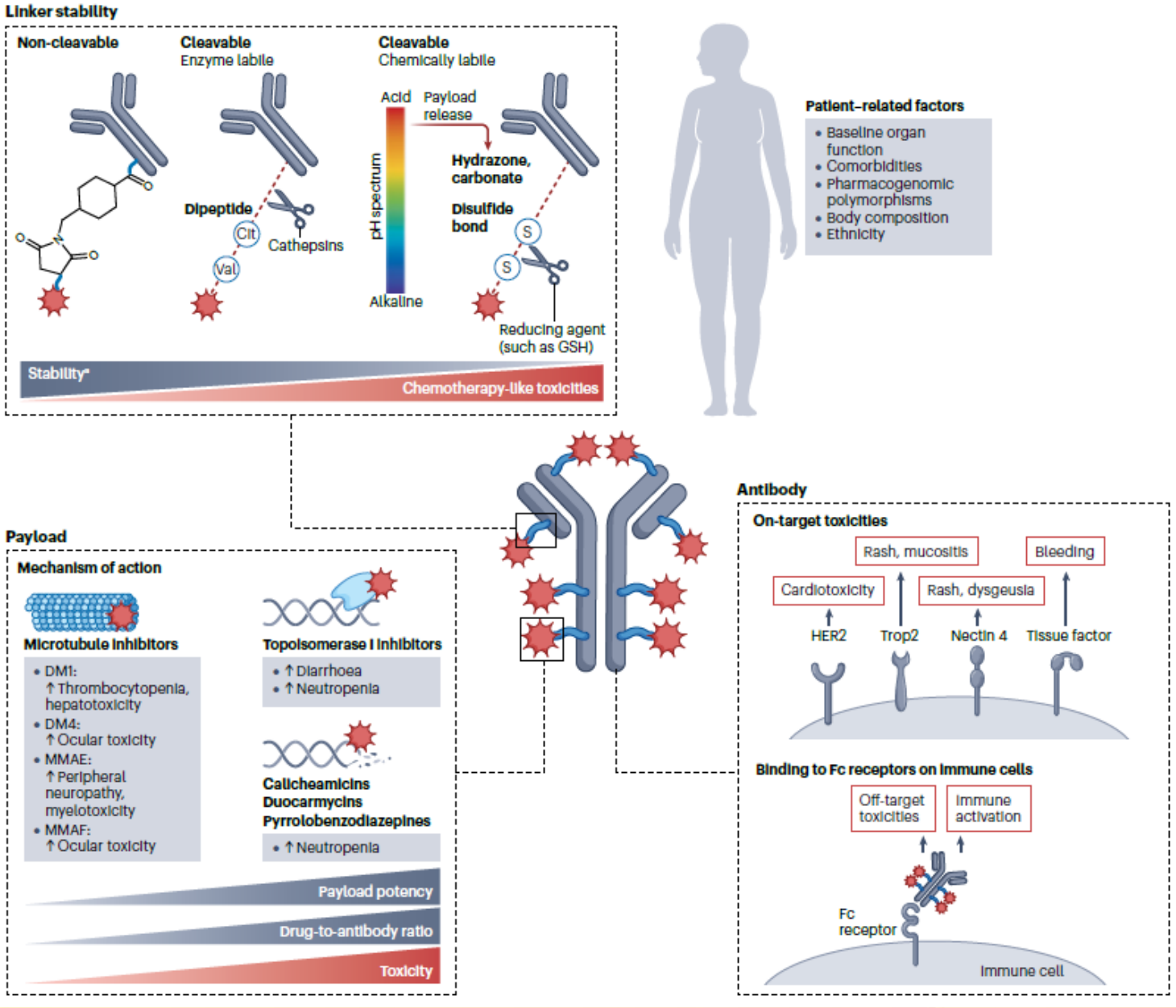


Optimizing the safety of antibody–drug conjugates for patients with solid tumours; Tarantino et al Nature Review Clin Onc 2023 https://doi.org/10.1038/s41571-023-00783-w

CICLO

- Después de la inyección
  - ADC intacto (>90% de la composición)
  - el fármaco no conjugado (fármaco-linker)
  - el anticuerpo disociado.
- Desde la circulación, los ADCs se difunden progresivamente en los espacios intersticiales de los tejidos corporales, llegando finalmente a las células tumorales objetivo, con una **fracción estimada de aproximadamente el 0.1% para los tumores sólidos.**

Determinants of the toxicities of ADCs



Optimizing the safety of antibody–drug conjugates for patients with solid tumours; Tarantino et al Nature Review Clin Onc 2023 https://doi.org/10.1038/s41571-023-00783-w

