癌症標靶治療藥物
Target therapy classification
Cancer Monoclonal antibody development
（單株抗體發展史與臨床應用）part 3
(Antibody-drug conjugate)

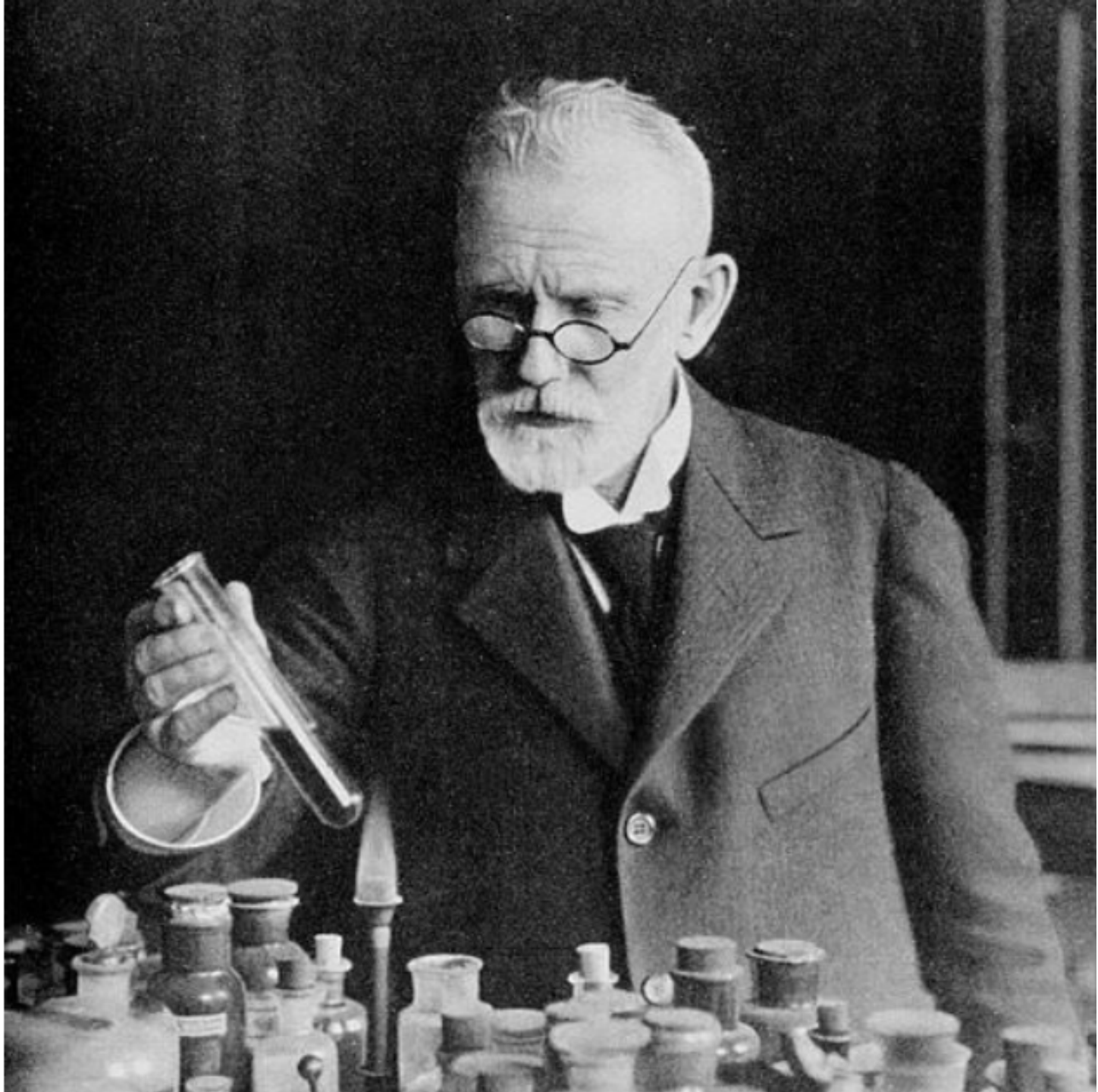
Clinical pharmacist: Lihua Fang

大綱

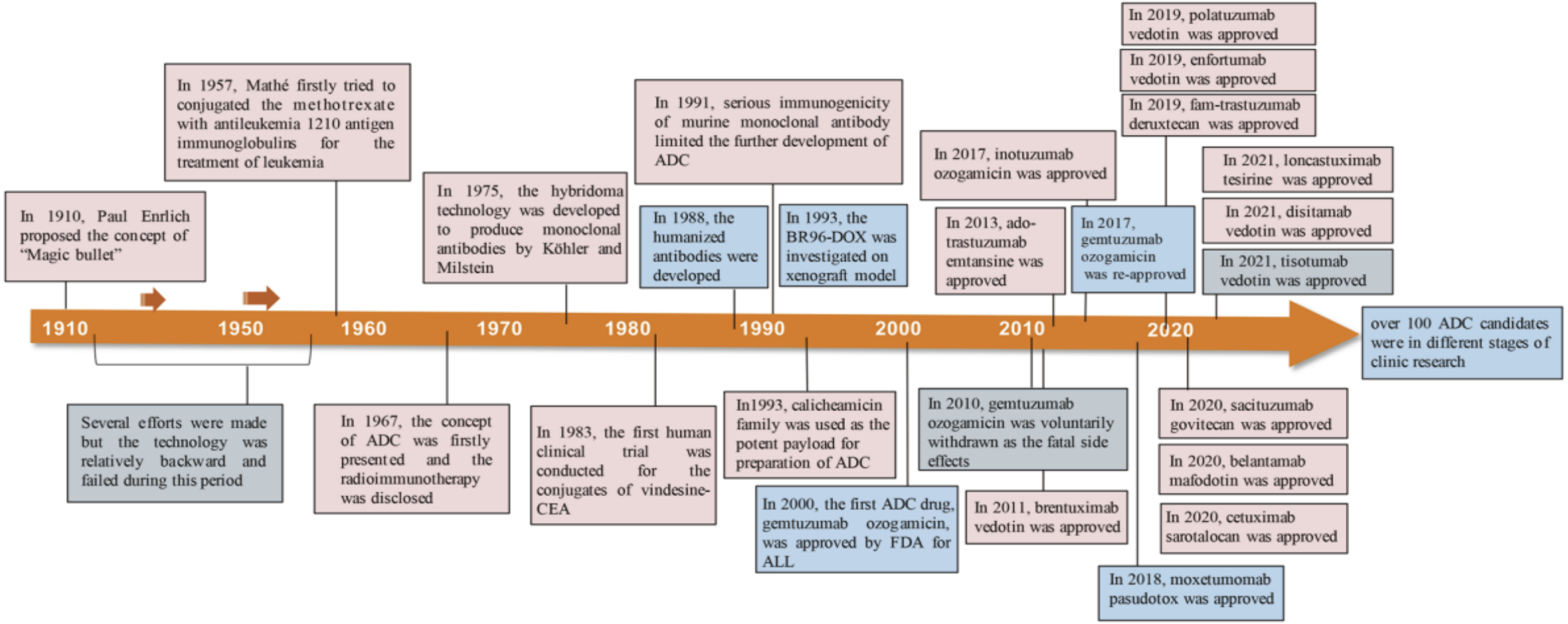
- 標靶治療誕生 ： 在1975年，柯勒(Kohler)與麥爾斯坦(Milstein)將B細胞與骨髓瘤細胞(myeloma cells)成功地合成融合瘤細胞，這劃時代的創舉，便開啟了應用單株抗體的新紀元。
- 單株抗體開啟在癌症與免疫治療的新紀元
- 單株抗體的藥物命名
- 單株抗體的演化
  - 單株抗體變型
  - 抗體藥物複合體(antibody-drug conjugate, ADC)
  - 雙特異性抗體 (bispecific T-cell Enganger,BiTE)
  - 三功能性抗體(Trifunctional Antibody)

115 years since the magic bullet

- The story of Paul Ehrlich, who devoted his life to research and revolutionised medicine with the first antibiotic and origin of chemotherapy (1910)

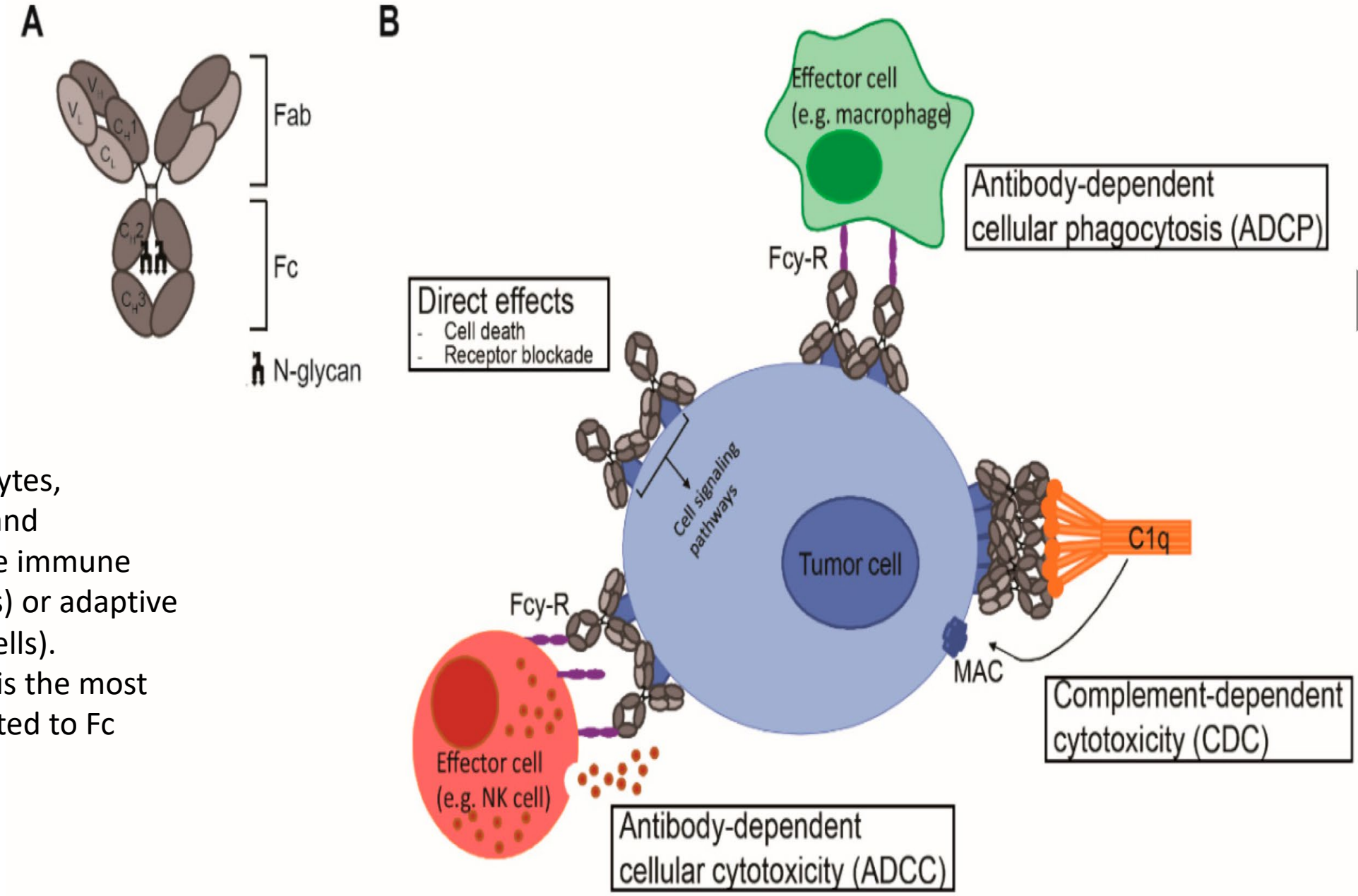


Timeline depicting important events in the development and approval of ADC drugs



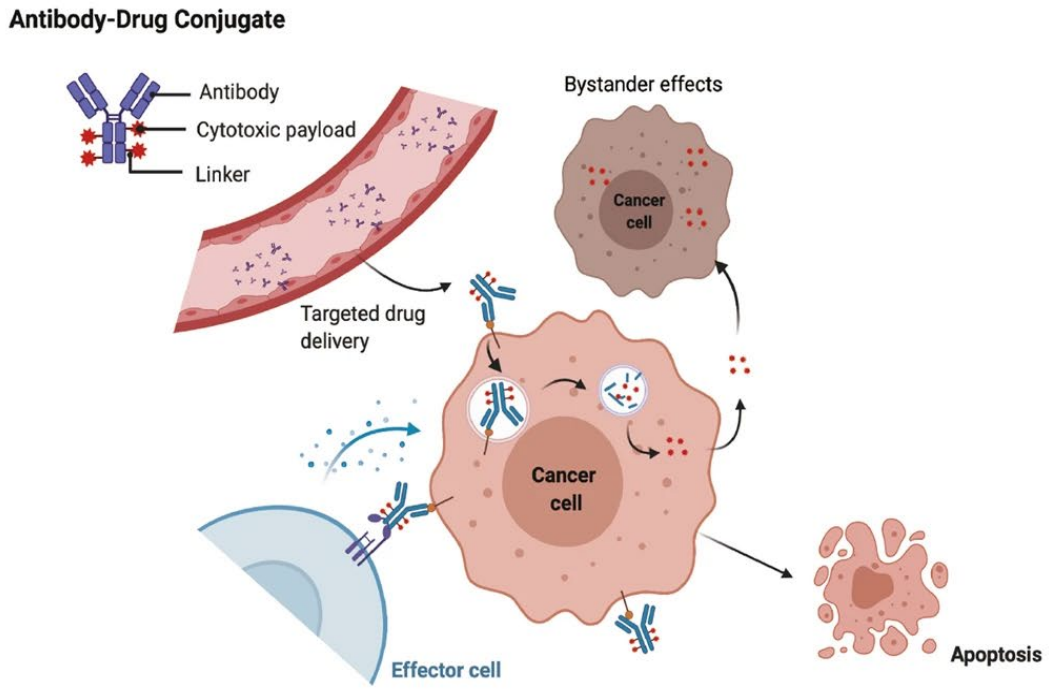
Signal Transduction and Targeted Therapy (2022) 7:93