CLASIFICACIÓN DE LA TOXICIDAD SEGÚN EL MECANISMO

Target-independent toxicity

Off-target delivery of ADC payload

Off-target receptor-mediated uptake of ADC

On-target toxicity

Off-site, on-target

Nguyen T.D, et al. *Cancers* **2023**

TARGET-INDEPENDENT TOXICITY: OFF-TARGE, OFF-SITE

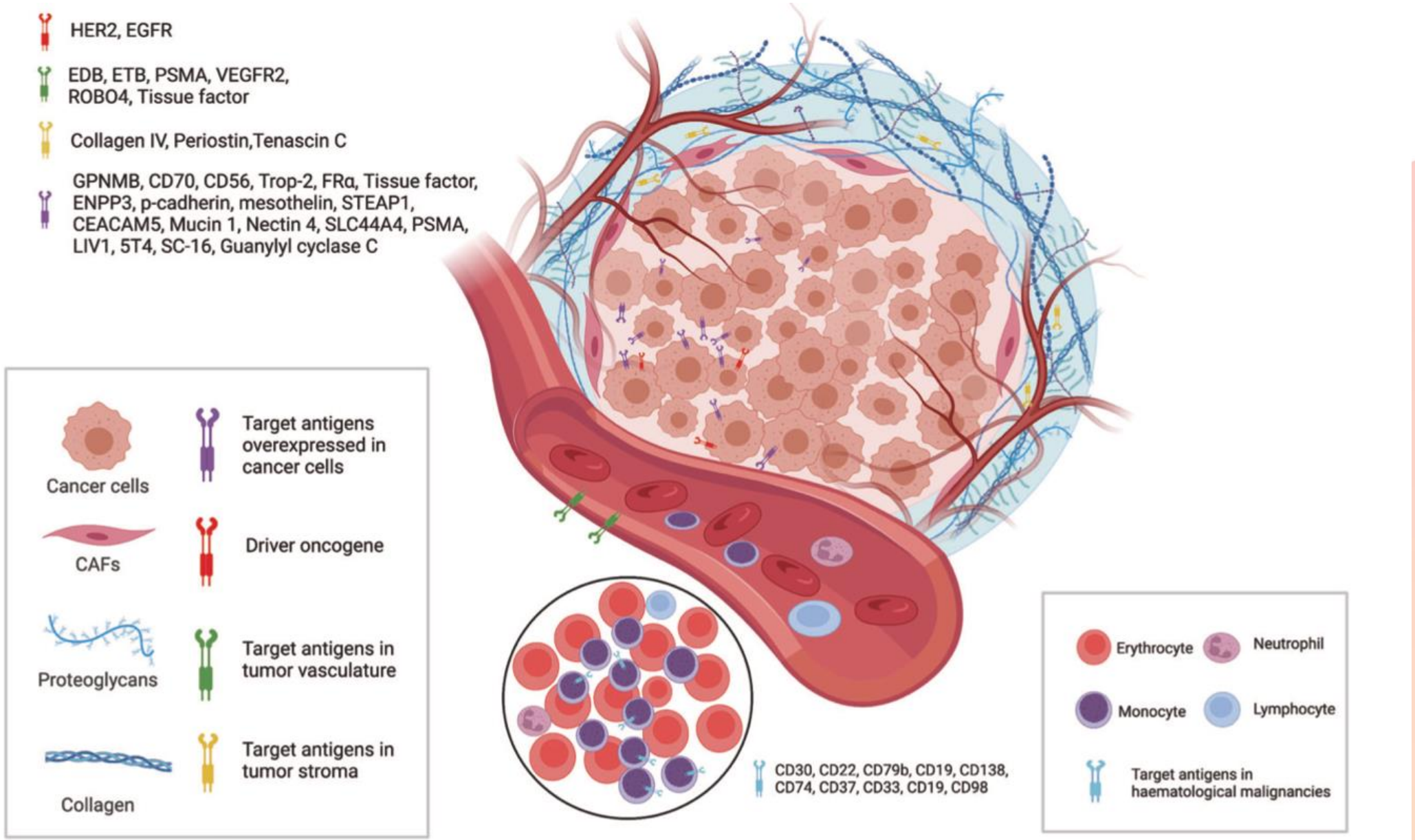
1. Dose-limiting toxicities **(DLTs) are rarely driven by target expression** in healthy tissues.

2. ADCs with the **same class of linker/payload typically share highly similar toxicity profiles**, DLTs, and maximum tolerated doses (MTDs), regardless of the antigen targeted and regardless of the extent of the antigen's expression in healthy tissues

All eight MMAE ADCs with similar DLTs (severe bone marrow toxicity, sepsis, and severe motor neuropathy).

3. **Grade 3/4 toxicities** associated ADCs were consistent with their **payload class**

Saber, H. *Regul. Toxicol. Pharmacol.* **2015**



Z Fu. Signal Transduction and Targeted Therapy (2022)

OFF-TARGET DELIVERY OF ADC PAYLOAD

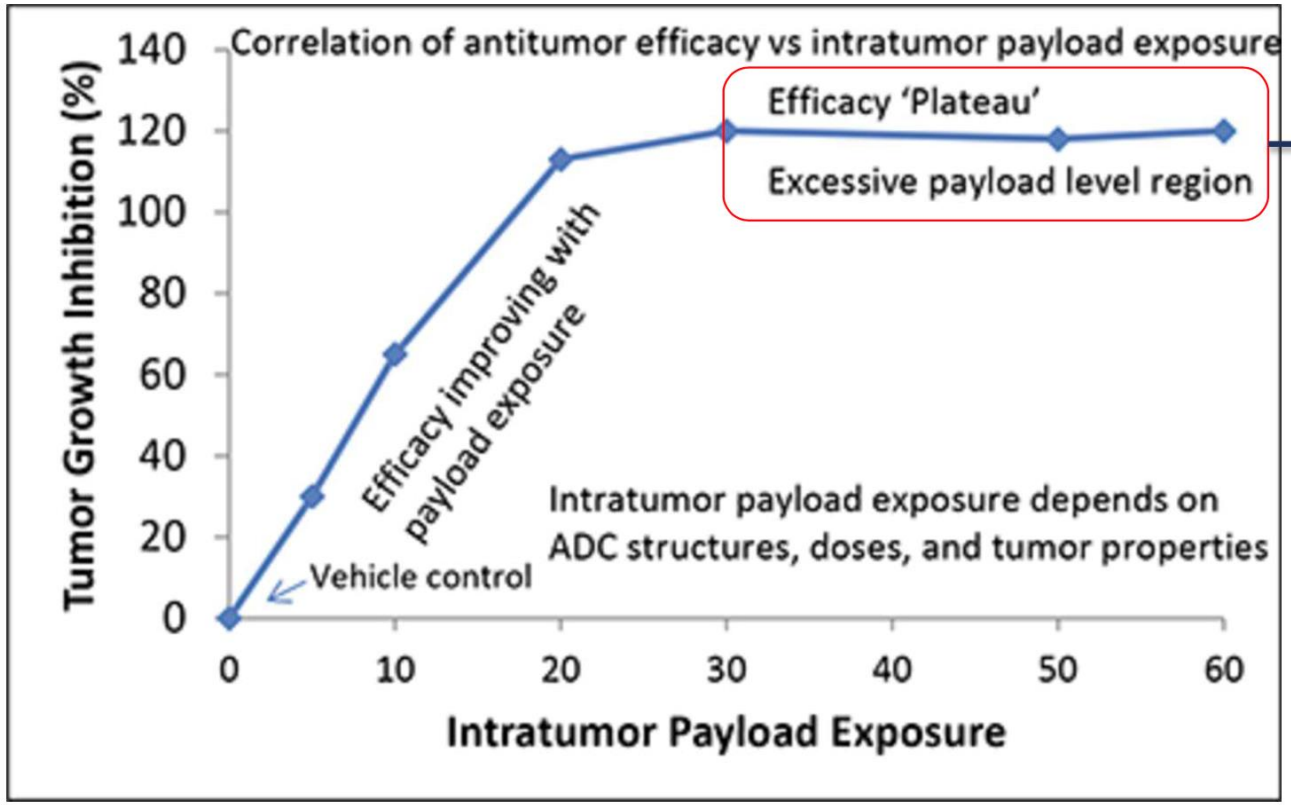
Plasma exposure to **free payload** relates, in part, to **premature deconjugation** of the payload in the systemic circulation (e.g., due to **inadequate linker stability**)

Zhang et al. Drug Metab Dispos 2019;47:1146-1155

OFF-TARGET DELIVERY OF ADC PAYLOAD

LINKERS → CLEAVABLE

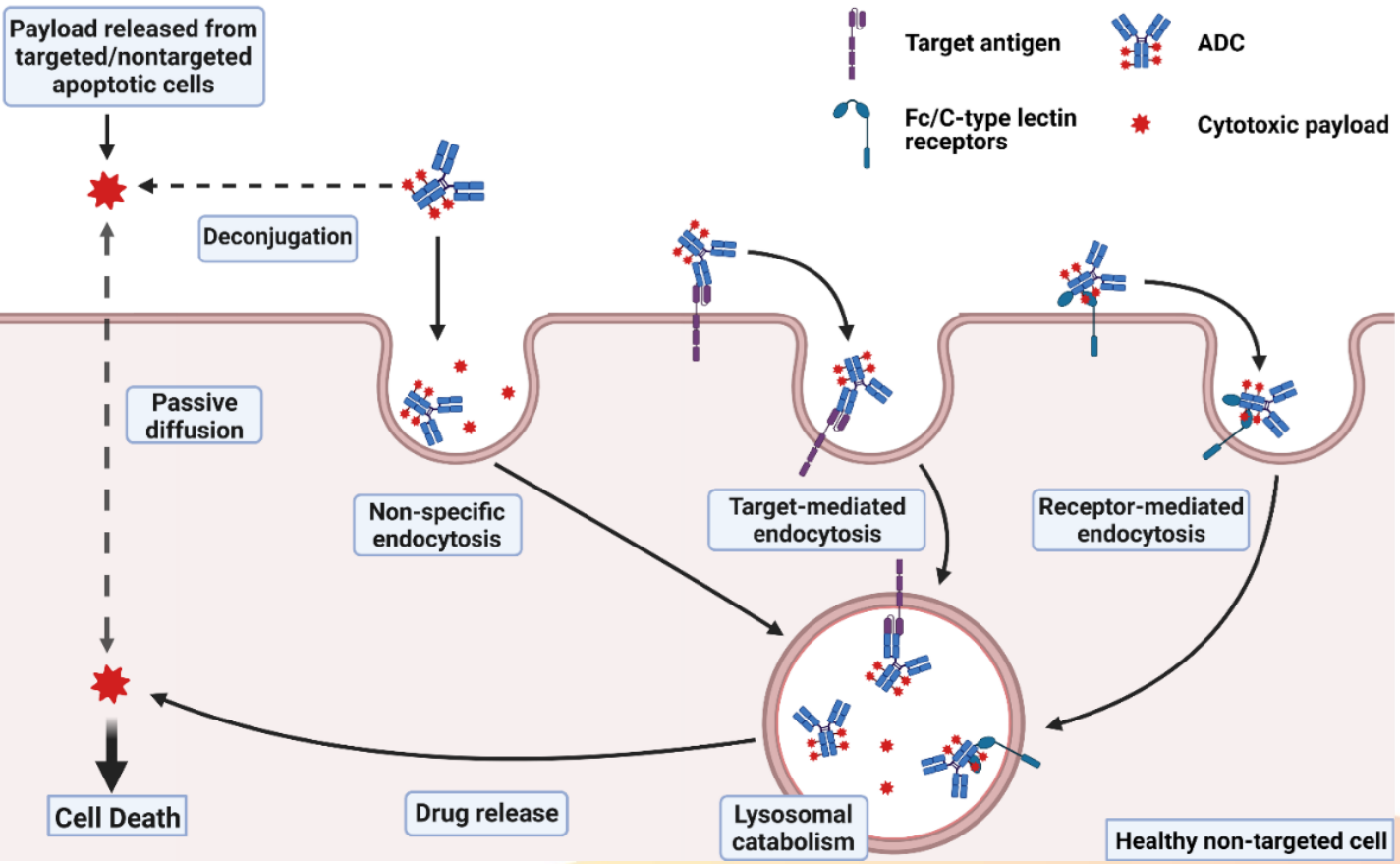
LINKERS → NON-CLEAVABLE



Only increase in AE's

Zhang et al. Drug Metab Dispos 2019;47:1146-1155

OFF-TARGET DELIVERY OF ADC PAYLOAD

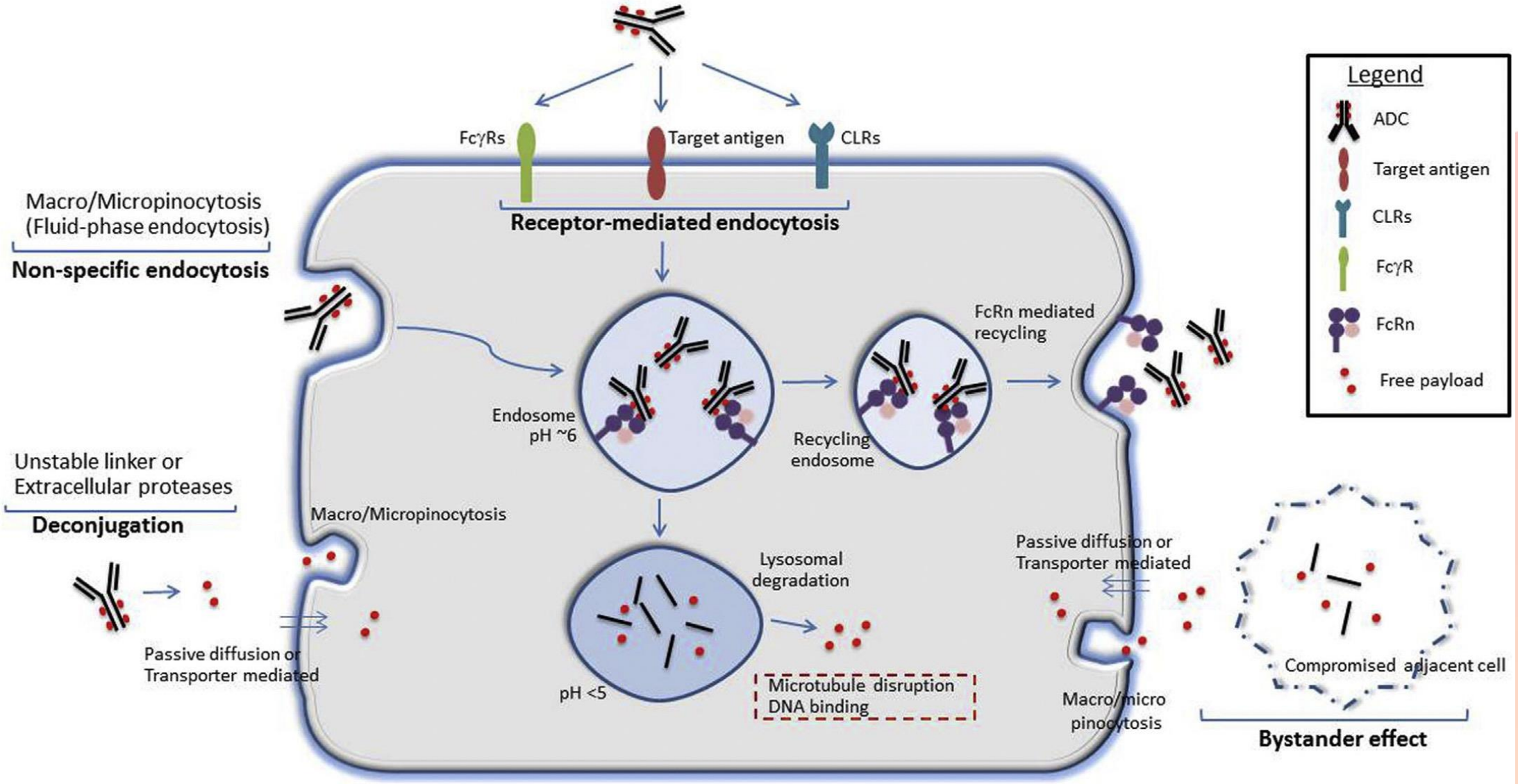


Non-specific endocytosis of the intact ADC
(hydrophobicity and charge)