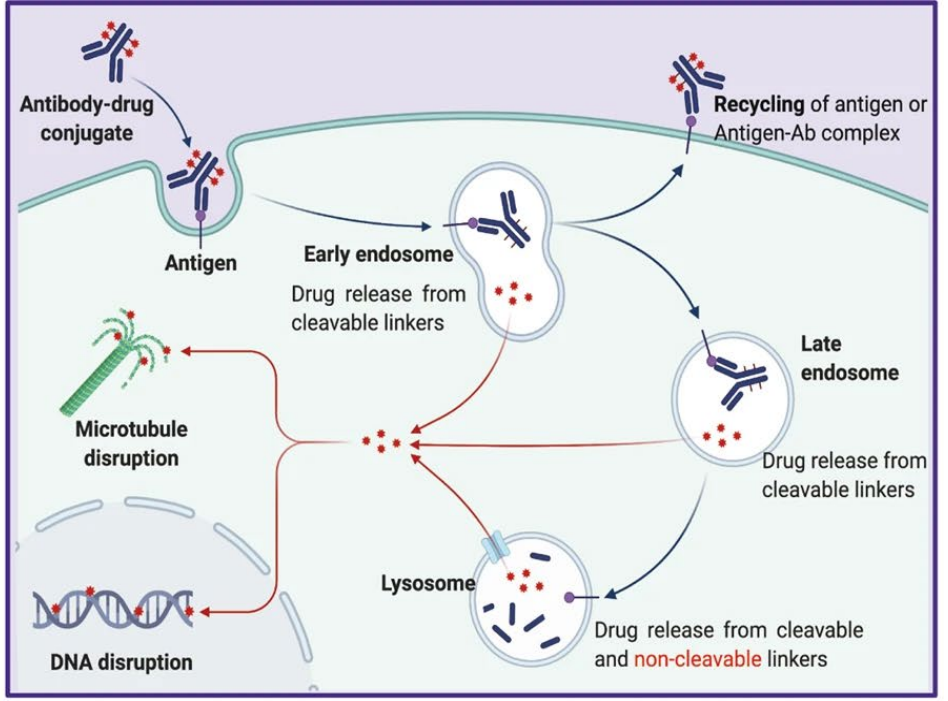
Fc domain

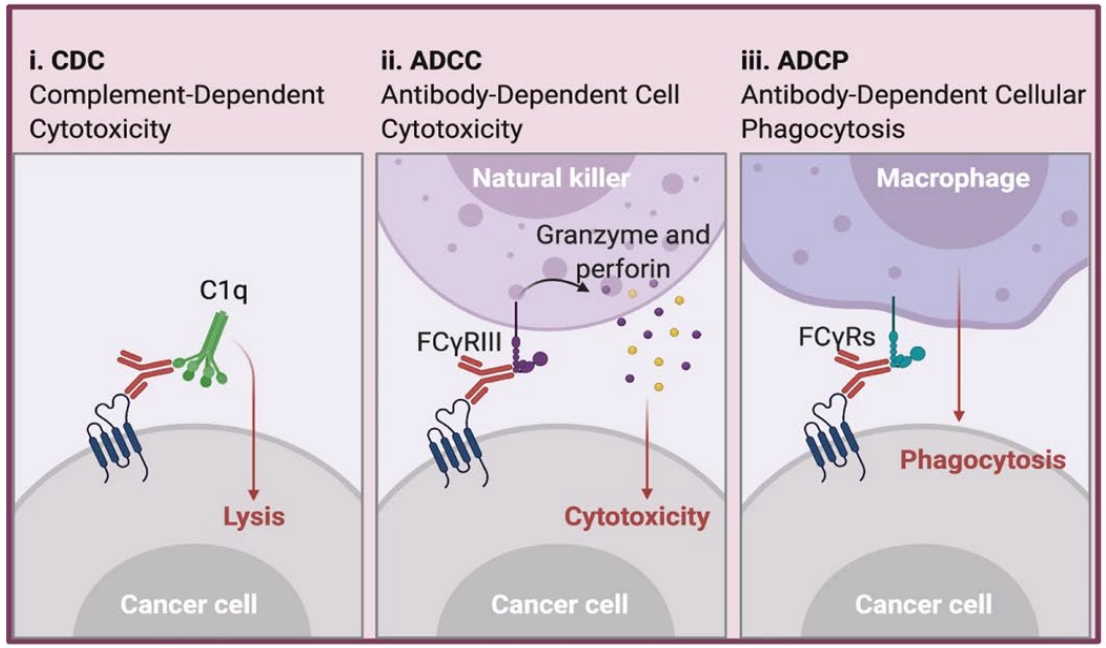


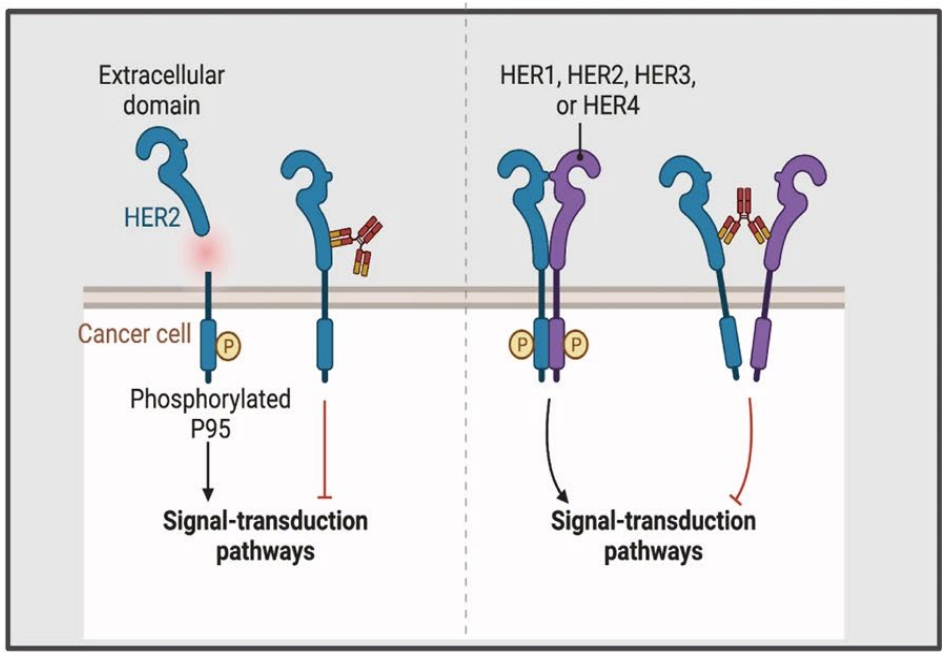
Function of Fc receptor

macrophages and monocytes, neutrophils, eosinophils and lymphocytes of the innate immune system (natural killer cells) or adaptive immune system (e.g., B cells). Activation of phagocytes is the most common function attributed to Fc receptors.









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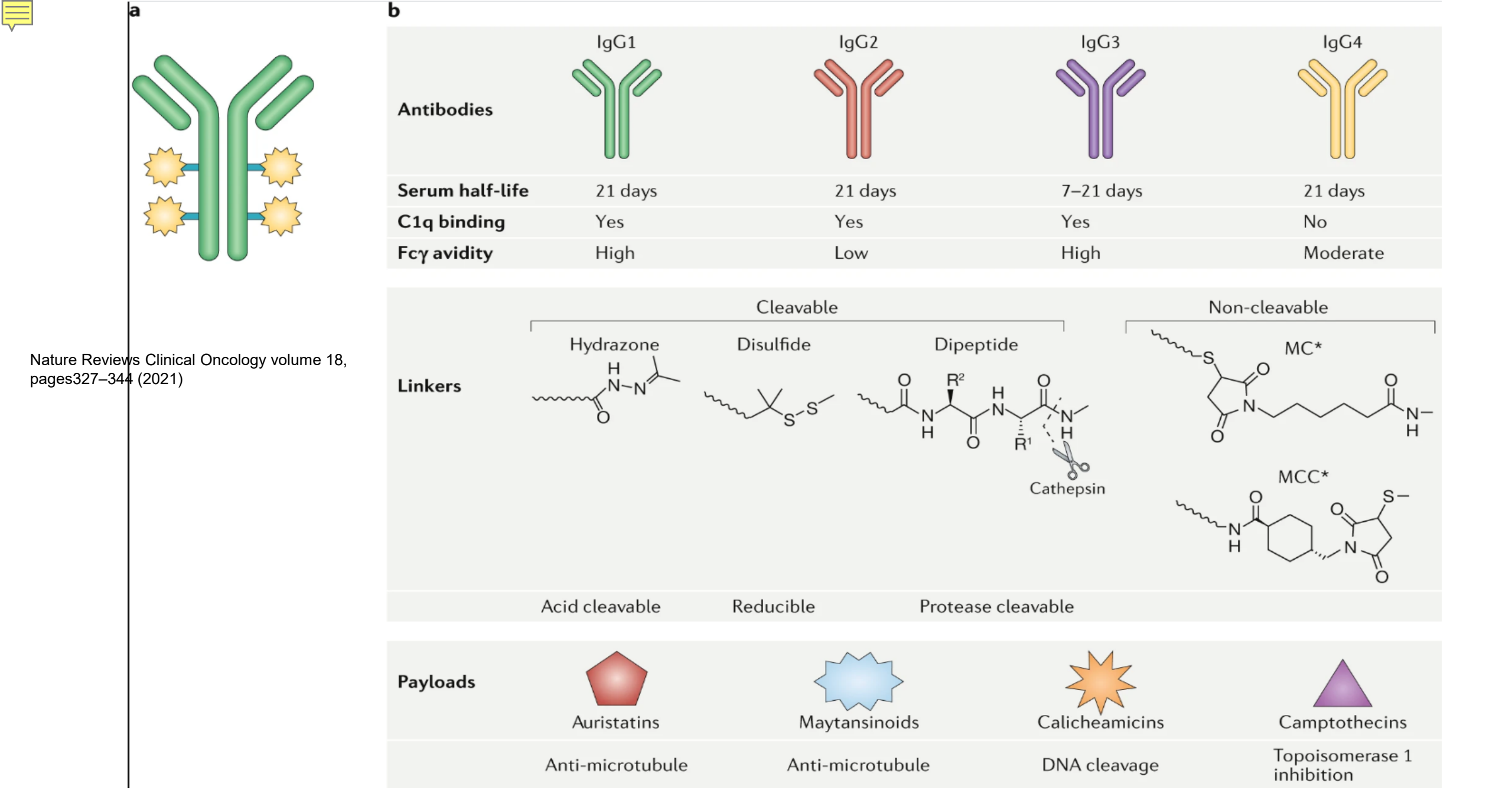


Nature Reviews Clinical Oncology volume 18, pages327–344 (2021)

Monomethyl auristatin E : (Synonyms: MMAE; Vedotin) : 200 times that of vinblastine, another antimitotic drug used for Hodgkin lymphoma as well as other types of cancer. Maytansine binds tubulin at the vinca-binding site, similar to vinca alkaloids,

ADC, antibody–drug conjugate

ADC	Target antigen	mAb isotype	Linker type	Payload	Payload class	Payload action	DAR	Disease indication (year of approval)
Gemtuzumab ozogamicin	CD33	IgG4	Cleavable	Ozogamicin	Calicheamicin	DNA cleavage	2–3	$CD33^+$ R/R AML (2000)[a]
Brentuximab vedotin	CD30	IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	4	R/R sALCL or cHL (2011) R/R pcALCL or $CD30^+$ MF (2017) cHL, sALCL or $CD30^+$ PTCL (2018)[b]
Ado-trastuzumab emtansine (T-DM1)	HER2	IgG1	Non-cleavable	DM1	Maytansinoid	Microtubule inhibitor	3.5 (mean)	Advanced-stage $HER2^+$ breast cancer previously treated with trastuzumab and a taxane (2013); early stage $HER2^+$ breast cancer in patients with residual disease after neoadjuvant trastuzumab–taxane-based treatment (2019)
Inotuzumab ozogamicin	CD22	IgG4	Cleavable	Ozogamicin	Calicheamicin	DNA cleavage	5–7	R/R B-ALL (2017)
Fam-trastuzumab deruxtecan-nxki (T-DXd)	HER2	IgG1	Cleavable	DXd	Camptothecin	TOPO1 inhibitor	8	Advanced-stage $HER2^+$ breast cancer after two or more anti-HER2-based regimens (2019)
Polatuzumab vedotin-piiq	CD79b	IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	3.5 (mean)	R/R DLBCL (2019)[c]
Sacituzumab govitecan-hziy	TROP2	IgG1	Cleavable	SN-38 (active metabolite of irinotecan)	Camptothecin	TOPO1 inhibitor	8	Advanced-stage, triple-negative breast cancer in the third-line setting or beyond (2020)
Enfortumab vedotin-ejfv	Nectin 4	IgG1	Cleavable	MMAE	Auristatin	Microtubule inhibitor	4	Advanced-stage urothelial carcinoma, following progression on a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy (2020)
Belantamab mafodotin-blmf	BCMA	IgG1	Non-cleavable	MMAF	Auristatin	Microtubule inhibitor	Unknown	R/R multiple myeloma in the fifth-line setting or beyond (2020)

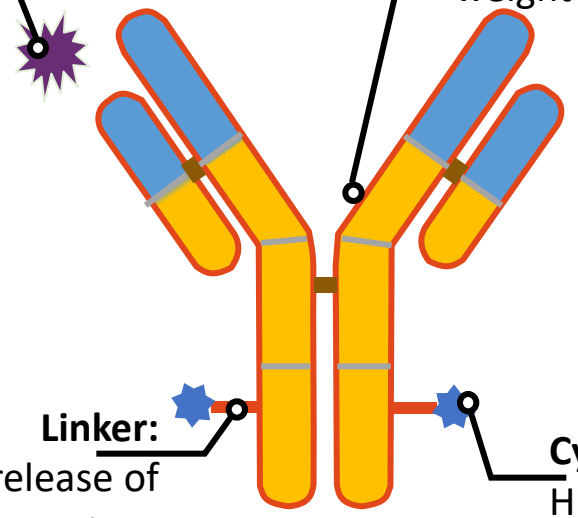
Nature Reviews Clinical Oncology **volume 18**, pages327–344 (2021)

Antibody–Drug Conjugates (ADC,抗體藥物複合體)

- Also known as **immunoconjugates**
- Represent a **new class** of targeted chemotherapeutic drug
- Composed of **monoclonal antibodies (mAbs)** tethered to a **cytotoxic drug** (known as the “payload” or “warhead”) via a **chemical linker**

Antigen:
High homogenous expression on tumor cells with low expression on healthy cells; high affinity/avidity for mAb recognition

mAb:
High affinity/avidity for tumor antigens; chimeric or humanized to decrease immunogenicity with long half-life and high molecular weight



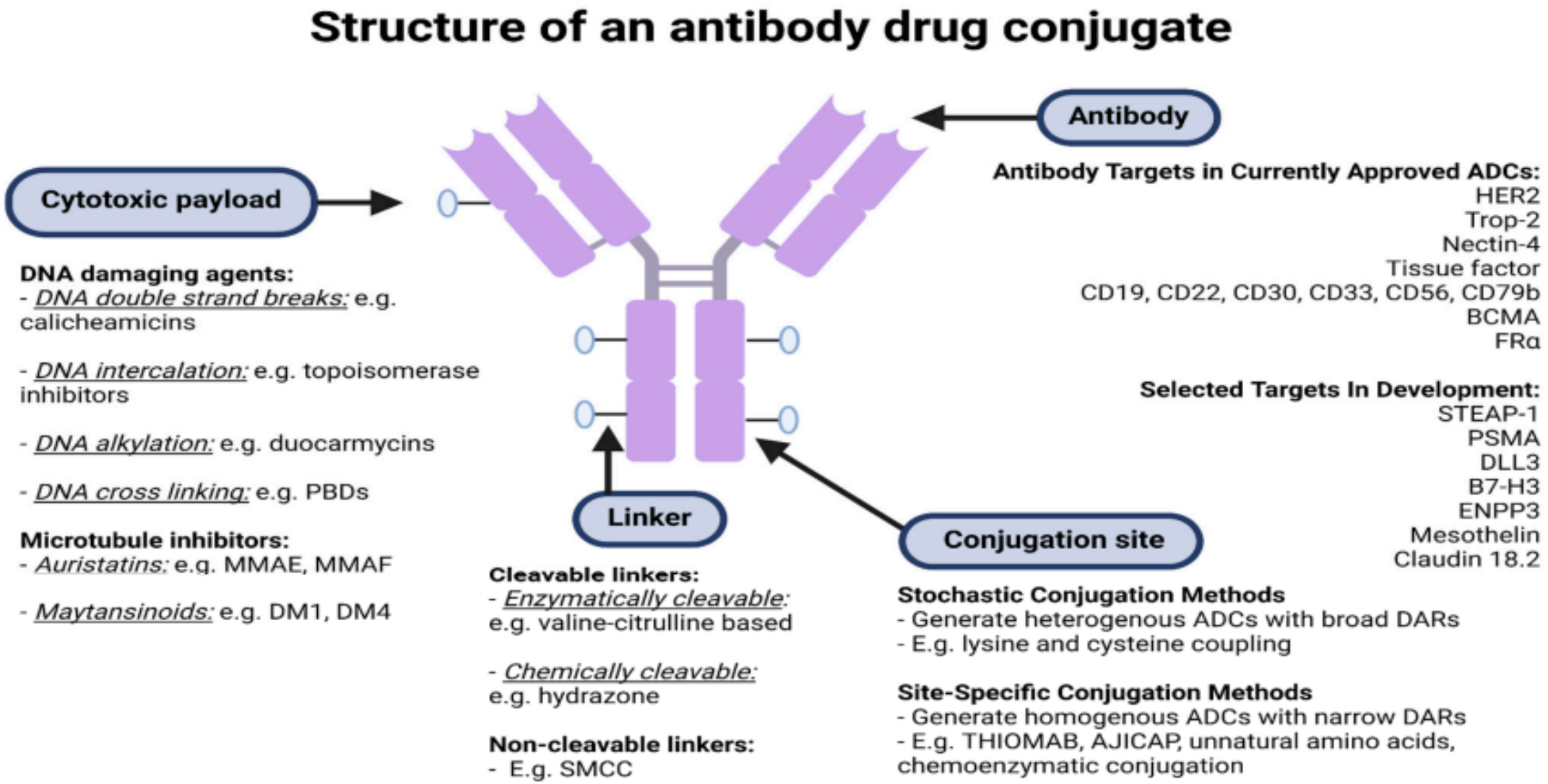
Linker:
Stable in circulation; efficient release of payload in target cell; no premature release of payload at nontarget tissue; efficient linker technology (cleavable vs noncleavable); site of conjugation affects drug distribution and PK data

Cytotoxic Agent:
Highly potent agent (IC_{50} in subnanomolar range) with optimal DAR

Chau. Lancet. 2019;394:793.