HYDROPHOBICITY
proportional to the drug loading
(drug-to-antibody ratio, DAR)

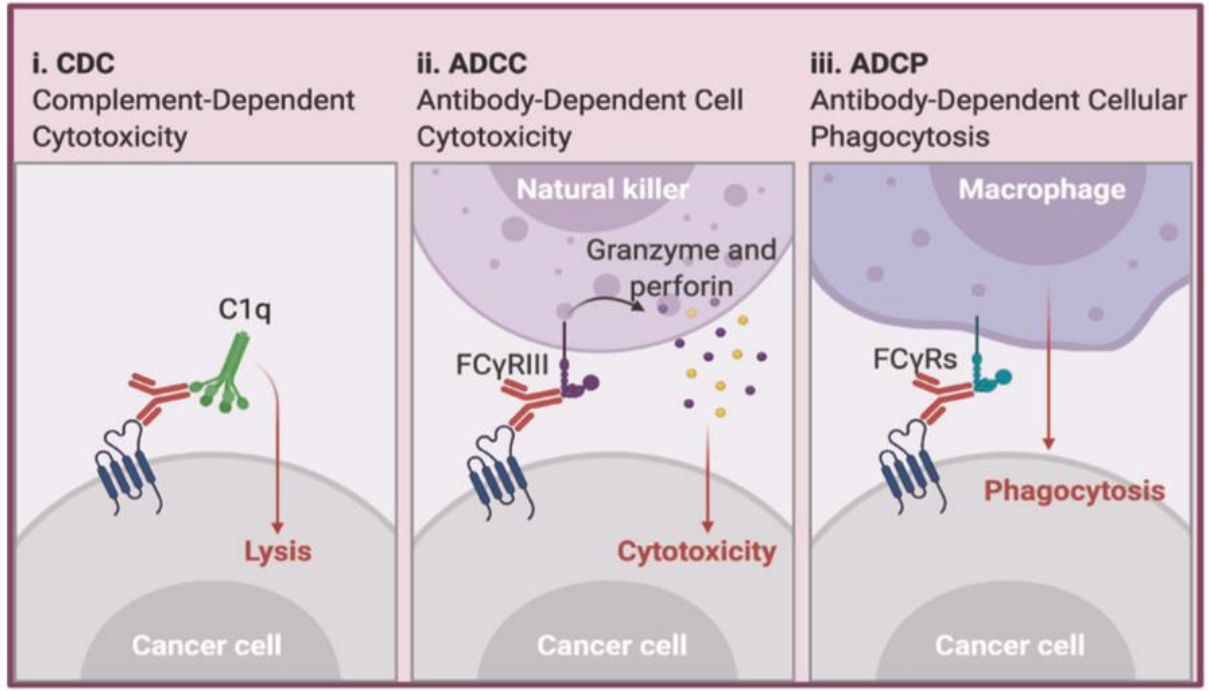
CHARGE
Positively charged molecules have increased endocytic uptake
(negatively charged cell membranas)

Nguyen T.D, et al. *Cancers* **2023**



Mahalingaiah, P.K. *Pharmacol. Ther.* 2019

OFF-TARGET RECEPTOR-MEDIATED UPTAKE OF ADC



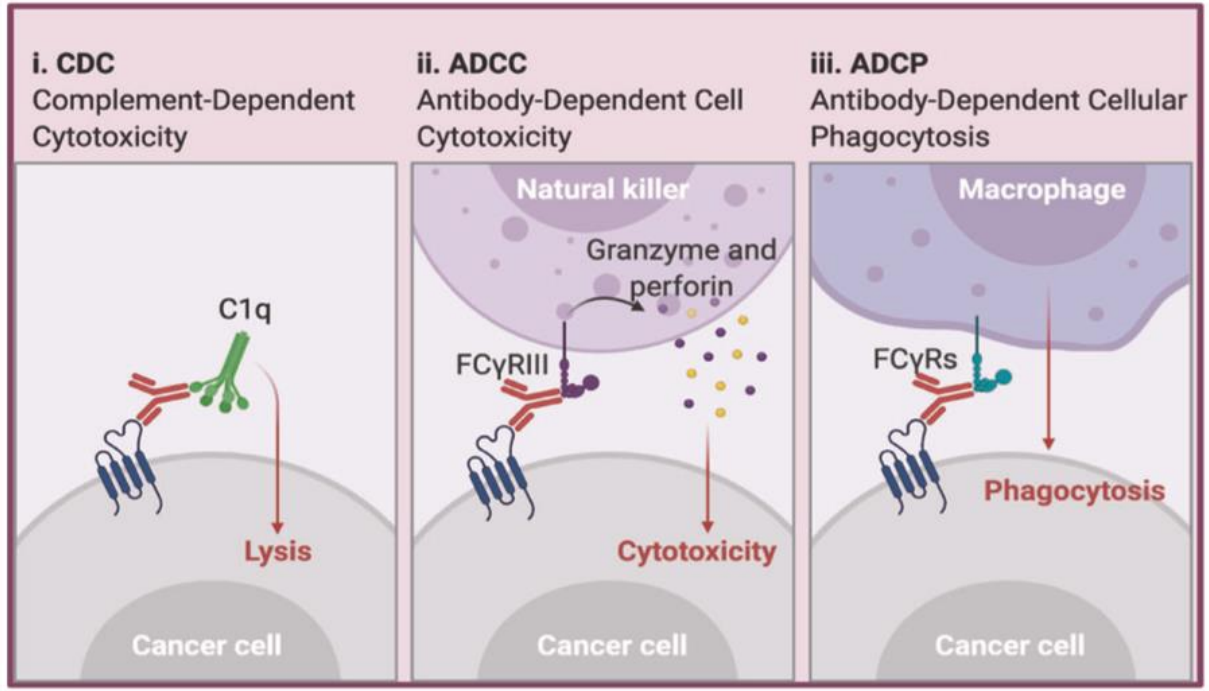
Interaction of the Fc domain with Fc receptors expressed on immune cells --> Fc gamma receptor (FcγR)

THROMBOCYTOPENIA AND T-DM1

- a target-independent toxicity
- platelets and platelet-forming megakaryocytes (MKs) have no expression of HER-2

Z Fu. Signal Transduction and Targeted Therapy (2022)

OFF-TARGET RECEPTOR-MEDIATED UPTAKE OF ADC



3 FACTS
Interstitial lung disease (ILD)/pneumonitis

1) Macrophages also exhibit a high expression level of FcγRs

2) Alveolar macrophages express high amounts of FcγR

3) Respiratory alveoli exhibit a low expression of HER2

Investigations with engineered ADCs with ablated FcγR binding might help to define the role of FcγR in ADC-induced ILD

Z Fu. Signal Transduction and Targeted Therapy (2022)

OFF-SITE, ON-TARGET

ADCs producing toxicity that is not typically associated with their payload may be suggestive of an on-target mechanism

40% of patients treated with **enfortumab vedotin** experience **dysgeusia**:

→ expression of the ADC target (nectin-4) in the salivary glands

Trastuzumab-based ADC: ILD, cardiac toxicity

	DESTINY-Breast03 study	
	Any grade	Grade ≥3
LVEF decrease	2.7%	0%

Nguyen T.D, et al. *Cancers* **2023**

TOXICIDAD GASTROINTESTINAL: NÁUSEAS Y VÓMITOS

TRASTUZUMAB -DERUXTECAN

System Organ Class Preferred Term, n (%)	T-DXd n = 257 Any grade	 Grade ≥3
Blood and lymphatic system disorders		
Anemia	95 (37.0)	24 (9.3)
Platelet count decreased	64 (24.9)	20 (7.8)
White blood cell count decreased	60 (23.3)	16 (6.2)
Gastrointestinal disorders		
Nausea	198 (77.0)	18 (7.0)
Vomiting	133 (51.8)	4 (1.6)
Constipation	96 (37.4)	0
Diarrhea	83 (32.3)	3 (1.2)
General disorders		
Fatigue	79 (30.7)	15 (5.8)
Headache	61 (23.7)	1 (0.4)
Investigations		
Neutrophil count decreased	79 (30.7)	41 (16.0)
Aspartate aminotransferase increased	72 (28.0)	2 (0.8)
Alanine aminotransferase increased	59 (23.0)	4 (1.6)
Metabolism and nutrition disorders		
Decreased appetite	78 (30.4)	4 (1.6)
Weight decreased	58 (22.6)	6 (2.3)
Skin and subcutaneous tissue disorders		
Alopecia	102 (39.7)	1 (0.4)[a]

Adverse reactions in a pooled analysis of DESTINY-Breast01 and DS8201-A-J101.

TOXICIDAD GASTROINTESTINAL: NÁUSEAS Y VÓMITOS

Resumen de las reacciones adversas relacionadas con el tratamiento en la población de seguridad del estudio ASCENT

SACITUZUMAB-GOVITECAN

		TRODELVY (n=258)		
		Todos los grados n (%)	Grado 3 n (%)	Grado 4 n (%)
Cualquier reacción adversa		252 (98)	117 (45)	48 (19)
Hematológicos	Neutropenia†	163 (63)	88 (34)	44 (17)
	Anemia‡	89 (34)	20 (8)	0
	Leucopenia§	41 (16)	23 (9)	3 (1)
	Trombocitopenia¶	14 (5)	2 (1)	2 (1)
	Neutropenia febril	15 (6)	12 (5)	3 (1)
Gastrointestinales	Diarrea	153 (59)	27 (10)	0
	Náuseas	147 (57)	6 (2)	1 (<1)
	Vómitos	75 (29)	2 (1)	1 (<1)
	Estreñimiento	44 (17)	0	0
	Dolor abdominal	29 (11)	3 (1)	0
Trastornos generales y alteraciones en el lugar de administración	Fatiga	115 (45)	8 (3)	0
	Astenia	31 (12)	2 (1)	0
Trastornos de la piel y del tejido subcutáneo‖	Alopecia	119 (46)	0	0
Trastornos del metabolismo y de la nutrición	Apetito disminuido	51 (20)	4 (2)	0
Trastornos del sistema nervioso††		64 (25)	1 (<1)	0
Trastornos respiratorios, torácicos y mediastínicos††		41 (16)	5 (2)‡‡	0
Trastornos musculoesqueléticos y del tejido conjuntivo††		32 (12)	0	0
Infecciones e infestaciones††		30 (12)	6 (2)	1 (<1)

Bardia A, *et al*. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021;384(16):1529–1541.

TOXICIDAD GASTROINTESTINAL: NÁUSEAS Y VÓMITOS

NCCN Guidelines Version 1.2023 Antiemesis

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[a]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m^2	• Cisplatin • Cyclophosphamide >1500 mg/m^2 • Dacarbazine • Doxorubicin ≥60 mg/m^2 • Epirubicin >90 mg/m^2 • Fam-trastuzumab deruxtecan-nxki	• Ifosfamide ≥2 g/m^2 per dose • Mechlorethamine • Melphalan ≥140 mg/m^2 • Sacituzumab govitecan-hziy • Streptozocin

1. NCCN Guidelines Version 1.2023 Antiemesis
Adverse reactions in a pooled analysis of DESTINY-Breast01 and DS8201-A-J101.

TOXICIDAD GASTROINTESTINAL: DIARREA

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Skin and subcutaneous tissue disorders		
Alopecia	102 (39.7)	1 (0.4)[a]

TOXICIDAD GASTROINTESTINAL: DIARREA

SACITUZUMAB-GOVITECAN

La mayoría de los casos de diarrea ocurren en los 2 primeros ciclos y duran <7 días