Slide credit: clinicaloptions.com

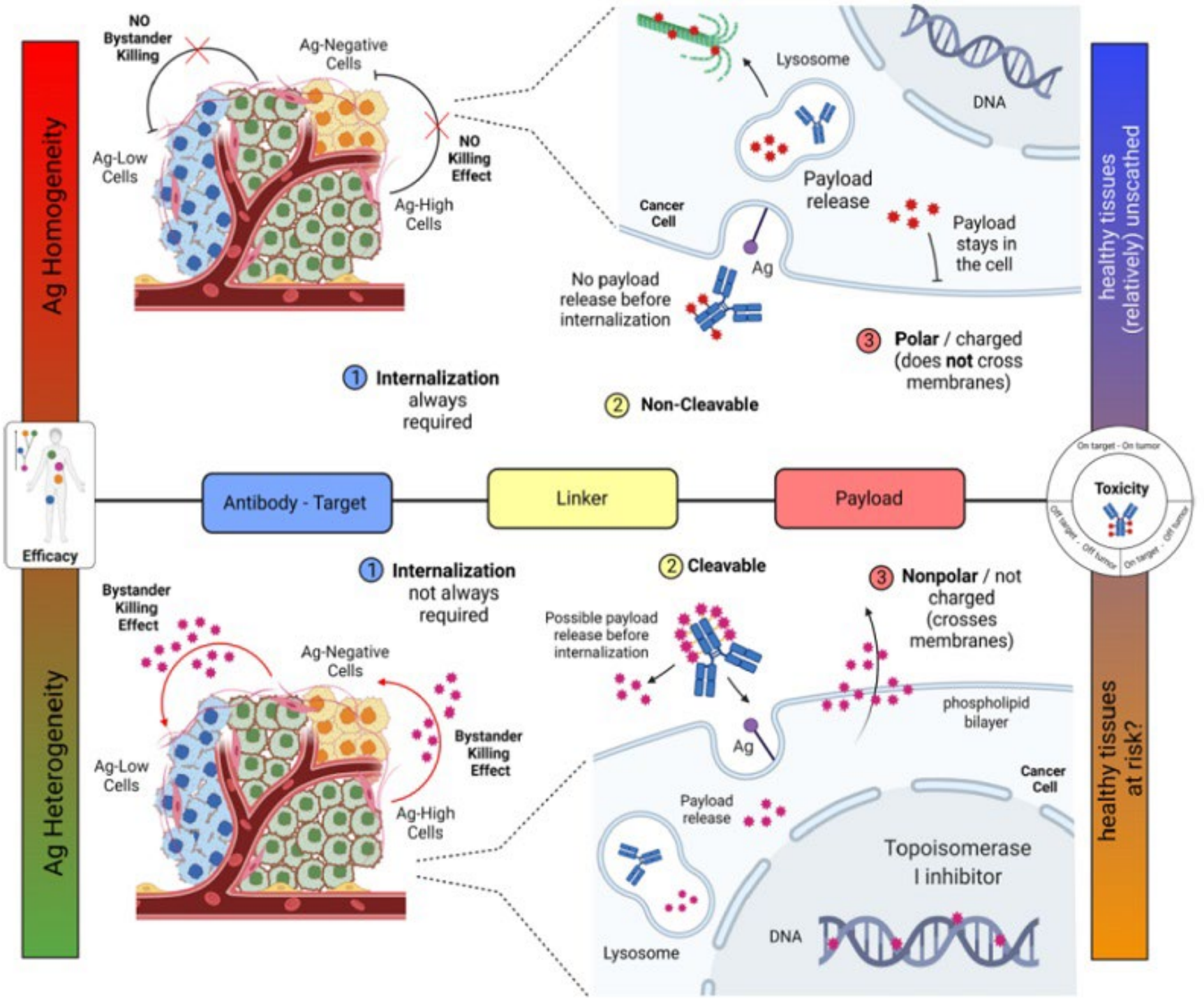
Antibody–Drug Conjugates



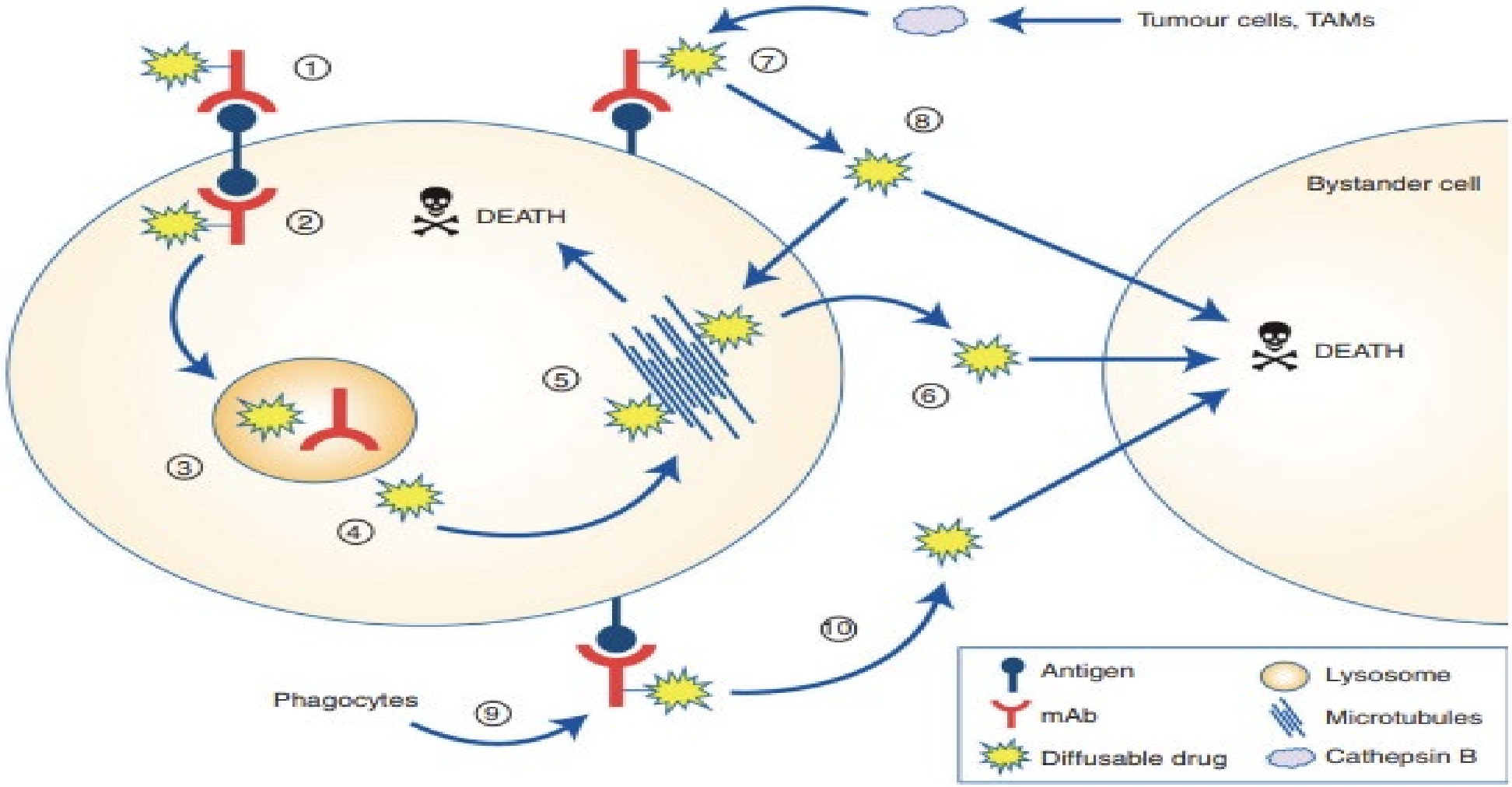
Pharmaceutics 2023, 15, 2017

A Paradigm Shift in Cancer Treatment

- Globally, more than **600 ADC clinical trials** have been conducted or are underway
- Based on their overall efficacy and adverse event profile, these drugs have the potential to cause **a paradigm shift in cancer treatment**
- Thus far, many patients who have failed multiple prior lines of therapy have achieved disease remission with an ADC



Curr Oncol Rep. 2022 Jul;24(7):809-817



ADC involves (1) binding of the ADC to the target antigen and (2) internalisation. (3) The ADC is transported to the lysosome where the linker is cleaved, producing free diffusible drug (4). This free drug can then bind to microtubules (5) or DNA (depending on drug type) within the target cells to induce cell cycle arrest and ultimately result in cell death. The free drug can also diffuse out of the target cell (6) and penetrate surrounding ‘bystander’ cells to cause cell death. After ADC binding to the target antigen (7) but before internalisation, an alternative route for ADC processing is cleavage by extracellular enzymes (such as cathepsin B), which are released by surrounding tumour cells and tumour-associated macrophages (TAMs) and which generate diffusible drug from the ADC (8). This free drug can then penetrate surrounding ‘bystander’ cells resulting in cell death. Also, the ADC-bound target tumour cell may be internalised through Fc-mediated phagocytosis (9), which upon degradation of the target tumour cell would also result in release of free, diffusible drug (10).

Linker Type	Description	Clinical Impact	Examples of ADCs
Cleavable Linkers	Linkers that can be cleaved by specific conditions in the tumor microenvironment or inside cancer cells (e.g., pH-sensitive, protease-cleavable).	Increased selectivity and reduced systemic toxicity.	Brentuximab vedotin (Adcetris), Inotuzumab ozogamicin (Besponsa)
Enzymatically Cleavable Linkers	cleaved by specific enzymes overexpressed in tumor cells.	Targeted delivery, minimizes off-target effects.	Sacituzumab govitecan (Trodelvy)
Acid-Labile Linkers	cleaved in the acidic environment of the tumor or endosomes.	Enhanced release of the cytotoxic payload in acidic environments.	Gemtuzumab ozogamicin (Mylotarg)
Disulfide Linkers	cleaved in the presence of reducing agents, often found in the intracellular environment.	Efficient payload release inside cancer cells.	Trastuzumab duocarmazine
Non-Cleavable Linkers	Linkers that remain intact until the ADC is internalized and metabolized inside the cell.	Higher stability in circulation, potentially more durable effects.	T-DM1 (Kadcyla),

Tissue-agnostic indications

- 2017: pembrolizumab : tumors deficient in mismatch repair (MMR) or with high microsatellite instability (MSI)
- 2018: larotrectinib : NTRK fusions-positive tumors
- 2019: entrectinib : NTRK fusions-positive tumors
- 2020: pembrolizumab : tumors with high tumor mutational burden (TMB) ≥10 mutations/megabase of DNA (mut/Mb)
- 2021: dostarlimab : mismatch repair deficient tumors
- 2022: dabrafenib + trametinib : BRAF V600E mutated tumors
- 2022: selpercatinib with REarranged during Transfection (RET) fusion (+)
- 2024 : trastuzumab deruxtecan for unresectable or metastatic HER2-positive solid tumors

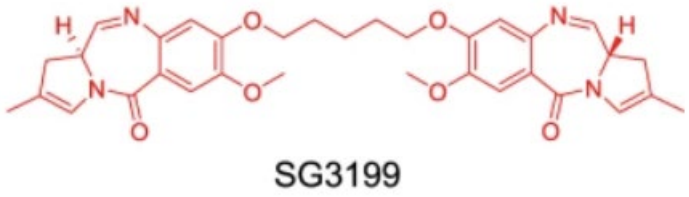
Drugs (Company)	Trade Names	Target antigens	Linkers	Payloads	Average DAR	FDA Approved	Approved indications
Gemtuzumab ozogamicin (Pfizer)	Mylotarg®	CD33	hydrazone	N-acetyl-γ-calicheamicin	2–3	2000 2017	newly-diagnosed CD33 (+) AML .
Brentuximab vedotin (Seagen)	Adcetris®	CD30	mc-VC-PABC	MMAE	4	2011	R/R CD30 (+) HL and systemic ALCL; in combination with chemotherapy including the treatment of certain types of PTCL and previously untreated stage III or IV cHL.
Ado-trastuzumab emtansine (Roche)	Kadcyla®	HER2	SMCC	DM1	3.5	2013	adjuvant therapy with HER2 (+) early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment.
Inotuzumab ozogamicin (Pfizer)	Besponsa®	CD22	hydrazone	N-acetyl-γ-calicheamicin	5–7	2017	R/R B-cell precursor ALL.
Moxetumomab pasudotox (AstraZeneca)	Lumoxiti®	CD22	mc-VC-PABC	PE38	NA	2018	R/R Hairy cell lymphoma have previously failed to receive at least two systemic therapies (including purine nucleoside analogs).(out) capillary leaking, hemolytic uremic syndrome
Polatuzumab vedotin (Roche)	Polivy®	CD79B	mc-VC-PABC	MMAE	3.5	2019	in combination with bendamustine plus rituximab for the treatment with R/R DLBCL, who have received at least two prior therapies.
Enfortumab vedotin (Seagen)	Padcev®	Nectin-4	mc-VC-PABC	MMAE	3.8	2019	locally advanced or metastatic urothelial cancer who have previously received platinum chemotherapy and a PD-L1/PD-1 inhibitor

Drugs (Company)	Trade Names	Target antigens	Linkers	Payloads	Average DAR	FDA Approved	Approved indications
Fam-trastuzumab deruxtecan (Daiichi Sankyo)	Enhertu®	HER2	tetrapeptide	DXd	7–8	2019	Unresectable or metastatic HER2(+) breast cancer who have received >2 lines anti-HER2 based regimens in the metastatic setting Locally advanced or metastatic HER2-(+) gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.
Belantamab mafodotin (GSK)	Blenrep®	BCMA	mc	MMAF	4	2020	R/R MM who have received at least four treatments, including anti-CD38 monoclonal antibodies, proteasome inhibitors and immunomodulators
Sacituzumab govitecan (Immunomedics)	Trodelvy®	Trop-2	CL2A	SN38	7.6	2020	unresectable locally advanced or metastatic TNBC who have two or more prior systemic therapies, at least one of them for metastatic disease.
Cetuximab sarotalocan (Rakuten Medical)	Akalux®	EGFR	NA	IRDye700 DX	1.3–3.8	2020	unresectable locally advanced or recurrent HNSCC
Disitamab vedotin (RemeGen)	Aidixi®	HER2	mc-VC-PABC	MMAE	4	2021	locally advanced or metastatic gastric ca have received at > 2 types of systemic chemotherapy
Tisotumab vedotin (Genmab/Seagen)	Tivdak®	TF	mc-VC-PABC	MMAE	4	2021	recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, is the first and only approved TF-directed ADC
Loncastuximab tesirine (ADC	Zynlonta®	CD19	dipeptide	PBD dimer	2.3	2021	R/R large B-cell lymphoma after ≥2 lines of systemic therapy, including DLBCL not otherwise specified,

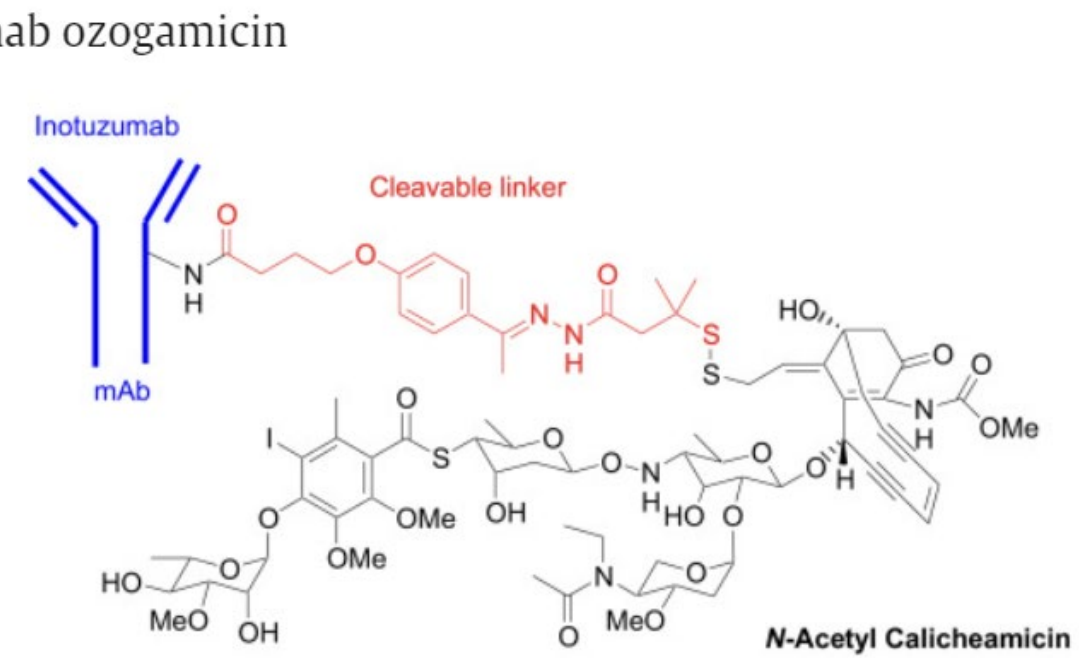
- CD1a, CD207: Langerhans cell histiocytosis cells.
- CD2, CD3, CD4, CD5, CD7, CD8: T cells.
- CD4: Helper T-cell marker
- CD8: Cytotoxic T-cell marker
- CD10: Early pre-B cells (immature B cells).
- CD11c, CD25, CD103, CD123: Hairy cell leukemia cells.
- CD13, CD33, CD117: Myeloid cells.
- CD14, CD64: Monocytic cells (AML-M4(+) and AML-M5(+).
- CD15: Reed-Sternberg cells, neutrophils.
- CD16, CD56: Natural killer cells.
- CD19, CD20, CD21, CD22 : B cells.
- CD23 and CD5: CLL /small lymphocytic lymphoma.
- CD23 (-) and CD5 (+) : Mantle cell lymphoma cells.
- CD30 and CD15: Reed-Sternberg cells.
- CD30 (+) and CD15 (-) : Anaplastic large cell lymphoma cells.
- CD31: Endothelial cells (positive in angiosarcoma), megakaryocytes and platelets.
- CD45: All leukocytes (except Reed-Sternberg cells!)
- CD33: Myeloid cells and precursors.
- CD34: Stem cells (also positive in angiosarcoma).
- CD41, CD61: Megakaryocytes and platelets (AML-M7(+).
- CD45 RO: Memory T cells.
- CD45 RA: Naive T cells.
- CD56: Natural Killer (NK) cells.
- CD56 Differentiate plasma cells in myeloma (CD56+) from reactive plasmacytosis or MGUS (CD56-).
- CD57 Marker of NK cells and neuroendocrine tumors.
- CD61: Platelets, megakaryocytes and platelet thrombi. Positive in TTP and AML M7.
- CD68: Histiocytes, malignant fibrous histiocytosis(+).
- CD71: Erythroid precursors.
- CD79a: General detection of B cells / B cell origin (with CD20).
- CD79b: B cells, plasma cells, and lymphoproliferative disorders.
- CD99: Ewings sarcoma cells.
- CD117: AML, mast cells, and GIST.
- CD200: CLL (+) and MCL (-).
- Myeloperoxidase (MPO): Myeloid leukemia and granulocytic sarcoma.