		TRODELVY (n=258)		
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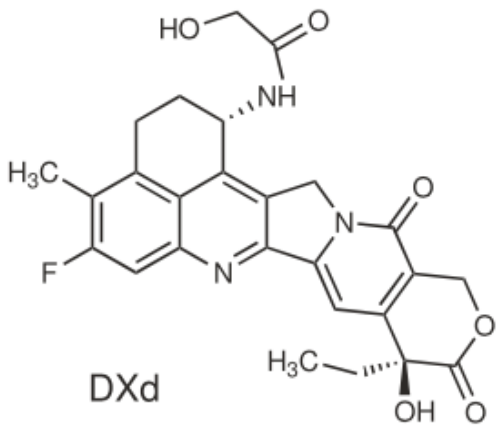
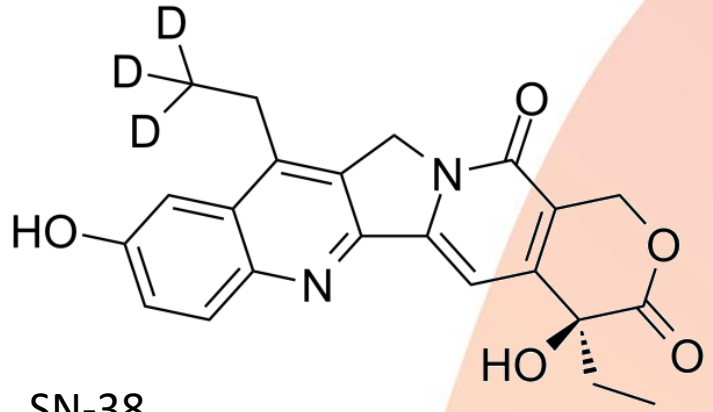
TOXICIDAD GASTROINTESTINAL: DIARREA

DERIVADOS DE CAMPTOTECINA



DXd

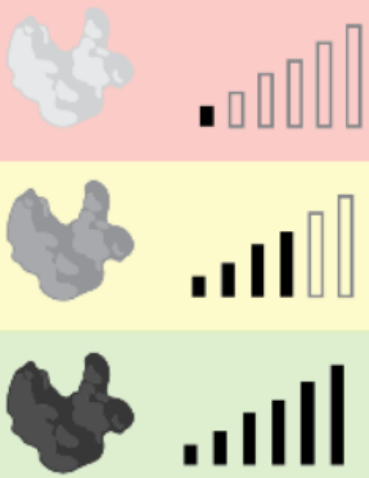
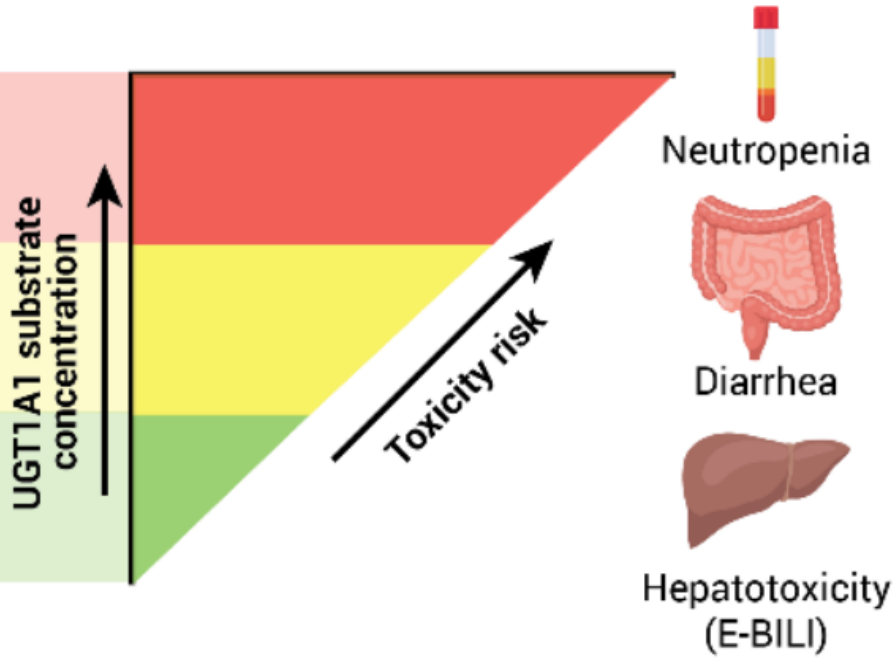


SN-38

¿Distinta incidencia de diarrea?

Bossi P et al. *Ann Oncol.* 2018;29(4):iv216-iv142.

FARMACOGENÓMICA UGT1A1

UGT1A1 functions	*UGT1A1* polymorphisms	UGT1A1 enzyme function	Toxicity risk
Cancer drug elimination Bilirubin elimination	UGT1A1 PMs (**6/*6, *6/*28, *28/*28*) UGT1A1 IMs (**1/*6, *1/*28*) UGT1A1 NMs (**1/*1, *1/*36, *36/*36*)		

RS Nelson. Cancers 2021

FARMACOGENÓMICA UGT1A1

Table 4. Key treatment-related adverse events of all grades in >20% and of grade ≥3 in >5% of patients treated with sacituzumab govitecan significantly impacted by UGT1A1 genotype.

TRAE[2], *n* (%)	SG (*n* = 243)[1]					
	*1/*1 wild type (*n* = 113)		*1/*28 heterozygous (*n* = 96)		*28/*28 homozygous (*n* = 34)	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Hematologic						
Neutropenia[3]	76 (67)	60 (53)	55 (57)	45 (47)	24 (71)	20 (59)
Anemia[4]	37 (33)	5 (4)	29 (30)	6 (6)	16 (47)	5 (15)
Leukopenia[5]	18 (16)	10 (9)	13 (14)	9 (9)	8 (24)	5 (15)
Lymphopenia[6]	10 (9)	1 (1)	5 (5)	1 (1)	4 (12)	2 (6)
Febrile Neutropenia	3 (3)	3 (3)	5 (5)	5 (5)	6 (18)	6 (18)
Thrombocytopenia[7]	3 (3)	0	6 (6)	0	4 (12)	4 (12)
Gastrointestinal						
Diarrhea	65 (58)	11 (10)	57 (59)	9 (9)	21 (62)	5 (15)

HS Rugo. NPJ Breast Cancer (2022)

Treatment-related adverse events of antibody–drug conjugates in clinical trials: A systematic review and meta-analysis

Meta-analysis:
169 studies
15,340 patients

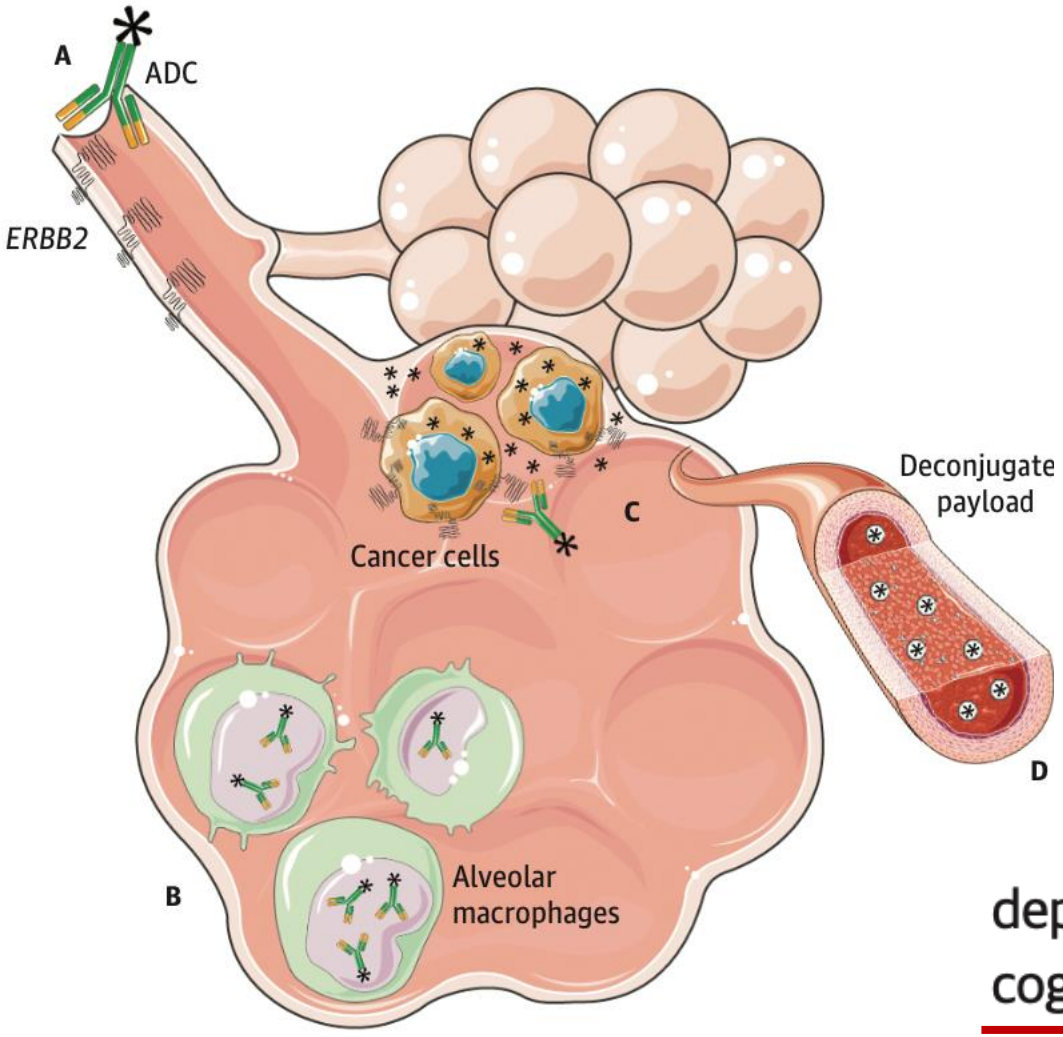
Treatment related deaths:
N = 204
1.3%
(95%CI: 1.1–1.5%)

- Unknown cause
  N = 35
- Known cause
  N = 169

Pneumonitis	(*n* = 21; 12.4%)
Pneumonia	(*n* = 17; 10.1%)
Sepsis	(*n* = 13; 7.7%)
Respiratory failure	(*n* = 11; 6.5%)

Zhu et al. Cancer. 2023;129:283–295

NEUMONITIS/ENF. PULMONAR INTERSTICIAL



A) ERBB2-dependent uptake of the ADC

B) ERBB2-independent uptake of the ADC in intra-alveolar immune cells.

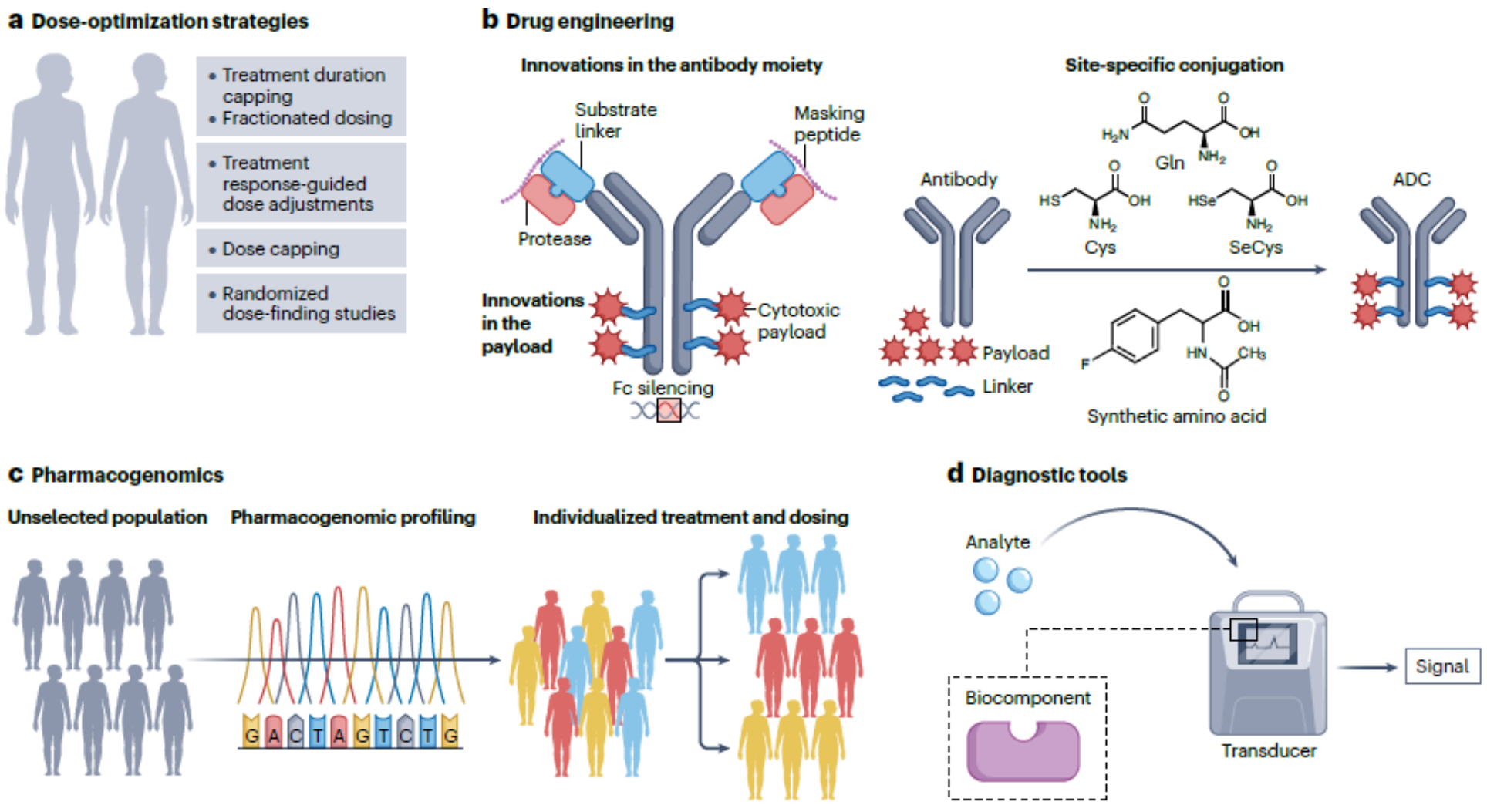
C) Bystander killing by free payload released from targeted cancer cells.