DNA cleavage by cross link

- Calicheamicin: a natural product derived from the bacterium Micromonospora echinospora.
  - Ozogamicin (modified Enediyne Core, Linker, Oligosaccharide)
- Tesirine : known as SG3199, is a pyrrolobenzodiazepine (PBD) dimer that binds to the DNA minor groove, causing DNA cross-linking,



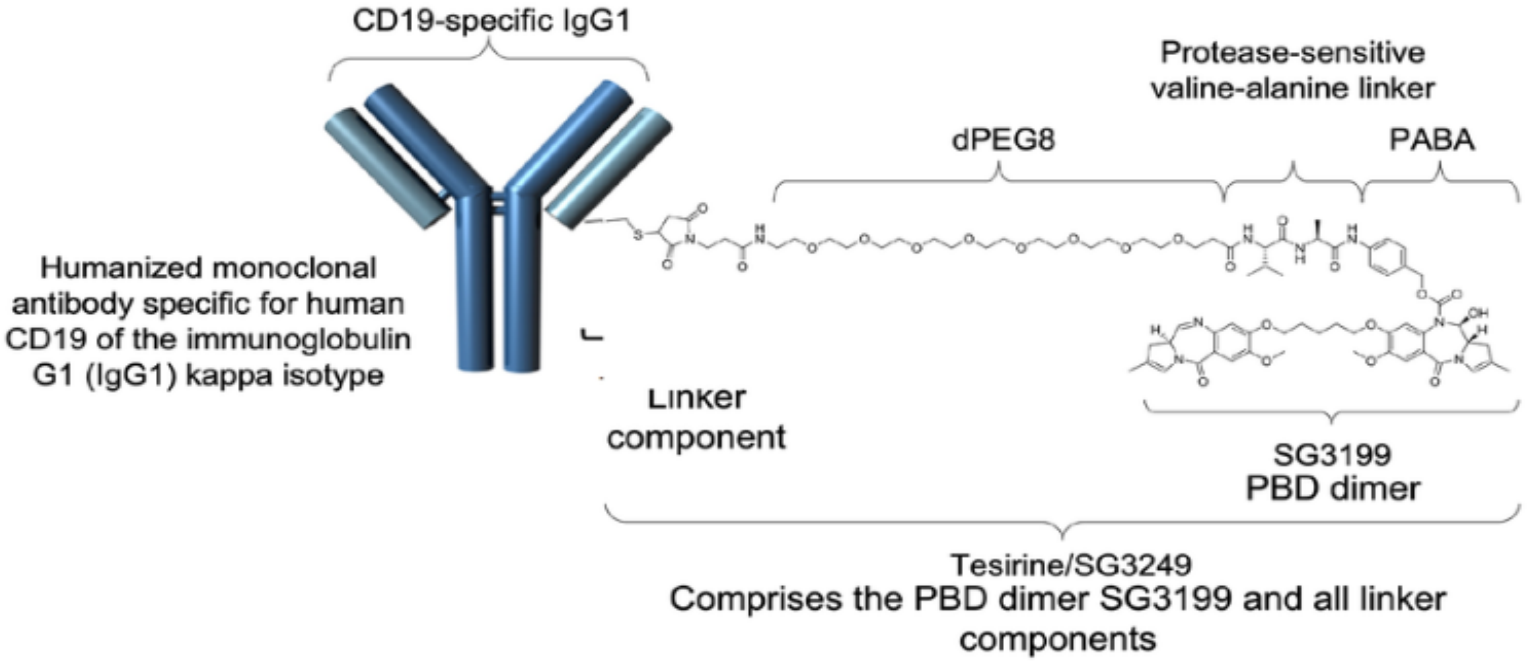
SG3199

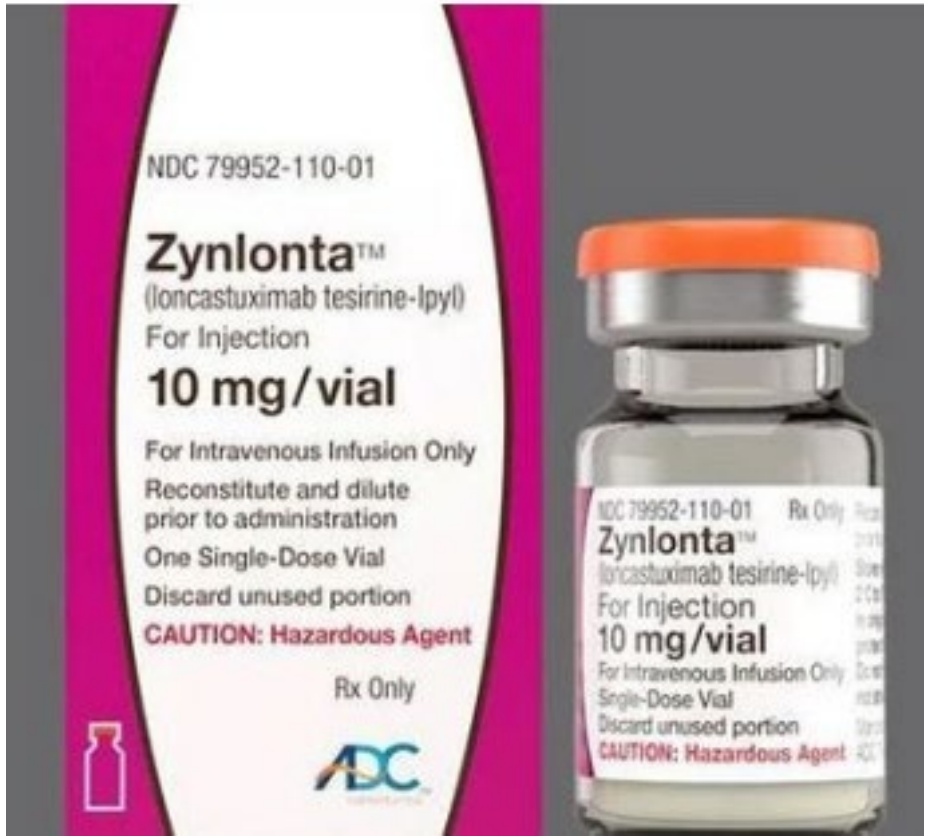


Parameter	Gemtuzumab Ozogamicin (CD33)	Inotuzumab Ozogamicin (CD22)	Loncastuximab Tesirine (CD19)
Indication **Hematologic Malignancies**	Acute Myeloid Leukemia (AML) greatest in favorable-risk or intermediate-risk cytogenetics, but not poor-risk features such as del(5), del(7), or complex karyotypes.	Relapsed or Refractory B-cell Precursor ALL 0.8 mg /m2 on day 1, 0.5 mg/m2 on days 8 and 15. Cycle 1 for 21 days and the subsequent cycles each for 28 days for 6 cycles	Relapsed or Refractory Large B-cell Lymphoma 0.15 mg/kg on day 1 Q 3 weeks for 2 cycles, followed by 0.075 mg/kg on day 1 Q 3 weeks 1 yr or until disease progression
Trial Comparative Drug	GO (3 mg/m2 [max 5 mg] on days 1, 4, 7) vs "7+3" cytarabine (200 mg/m2 for 7 days)+ daunorubicin (60 mg/m2 on days 1–3)	Vs standard-therapy group (as bridge to HSCT)	Single arm
Overall Response Rate (ORR)	CR : 81% vs 75%	CR : 80.7% vs 29.4% (P<0.001). MRD (0.01% marrow blasts) 78.4% vs. 28.1%, P<0.001	CR + PR : 48·3% (CR: 24.8%)
Progression-Free Survival (PFS)	40.8% vs. 17.1%	5 months vs 1.8 months (P<0.001)	~4.9 months (CR, 72.5% with 24-month)
Overall Survival (OS)	53.2% vs. 41.9% at 2 yrs	7.7 months vs 6.7 months (P=0.04)	~9.9 months (CR: 68.2% with 24 months
Adverse Effects	Hepatotoxicity, veno-occlusive disease, myelosuppression	Cytopenia, liver toxicity, veno-occlusive disease, infections	neutropenia (26%), thrombocytopenia (18%], and increased GGT
Source Journal	Lancet 2012 Apr 21-27; 379:1508.	NEJM 2016;375:740-753	Lancet Oncol 2021 Jun;22(6):790-800 Haematologica . 2024 Apr 1;109(4):1184-1193

Alkylation agent

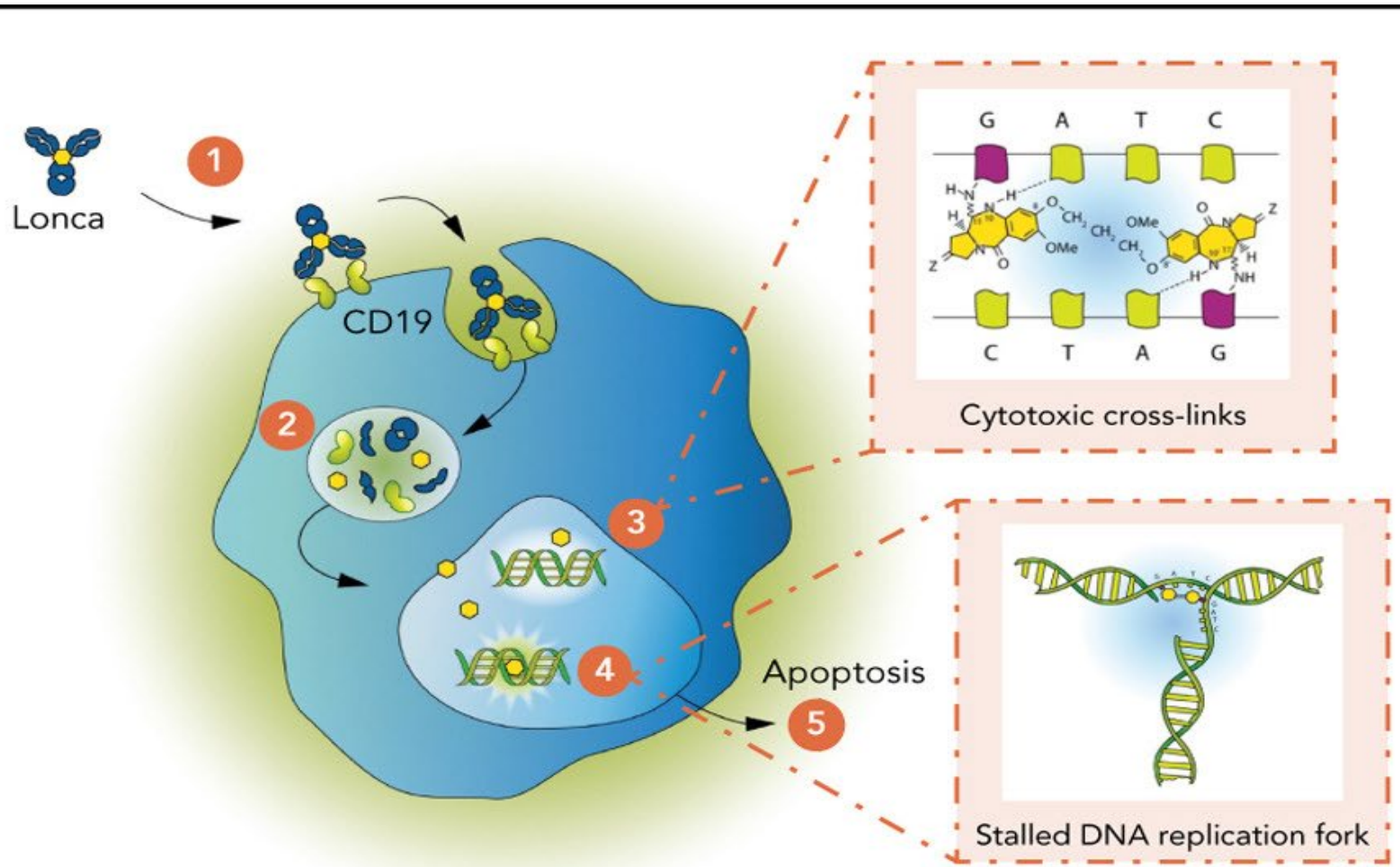
Tesirine : binding to the DNA minor groove, forming highly cytotoxic interstrand crosslinks : Loncastuximab Tesirine (PBD-ADCs is a pyrrolobenzodiazepine (PBD) dimer)





Alkylation agent

- Tesirine : binding to the DNA minor groove, forming highly cytotoxic interstrand crosslinks : **Loncastuximab Tesirine (PBD-ADCs** is a pyrrolobenzodiazepine (PBD) dimer)



Phase II study of loncastuximab tesirine in relapsed and refractory DLBCL

Patients:

- Relapsed and refractory DLBCL
- Median age 66 yrs
- Median number of prior therapies=3
- 20% primary refractory
- 10% double/triple hit DLBCL
- 20% transformed DLBCL
- 9% prior CAR T-cells

loncastuximab tesirine q3w 150 µg/Kg cycles 1–2, then q3w 75 µg/Kg

Outcomes (n=145)

Efficacy:

- ORR 48.3% (CR 24.1%)
- DOR 10.3 months
- CAR T-cells feasible after loncastuximab

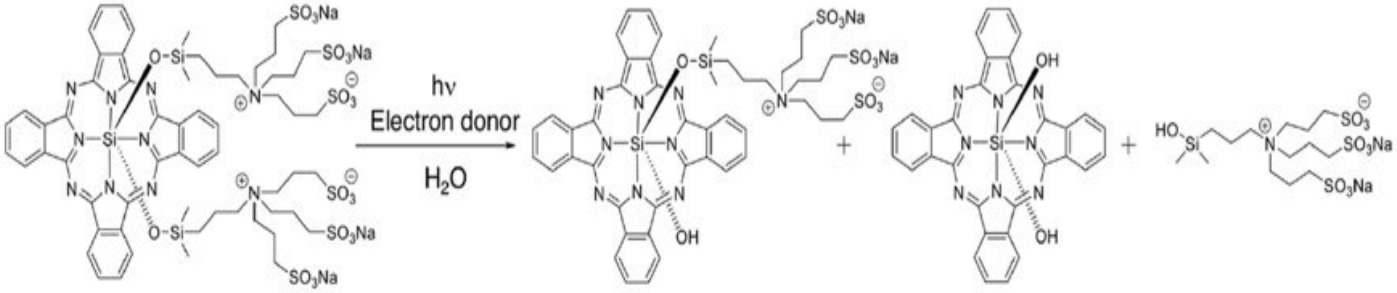
Safety:

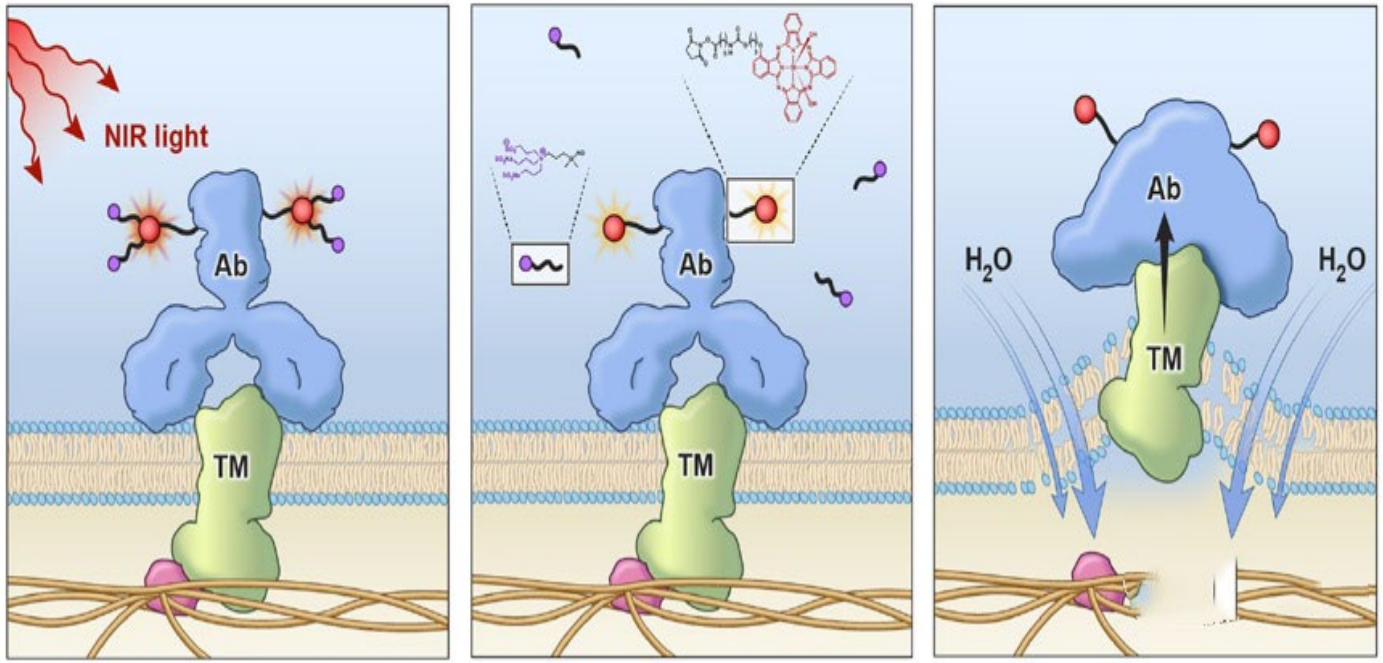
- 16% grade ≥3 elevation of GGT
- Skin rash/photosensitivity requiring/controlled with dexamethasone prophylaxis

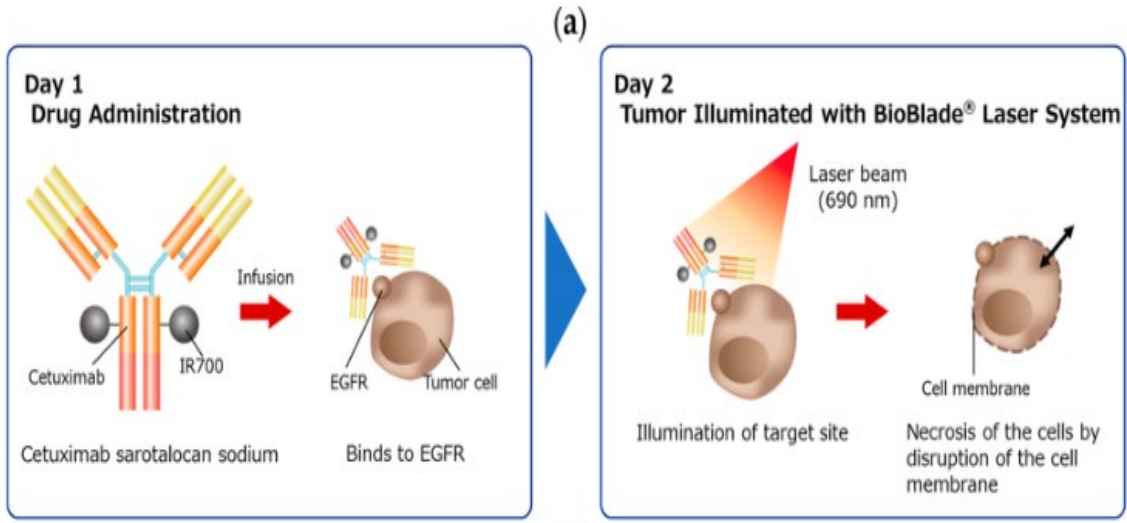
Blood. 2022 Jul 28;140(4):303-308.