D) Deconjugated payload circulating in the bloodstream.

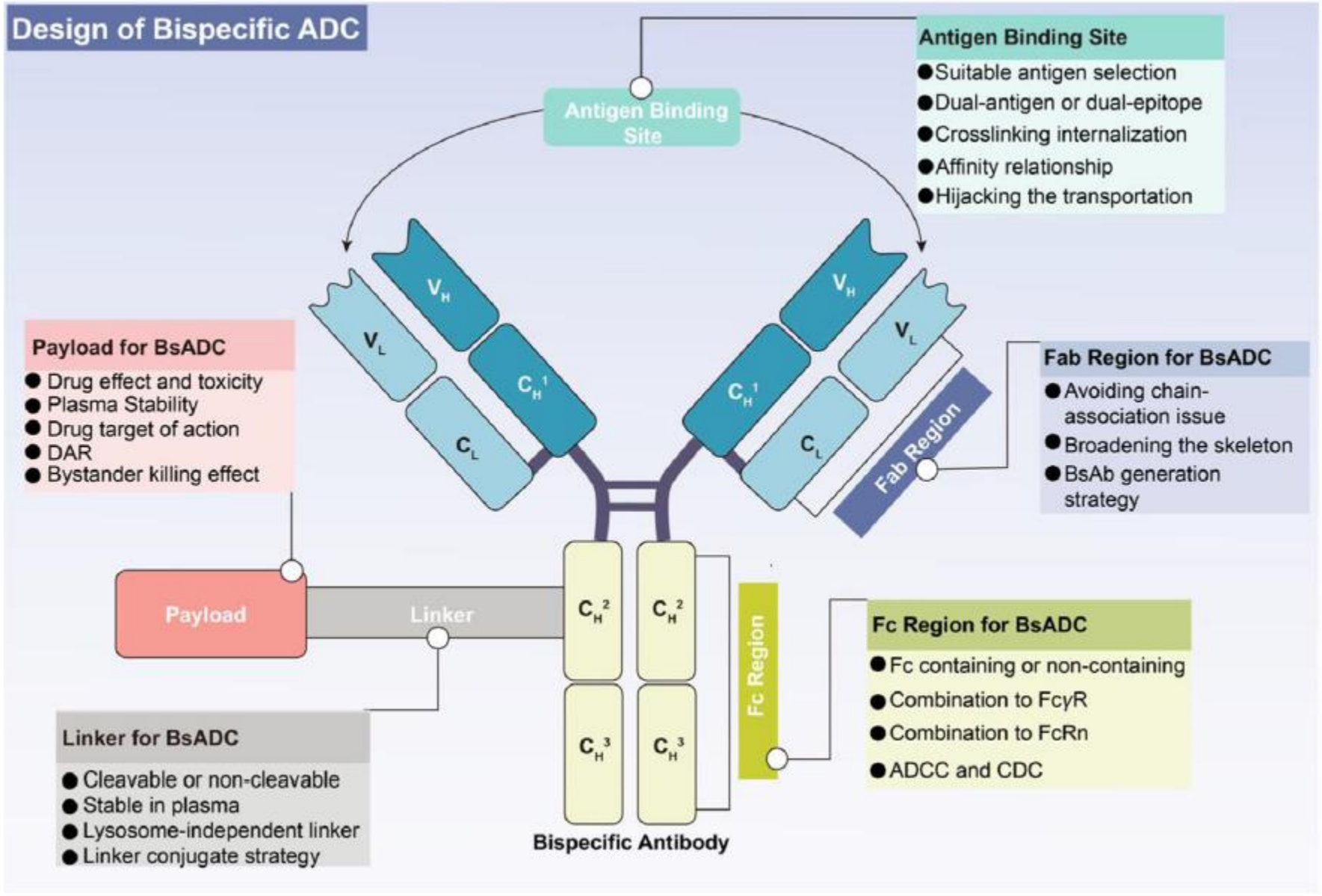
deplete or modulate such cells. In addition, the impact of pharmacogenomics should be explored, particularly for conjugates adopting topoisomerase I inhibitors as payloads (eg, trastuzumab deruxtecan), because pharmacogenomic testing is already standard of care when prescribing irinotecan.[70]

P. Tarantino. JAMA Oncol 2021

Strategies being tested to potentially optimize the safety of ADCs



Optimizing the safety of antibody–drug conjugates for patients with solid tumours; Tarantino et al Nature Review Clin Onc 2023 https://doi.org/10.1038/s41571-023-00783-w



Gu Yilin et al., Bispecific antibody drug conjugates: Making 1þ1>2, Acta Pharmaceutica Sinica B, https://doi.org/10.1016/ j.apsb.2024.01.009

Table 2 | Pharmacological determinants of the toxicity of ADCs

Category	Mechanism	Refs.
Pharmacodynamic		
Uptake of intact ADCs into non-malignant cells	Uptake by Fc and/or C-type lectin receptors	24,31
	Non-specific endocytosis	31
	Endocytosis following on-target, off-tumour activity	31
	Passive diffusion	28
Bystander effect	Payload released from apoptotic cancer cells	25
	Payload released from apoptotic non-malignant cells	25
Deconjugation and linker stability	Premature release of payload in the systemic circulation	14
Drug-to-drug antibody ratio	Increased total payload dose	56
Tumour penetration and accumulation	Limited tumour penetration increases systemic toxicity	131

Pharmacokinetic		
Target-specific binding	Limited target-specific binding increases non-target exposure	68,69
Absorption and distribution	Increased systemic concentration	32
Decreased catabolism	Increased systemic concentration	32
Excretion properties	Prolonged exposure	32
Increased half-life	Prolonged exposure	32
Proteolysis-mediated catabolism	Prolonged exposure	32
Albumin binding	Prolonged exposure	14,33
Payload biochemical properties	Lipophilic payloads have higher tissue penetrance	14,34,48

CONCLUSIONES

- **ADCs son fármacos con nuevo mecanismo de acción y nueva farmacodinámica, con toxicidades “ya conocidas”…y otras nuevas**
- **Algunas de las toxicidades son debidas al anticuerpo (on-target) y otras atribuibles directamente al payload (off-target)**
- **La toxicidad gastrointestinal (náuseas, vómitos y diarrea) y la hematológica (neutropenia) son los AE más frecuentes**
- Muchos de los AEs producidos son por mecanismos desconocidos

El hombre sabio teme al peligro y se prepara para ello; el insensato va a ciegas y sufre las consecuencias

¡Gracias!