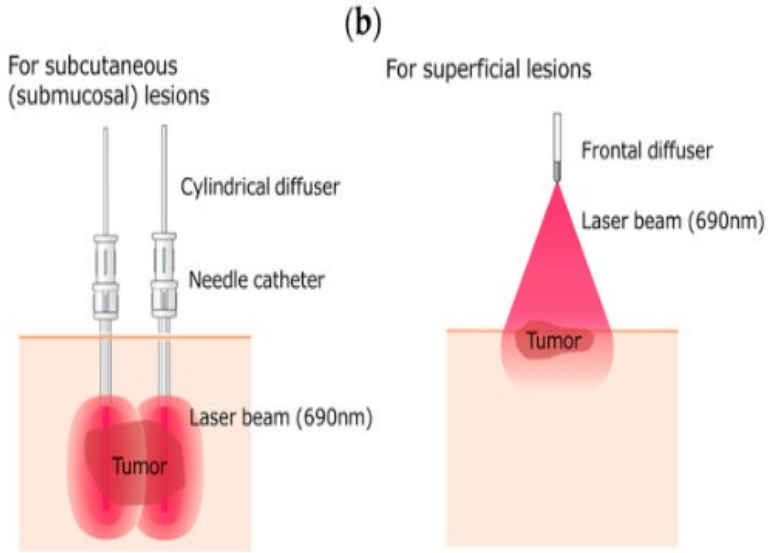
Cetuximab sarotalocan (Rakuten Medical)

Sarotalocan is a photosensitizer that accumulates in tumor cells. When exposed to specific wavelengths of light, sarotalocan becomes activated, leading to the generation of reactive oxygen species (ROS). These ROS damage cellular components, resulting in cell death.







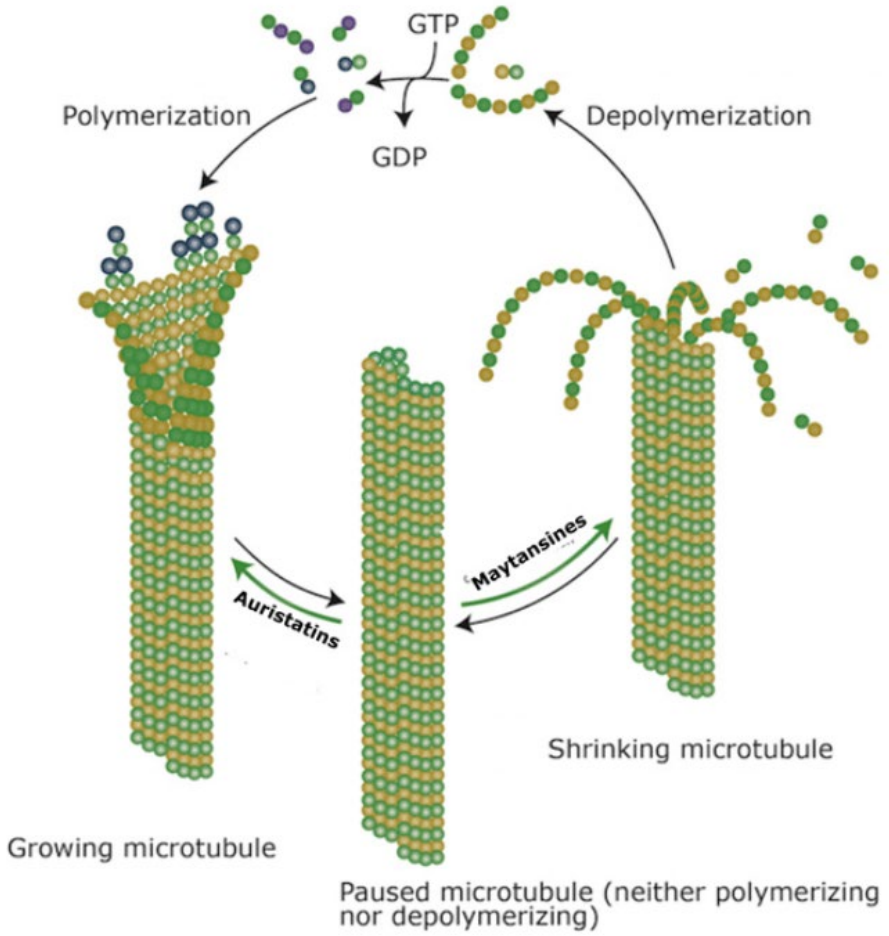


Category	Details
Type of Study	Phase 2a, Multicenter, Open-label
Indication	Loco regional rHNSCC
Name of Drug	RM-1929 PIT
Overall Response Rate (ORR)	50% (15/30)
Complete Response (CR)	16.7% (5/30)
Disease Control Rate (DCR)	86.7% (26/30)
Progression-Free Survival (PFS)	Median PFS data
Overall Survival (OS)	Median OS data forthcoming
Adverse Effects (AEs)	Most mild to moderate; 1 Grade 1 photosensitivity 96.7% and Grade 2 : 83.3% ; SAEs possibly/probably related to treatment include site/oral pain, tumor hemorrhage, and airway obstruction. 13 (43.3%)

May 2019Journal of Clinical Oncology 37(15_suppl):6014-6014

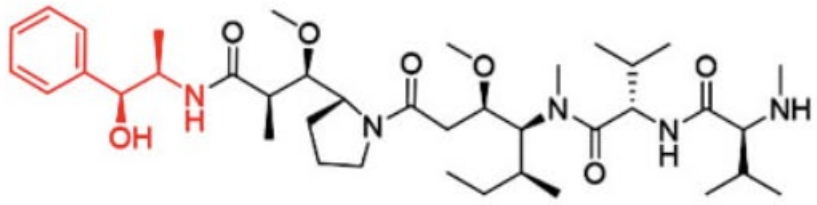
Microtubule inhibitors

- Auristatins primarily inhibit tubulin polymerization, preventing microtubule formation.
- In contrast, maytansinoids interfere with microtubule stability by promoting disassembly, disrupting already formed microtubules.

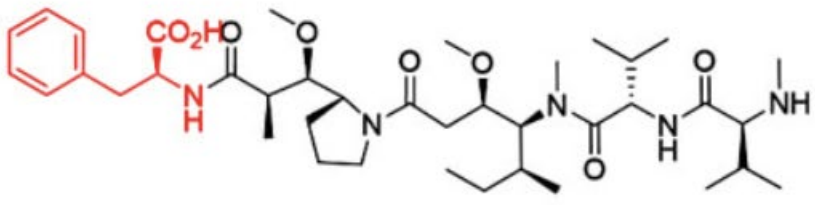


Microtubule inhibitor :

- Maytansinoids are derived from plant alkaloids (solid tumors)
  - DM1(Emtansine) : Trastuzumab Emtansine hydrophilic payloads diffuse out of cancer cells at a slower rate.
  - DM4 (Soravtansine) : Mirvetuximab soravtansine (targeting folate receptor α (FRα), is approved for the treatment of platinum-resistant ovarian cancer .) electrically neutral and lipophilic.
- Auristatins : marine peptides are synthetic derivatives (hematologic cancer)
  - Monomethyl auristatin E (MMAE, Vedotin) : can readily enter cells via passive diffusion
  - F (MMAF, mafodotin) : contains a charged carboxylic acid terminus, which limits its passive diffusion into surrounding cells

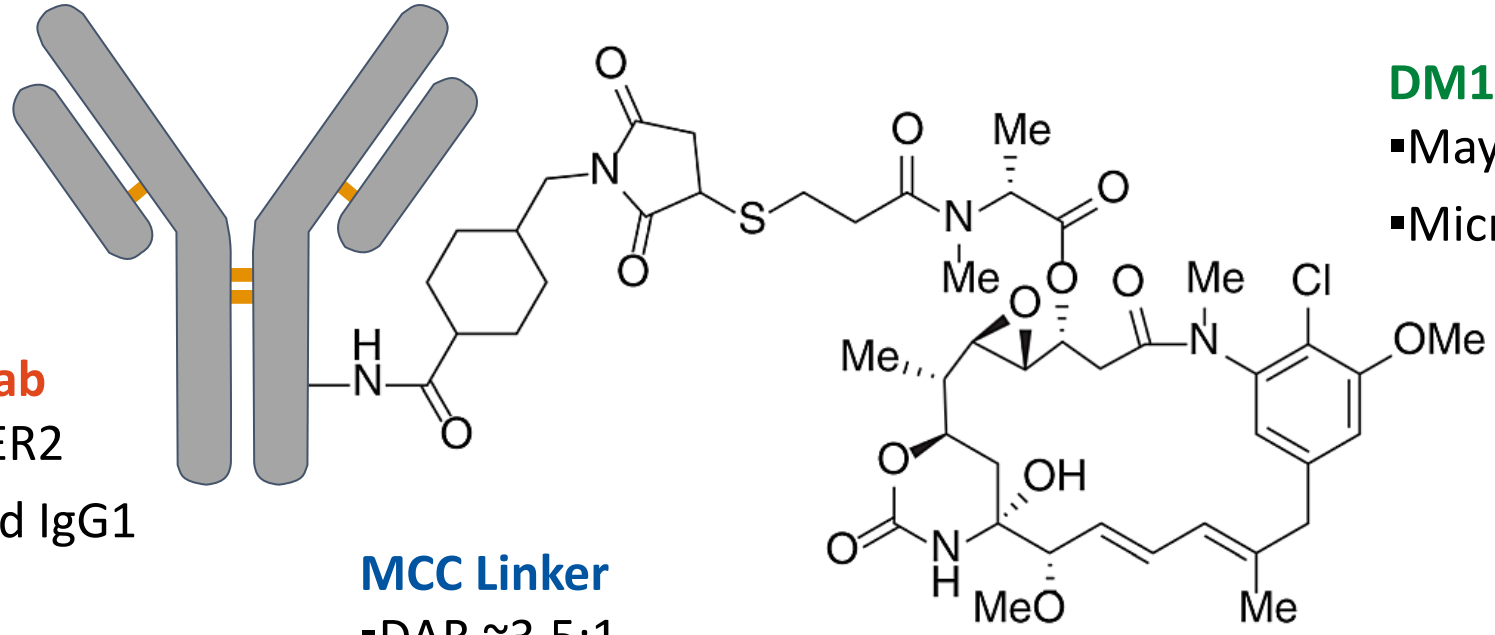


N-methyl auristatin E (MMAE)



N-methyl auristatin F (MMAF)

Trastuzumab Emtansine(T-DM1): HER2-Targeted ADC



Trastuzumab

- Targets HER2
- Humanized IgG1

MCC Linker

- DAR ~3.5:1
- Noncleavable thioether linker
- Lysosomal proteolytic degradation releases Lys-MCC-DM1 into the cell

DM1 Payload

- Maytansine derivative
- Microtubule inhibitor

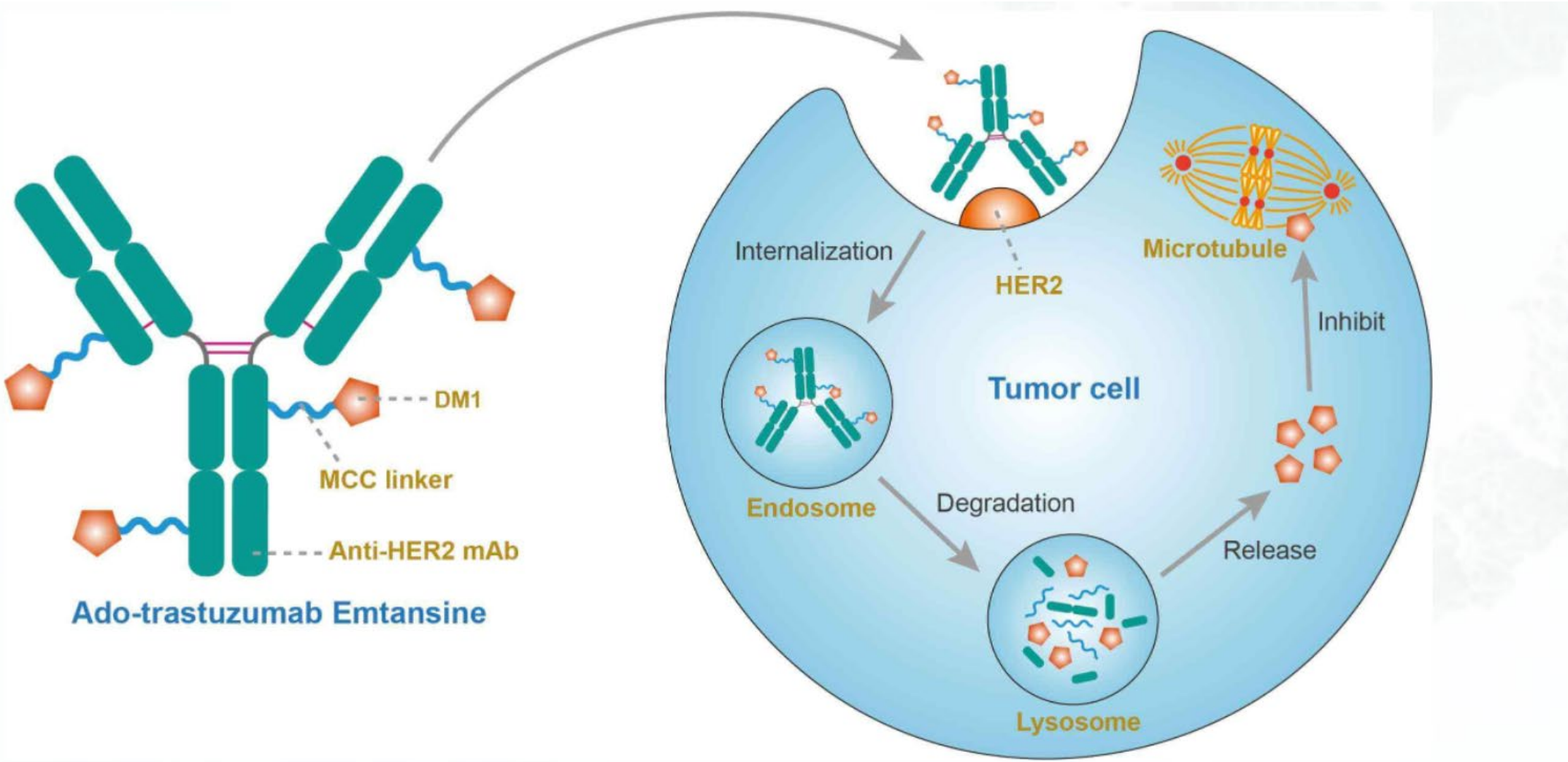


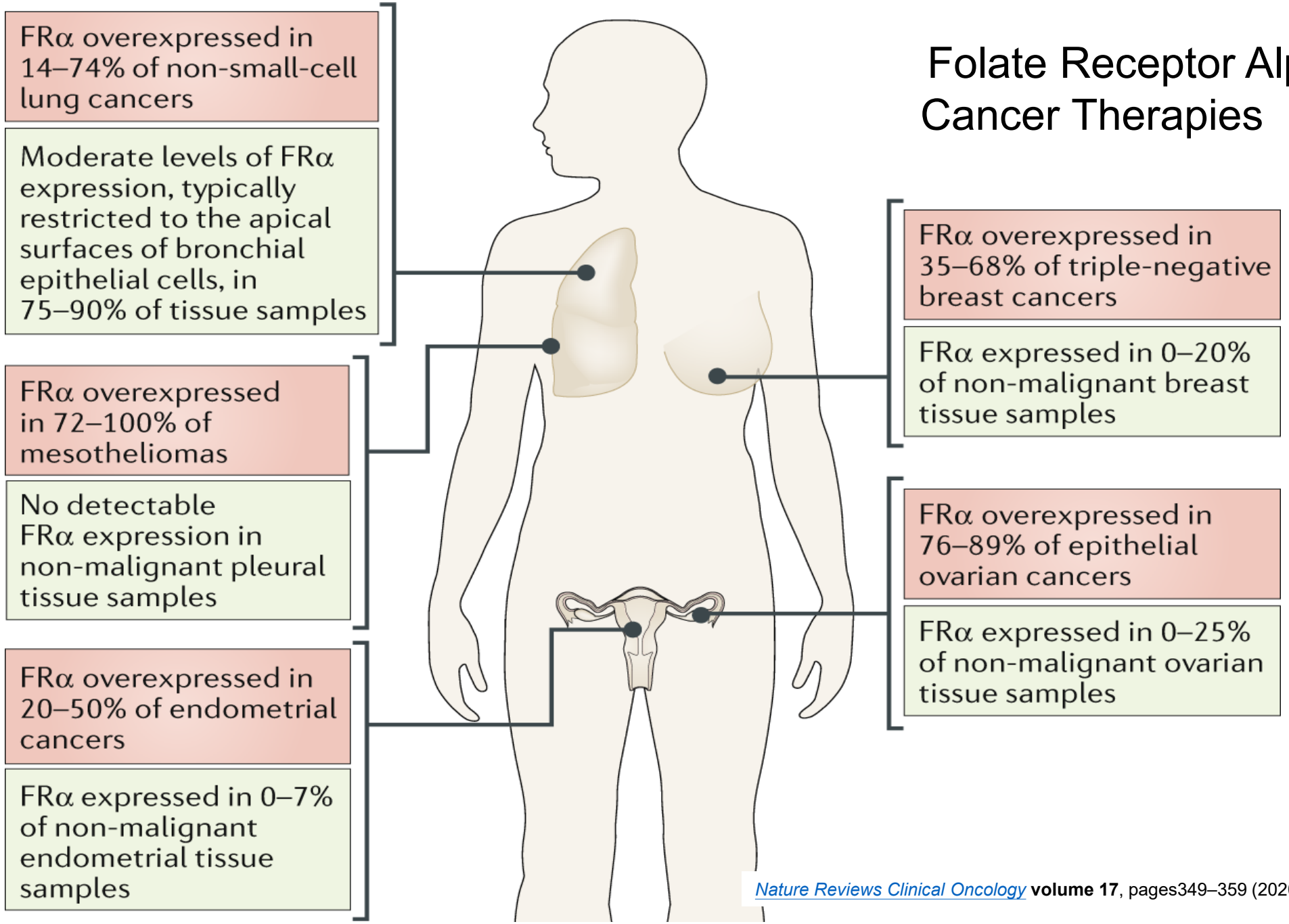
Fig.1 Mechanism of action of ado-trastuzumab emtansine

T-DM1: 2 FDA-Approved Indications

	HER2+ MBC	HER2+ EBC (Adjuvant)
Trial	EMILIA: T-DM1 vs lapatinib + capecitabine	KATHERINE: T-DM1 vs trastuzumab
ORR, %	44 vs 31	--
PFS or iDFS	**mPFS:** 9.6 vs 6.4 mo (HR: 0.65; 95% CI: 0.55-0.77; *P* <.001)	**7-yr iDFS:** 80.8% vs 67.1% (HR: 0.54; 95% CI: 0.44-0.66; nominal *P* <.0001)
OS	**mOS:** 30.9 vs 25.1 mo (HR: 0.68; 95% CI: 0.55-0.85; *P* <.001)	**7-yr OS:** 89.1% vs 84.4% (HR: 0.66; 95% CI: 0.51-0.87; *P* = .0027)
FDA approval	February 2013 (full)	May 2019 (full)
Indication	HER2+ MBC previously treated with trastuzumab and a taxane, separately or in combination, with either: ▪Prior tx for metastatic disease ▪Disease recurrence during/within 6 mo of completing adjuvant tx	Adjuvant treatment of HER2+ EBC with residual invasive disease after neoadjuvant taxane and trastuzumab-based tx

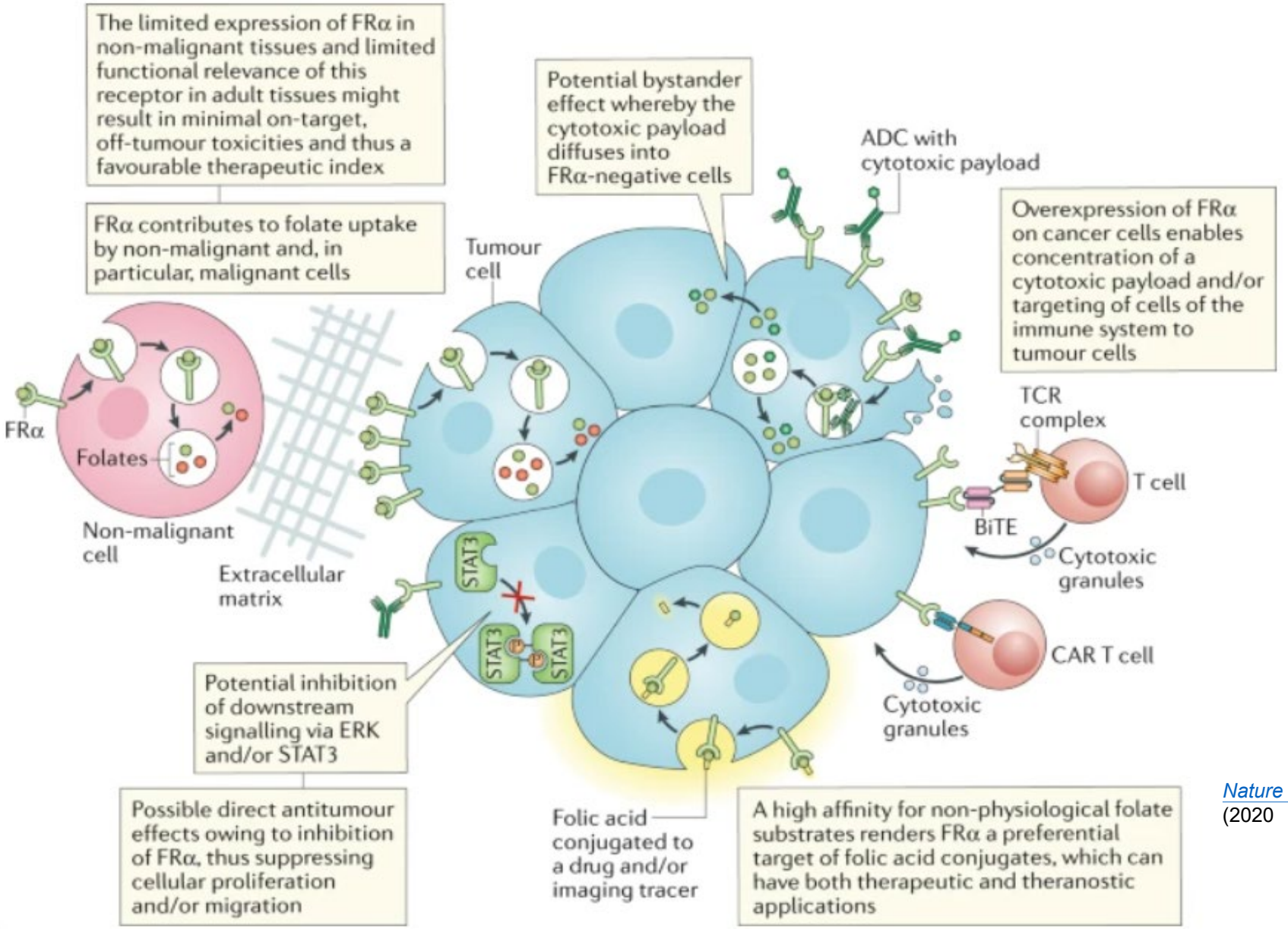
Trastuzumab emtansine PI. Verma. NEJM. 2012;367:1783. Loibl. SABCS 2023. Abstr GS03-12.
NCCN. Clinical practice guidelines in oncology: breast cancer. v.1.2024. nccn.org.

Folate Receptor Alpha for Anti-Cancer Therapies



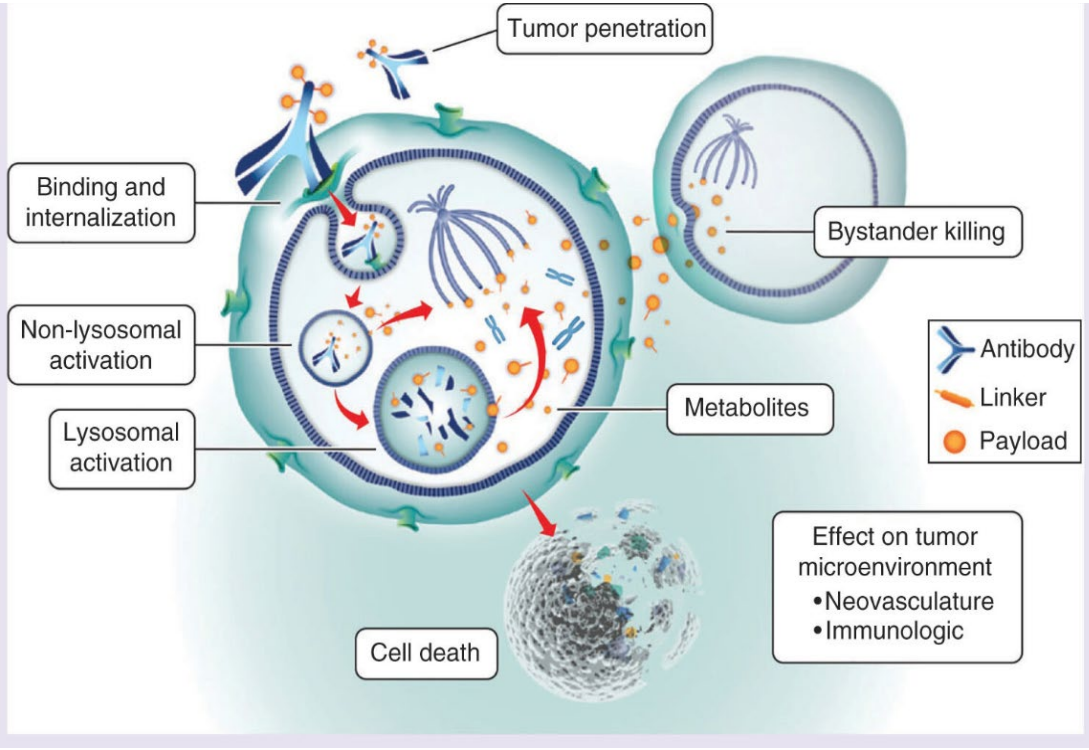
Nature Reviews Clinical Oncology **volume 17**, pages349–359 (2020

FRα as a treatment target in patients with cancer



Nature Reviews Clinical Oncology **volume 17**, pages349–359 (2020

Category (DM4)	**Mirvetuximab Soravtasine (DM4)**
Indication	phase III study : first-in-class ADC targeting folate receptor α (FRα), is approved for the treatment of platinum-resistant ovarian cancer. with ≤3 prior systemic therapies, including bevacizumab
Comparative Regimens (Pts: 453)	FRα tumor expression (≥75% of cells with ≥2+ staining intensity) MIRV (6 mg/kg of adjusted ideal body weight q 3 weeks) vs chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan).
Overall Response Rate (ORR)	42.3% (MIRV) vs 15.9% (chemotherapy) (P<0.001)
Median Progression-Free Survival (PFS)	5.62 months (MIRV) vs 3.98 months (chemotherapy) (P<0.001).
Overall Survival (OS)	16.46 months vs. 12.75 months (P=0.005)
Adverse Reactions	fewer adverse events of grade 3 or higher occurred with MIRV than with chemotherapy (41.7% vs. 54.1%),
Source	N Engl J Med 2023;389:2162-2174



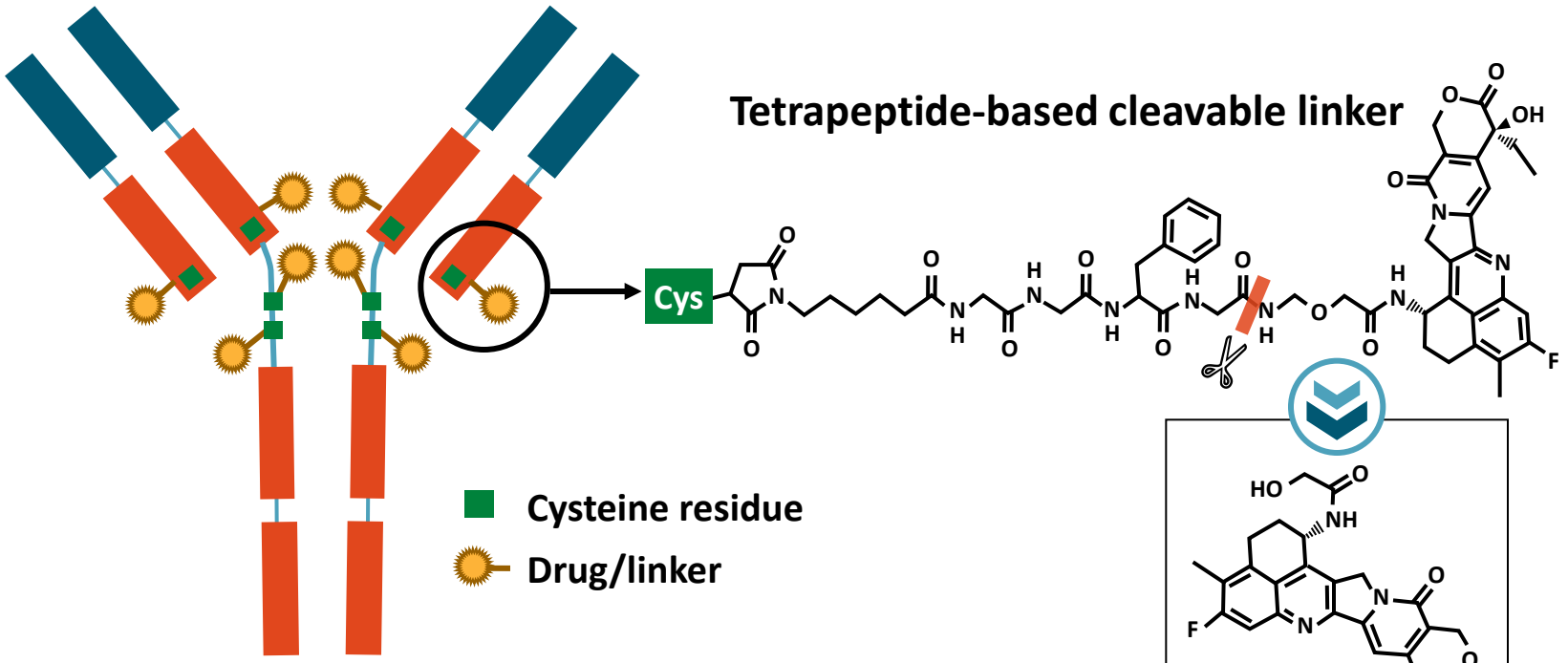
Future Oncology, *14*(17), 1669–1678.

Camptothecins (Topoisomerase 1 inhibitor)

- Trastuzumab Deruxtecan SN38
- Sacituzumab Govitecan

HER2-Targeted ADC: Trastuzumab Deruxtecan (Enhertu)

Humanized anti-HER2 IgG1 mAb with same AA sequence as trastuzumab



Tetrapeptide-based cleavable linker

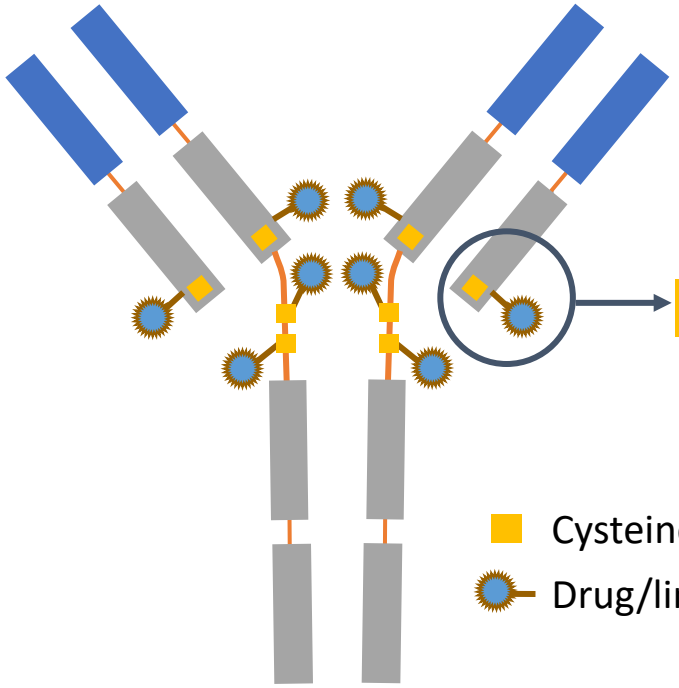
Topoisomerase I inhibitor (DXd) payload (exatecan derivative)

- High drug:antibody ratio: ~ 8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Trail. Pharmacol Ther. 2018;181:126. Ogitani. Cancer Sci. 2016;107:1039.

Slide credit: clinicaloptions.com

Trastuzumab Deruxtecan: HER2-Targeted ADC

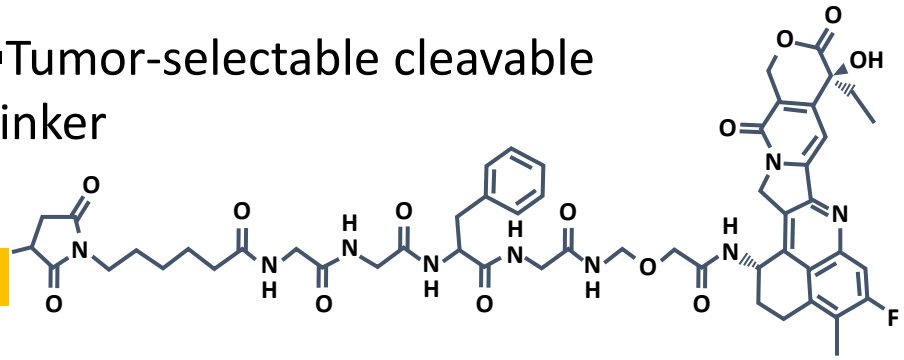


Anti-HER2 mAb

- Same AA sequence as trastuzumab
- Humanized IgG1

Tetrapeptide-Based Linker

- DAR ~8:1
- Tumor-selectable cleavable linker



DXd Payload

- Exatecan derivative
- Topoisomerase I inhibitor
- Membrane permeable
- Short systemic half life
- **Bystander killing effect**

FDA approved in advanced settings for:

- HER2+ MBC
- HER2-low MBC
- HER2+ gastric/GEJ adenocarcinoma
- *HER2*-mutated NSCLC

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173. Ogitani. Clin Cancer Res. 2016;22:5097.

T-DXd: 2 FDA-Approved Indications in Breast Cancer

	HER2+ MBC	HER2-Low MBC
Trial	DESTINY-Breast03: T-DXd vs T-DM1	DESTINY-Breast04: T-DXd vs physician's choice
ORR, %	79 vs 35	52.3 vs 16.3
mPFS, mo (HR; 95% CI)	28.8 vs 6.8 (0.33; 0.26-0.43; *P* <.0001)	10.1 vs 5.4 (0.51; *P* <.001)
mOS, mo (HR; 95% CI)	NR vs NR (0.64; 0.47-0.87; *P* = .0037)	23.4 vs 16.8 (0.64; 0.49-0.84; *P* = .001)
FDA approval	December 2019 (accelerated) May 2022 (full)	August 2022 (full)
Indication	Unresectable or metastatic HER2+ BC after a HER2-based regimen in either metastatic setting or neo/adjuvant setting with recurrence during/within 6 mo of completing tx	Unresectable or metastatic HER2-low BC after prior CT in metastatic setting or had recurrence during/within 6 mo of completing adjuvant CT

HER2+ = IHC3+ or IHC2+/ISH+
(In situ hybridization (ISH).

HER2 low = IHC 1+ or IHC 2+/ISH-

Trastuzumab deruxtecan PI. Hurvitz. Lancet. 2023;401:105. Modi. ASCO 2022. LBA3. Modi. NEJM. 2022;387:9.

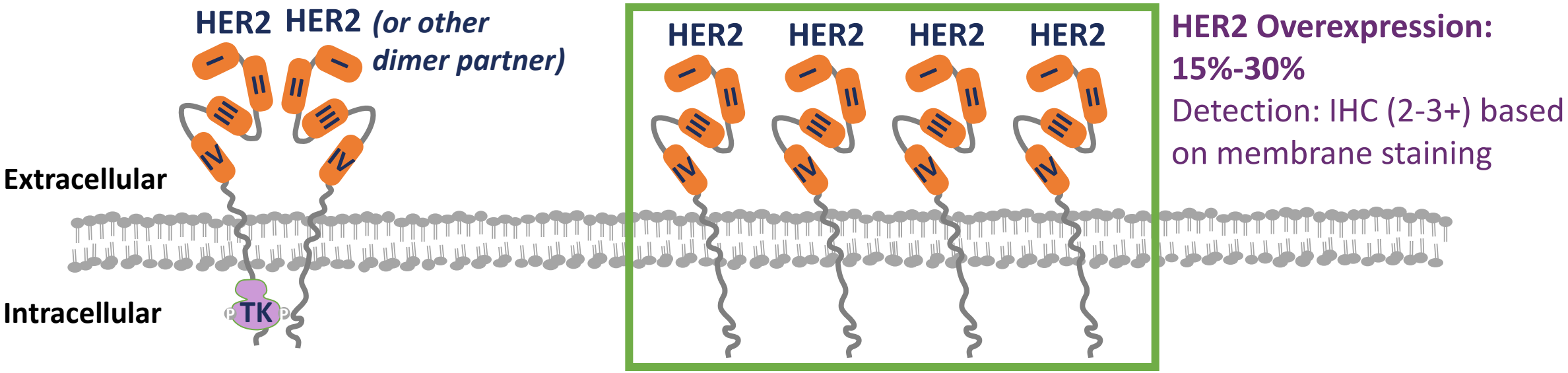
T-DXd: FDA-Approved Indication in HER2+ Gastric/GEJ Adenocarcinoma

- **HER2 positivity in gastric/GEJ adenocarcinoma** defined as:
  - *HER2* gene amplification and/or HER2 protein overexpression
  - IHC 3+ *or* IHC 2+/ISH+

	HER2+ Gastric/GEJ Adenocarcinoma
Trial	DESTINY-Gastric01: T-DXd vs physician's choice
ORR, %	51 vs 14
mPFS, mo (HR; 95% CI)	5.6 vs 3.5 (0.47; 0.31-0.71)
mOS, mo (HR; 95% CI)	12.5 vs 8.9 (0.60; 0.42-0.86)
FDA approval	January 2021 (full)
Indication	LA or metastatic HER2+ gastric/GEJ adenocarcinoma after trastuzumab-based regimen

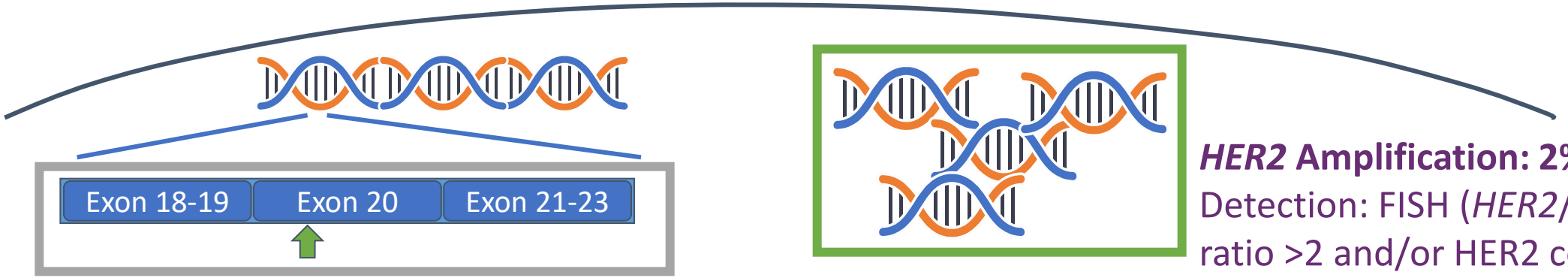
Trastuzumab deruxtecan PI. Shitara. Lancet Oncol. 2019;20:827. Shitara. NEJM. 2020;382:2419. Yamaguchi. ASCO GI 2022. Abstr 242.

HER2-Positive NSCLC



HER2 Overexpression: 15%-30%

Detection: IHC (2-3+) based on membrane staining



***HER2* Gene Mutation: 1%-3%**

Detection: NGS (activating *HER2*/*ERBB2* mutation)

***HER2* Amplification: 2%-5%**

Detection: FISH (*HER2*/*CEP17* ratio >2 and/or HER2 copy number >6)

Yu. Front Oncol. 2022;12:860313.

T-DXd: FDA-Approved Indication in *HER2*-Mutated NSCLC

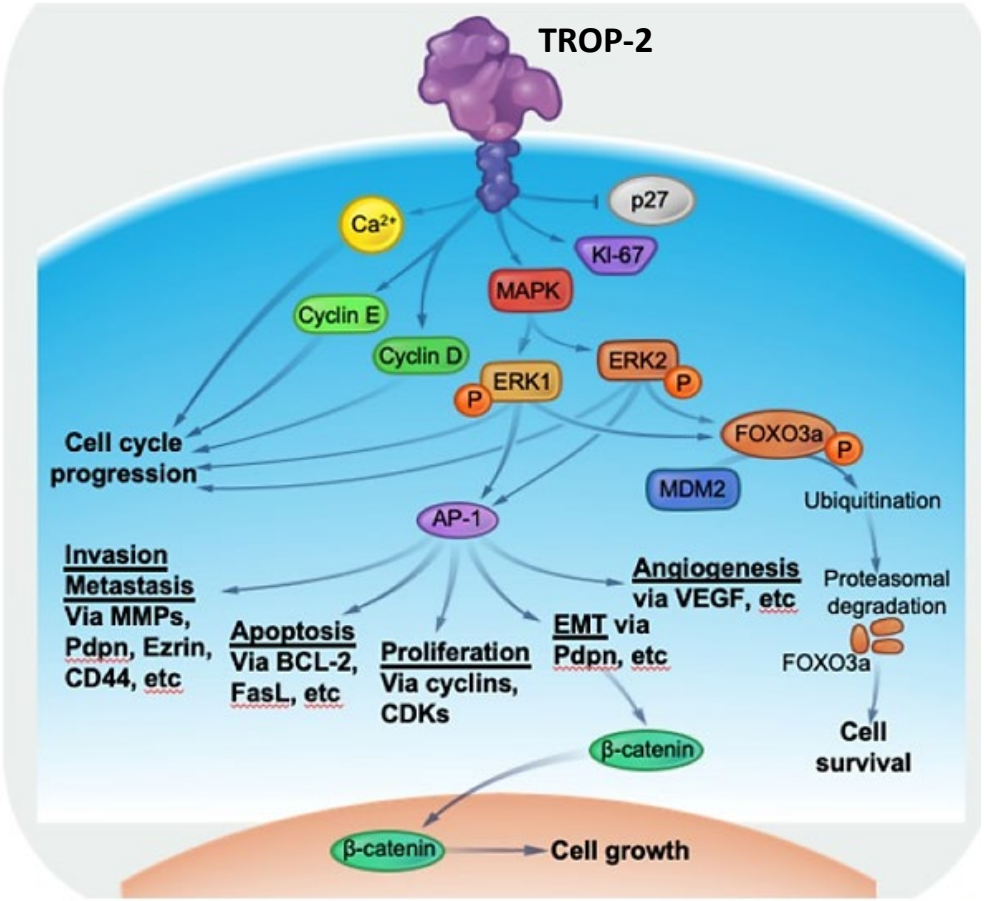
	***HER2*-Mutated NSCLC**
Trial	DESTINY-Lung02: T-DXd
ORR, %	49
mPFS, mo **(HR; 95% CI)**	9.9 --
mOS, mo **(HR; 95% CI)**	19.5 --
FDA approval	August 2022 (accelerated)
Indication	Unresectable or metastatic *HER2*-mutated NSCLC with a prior systemic tx

Trastuzumab deruxtecan PI. Goto. JCO. 2023;41:4852. Jänne. WCLC 2023. Abstr MA13.10.

TROP-2 as a Therapeutic Target

- TROP-2:
  - Epithelial adhesion molecule
  - Transmembrane glycoprotein
  - Regulates stem cell marker–associated cell regeneration
- TROP-2 is overexpressed in solid tumors, including TNBC and NSCLC

TROP-2: Cell Signaling

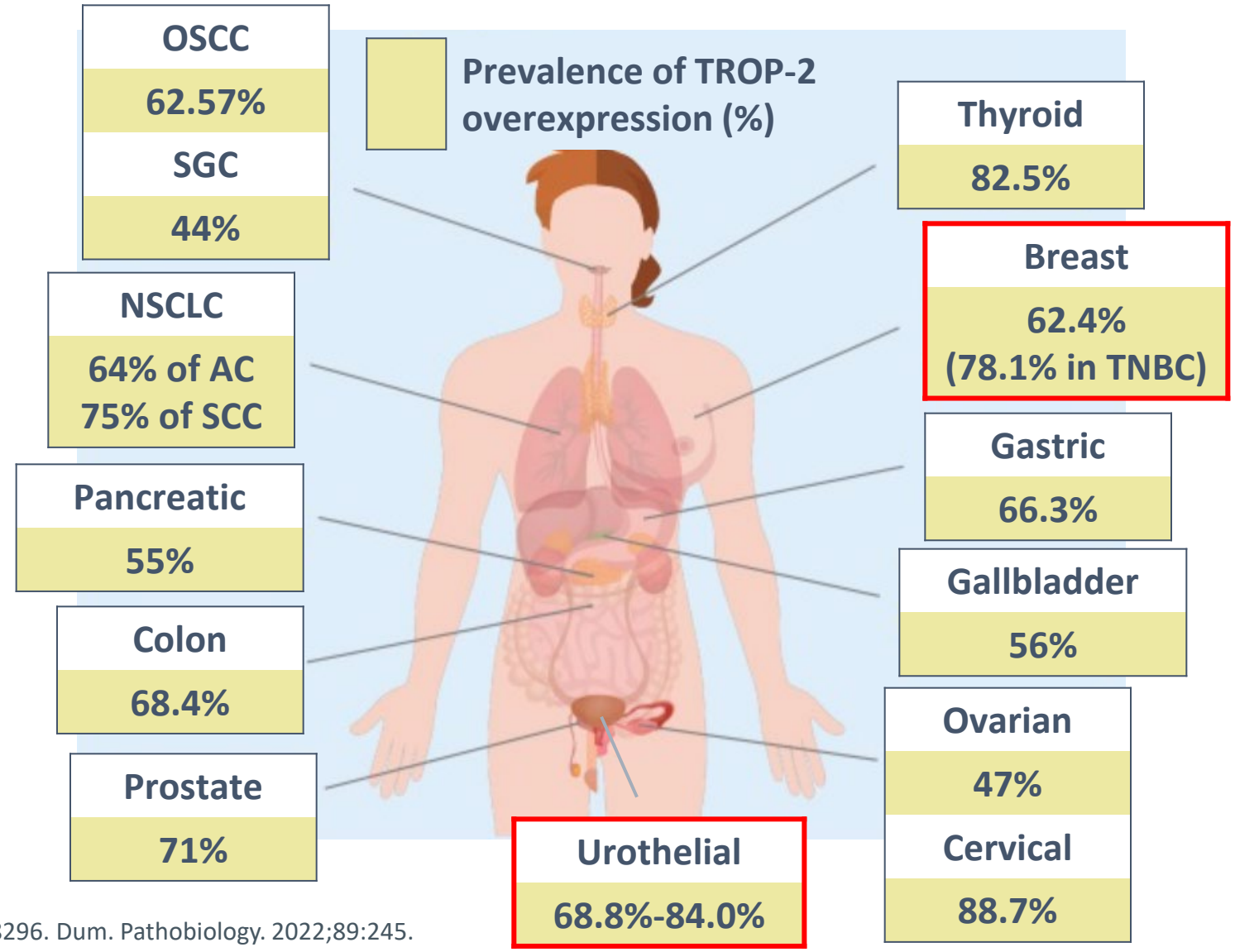


Jiang. Oncol Lett. 2013;6:375. Shvartsur. Genes Cancer. 2015;6:84.

TROP-2 Overexpression Across Tumor Types

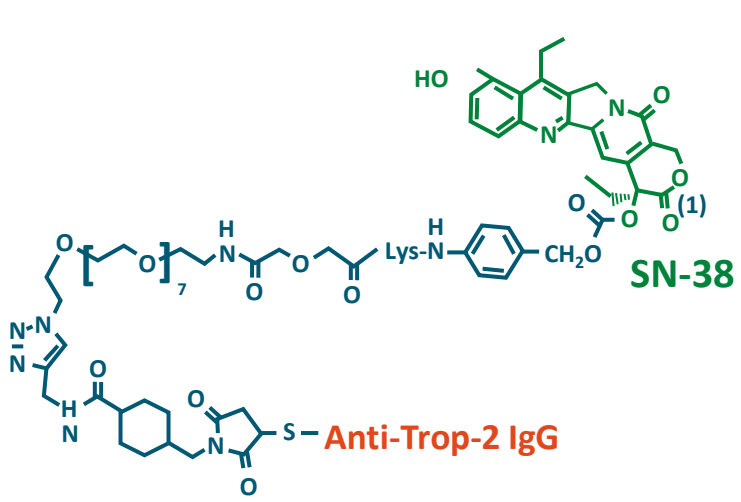
Oral squamous cell carcinoma (OSCC)

Salivary gland carcinomas (SGCs)



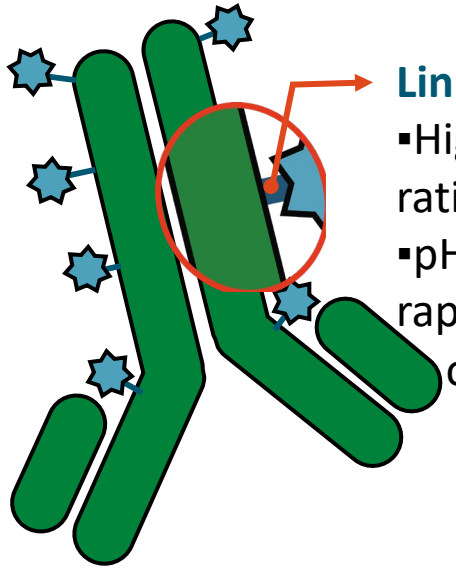
Liu. Pharmacol Ther. 2022;239:108296. Dum. Pathobiology. 2022;89:245.

Sacituzumab Govitecan (IMMU-132): Trop-2–Targeted Antibody-Drug Conjugate



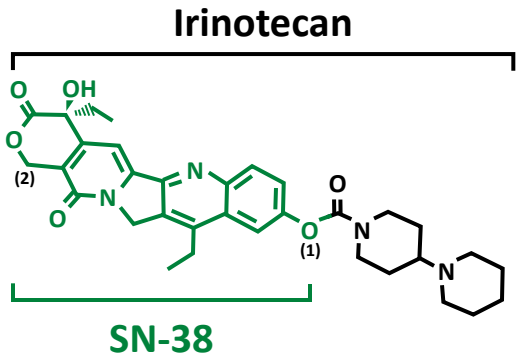
SN-38 Payload
- Targets 136-fold more than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor

Humanized RS7 Antibody
- Targets Trop-2, an antigen expressed in many epithelial cancers, including mTNBC (88%)
- Antibody type: h-IgG1



Linker for SN-38
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload or inside tumor

Irinotecan (Topoisomerase Inhibitor)



Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti–Trop-2 antibody, diffuses into neighboring Trop-2–negative cells

Khoury. ASCO 2019. Abstr e14651. Bardia. JCO. 2017;35:2141.

Slide credit: clinicaloptions.com

Sacituzumab Govitecan: 3 FDA-Approved Indications

	TNBC	HR+/HER2- BC	Urothelial Cancer
Trial	ASCENT: SG vs TPC	TROPiCS-02: SG vs CT	TROPHY-U-01 Cohort 1: SG
ORR, %	31 vs 5	21 vs 14	28
mPFS, mo (HR; 95% CI)	5.6 vs 1.7 (0.39; 0.31-0.49; *P* <.0001)	5.5 vs 4.0 (0.65; 0.53-0.81; nominal *P* = .0001)	5.4 --
mOS, mo (HR; 95% CI)	12.1 vs 6.7 (0.48; 0.39-0.59; *P* <.0001)	14.5 vs 11.2 (0.79; 0.65-0.95; nominal *P* = .0133)	10.9 --
FDA approval	April 2020 (accelerated) April 2021 (full)	February 2023 (full)	April 2021 (accelerated)
Indication	Unresectable LA or metastatic TNBC after ≥2 prior systemic tx (≥1 for metastatic disease)	Unresectable LA or metastatic HR+/HER2- BC after endocrine-based tx and ≥2 additional systemic tx in metastatic setting	LA or metastatic urothelial cancer after platinum-containing CT and PD-1/PD-L1 inhibitor

Sacituzumab govitecan PI. Bardia. ASCO 2022. Abstr 1071. Bardia. NEJM. 2021;384:1529.
Tolaney. ASCO 2023. Abstr 1003. Tagawa. ASCO GU 2023. Abstr 526. TPC: treatment of physician's choice

Premedication for Approved ADCs

Premedication Consideration	T-DM1	T-DXd	Sacituzumab Govitecan
Infusion reactions	▪ None recommended	▪ None recommended	▪ Antipyretics, H_1 and H_2 blockers ▪ Consider corticosteroids for those with prior infusion reactions
Chemotherapy-induced nausea and vomiting	▪ None recommended	▪ 3-drug combination regimen (dexamethasone + 5-HT_3 receptor antagonist + NK1 receptor antagonist)	▪ 2- to 3-drug combination regimen (eg, dexamethasone + either 5-HT_3 or NK1 receptor antagonist)

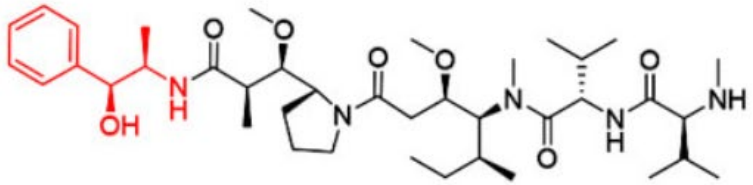
Trastuzumab emtansine PI. Trastuzumab deruxtecan PI. Sacituzumab govitecan PI.

Administration Considerations for Approved ADCs

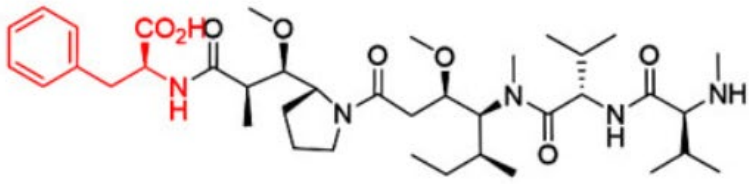
	T-DM1	T-DXd	Sacituzumab Govitecan
Preparation and infusion	▪ Diluent: normal saline ▪ 0.20- or 0.22-micron PES filter ▪ First infusion: administer over 90 min ▪ Subsequent infusions: administer over 30 min if prior infusions well tolerated	▪ Diluent: 5% dextrose ▪ 0.20- or 0.22-micron PES or PS filter ▪ Protect infusion bag from light ▪ First infusion: administer over 90 min ▪ Subsequent infusions: administer over 30 min if prior infusions well tolerated	▪ Diluent: normal saline ▪ Protect infusion bag from light ▪ First infusion: administer over 3 hr ▪ Subsequent infusions: 1-2 hr if prior infusions well tolerated ▪ Observe during infusion for signs or symptoms of IRRs
Post-infusion monitoring	▪ First infusion: observe for ≥90 min for fever, chills, or other IRRs ▪ Subsequent infusions: observe for ≥30 min	▪ None required	▪ Any infusion: observe for ≥30 min

Trastuzumab emtansine PI. Trastuzumab deruxtecan PI. Sacituzumab govitecan PI.

Microtubule inhibitors



N-methyl auristatin E (MMAE)

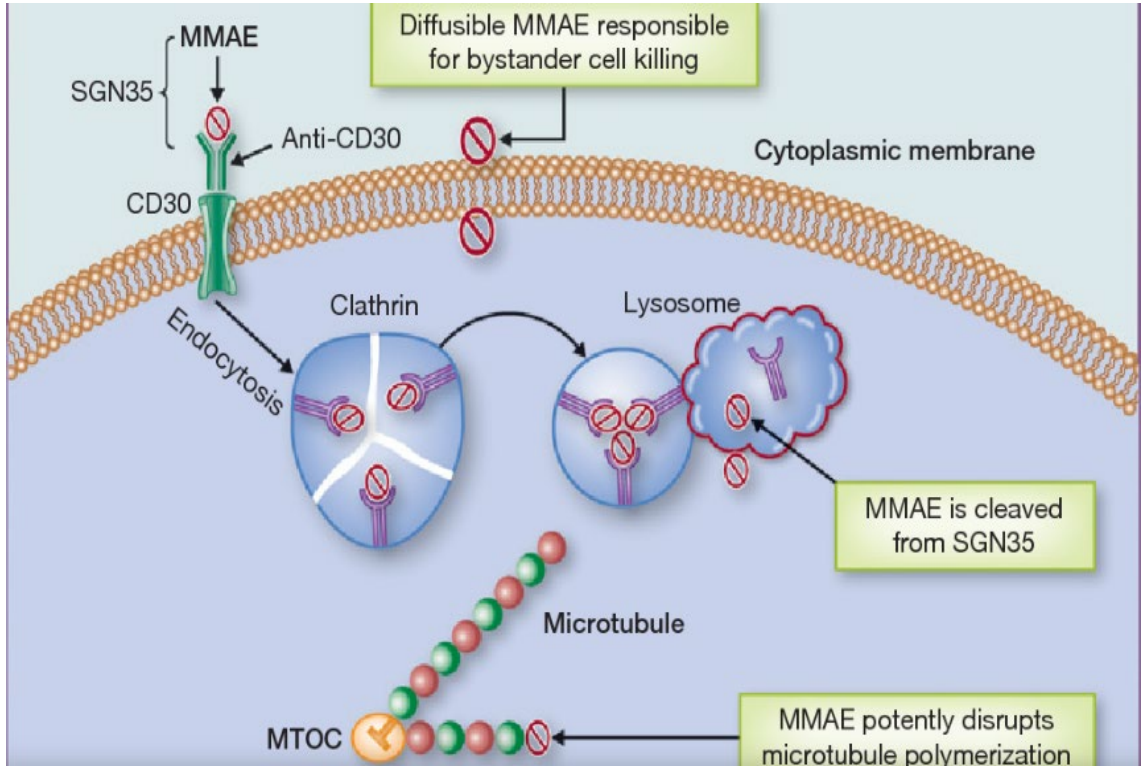


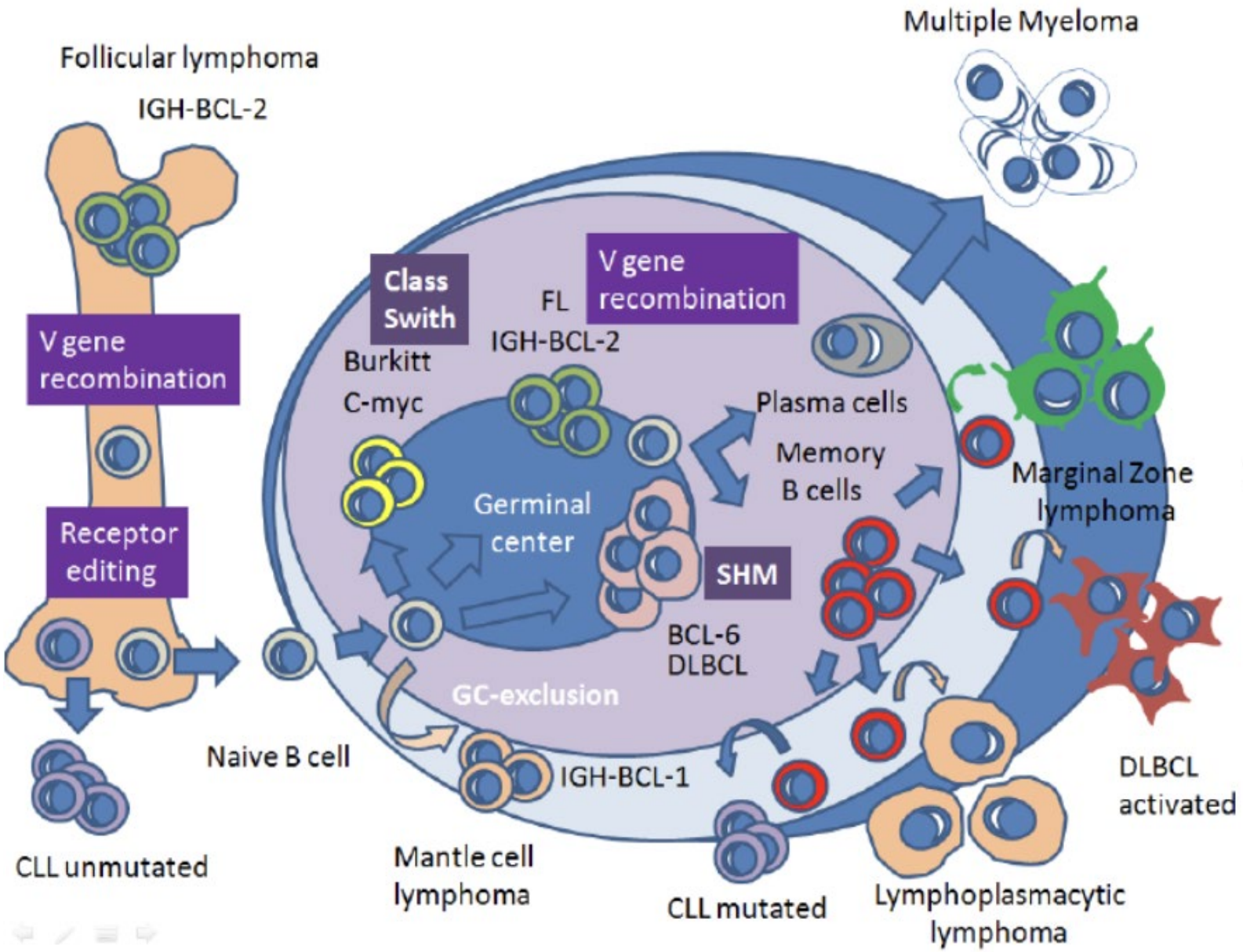
N-methyl auristatin F (MMAF)

- Auristatins : marine peptides are synthetic derivatives
  - Monomethyl auristatin E (MMAE, Vedotin) : can readily enter cells via passive diffusion : Brentuximab Vedotin , Polatuzumab vedotin (Roche)
  - Monomethyl auristatin F (MMAF, mafodotin) : contains a charged carboxylic acid terminus, which limits its passive diffusion into surrounding cells : Belantamab mafodotin (GSK, withdrawal)
- Maytansinoids are derived from plant alkaloids
  - DM1(Emtansine) : Trastuzumab Emtansine
  - DM4 (Soravtansine) : Mirvetuximab soravtansine

ADC : payload with vedotin

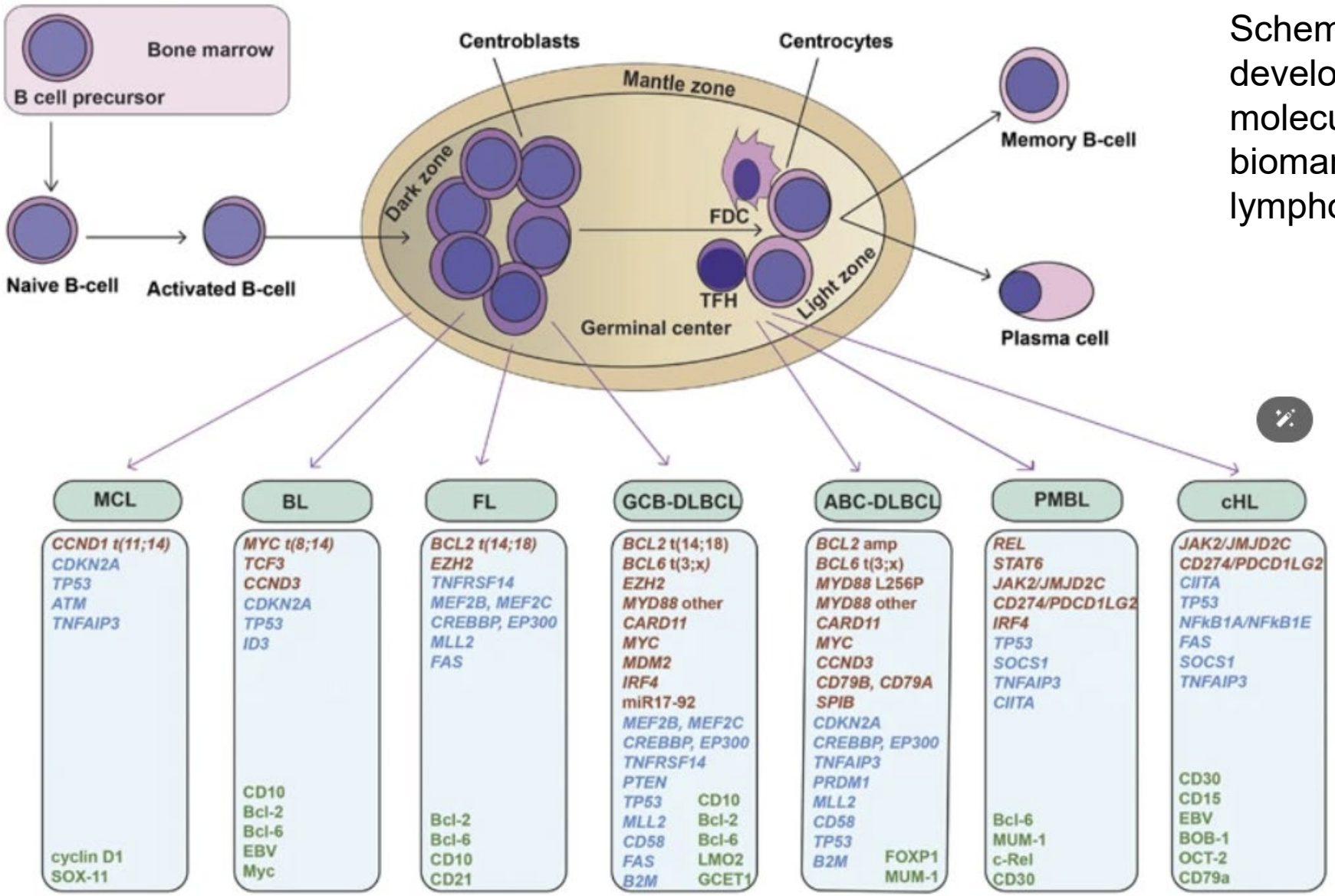
- Brentuximab Vedotin (Adcetris): Target: CD30
  - Uses: Primarily used for Hodgkin lymphoma and systemic anaplastic large cell lymphoma.
- Polatuzumab Vedotin (Polivy): Target: CD79b
  - Use: Used in combination with other chemotherapies for the treatment of diffuse large B-cell lymphoma (DLBCL).
- Tisotumab Vedotin (Tissue factor) : Target : TF (tissue factor)
  - Recurrent or metastatic cervical cancer
- Enfortumab Vedotin (Padcev): Target: Nectin-4
  - Bladder cancer and other urothelial cancers
- Belantamab mafodotin : target (B-Cell Maturation antigen)





Origin of Non Hodgkin B cell lymphomas.

Pre-germinal center : CLL unmutated and mantle cell lymphoma and some follicular lymphomas.
Germinal center : variable region gene recombination (BCL-2-IgH) in follicular lymphoma, somatic hypermutation (BCL-6) in diffuse large B cell lymphoma, or class switching in c-myc sporadic Burkitt´s lymphoma.
Post-germinal center B cell lymphomas : marginal zone lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia and plasmacytoma and are derived from memory B cells and plasma cells.
SHM : Aberrant somatic hypermutation



Schematic representation of B-cell development and summary of molecular and immunophenotypic biomarkers in B-cell non-Hodgkin lymphomas and Hodgkin lymphomas.

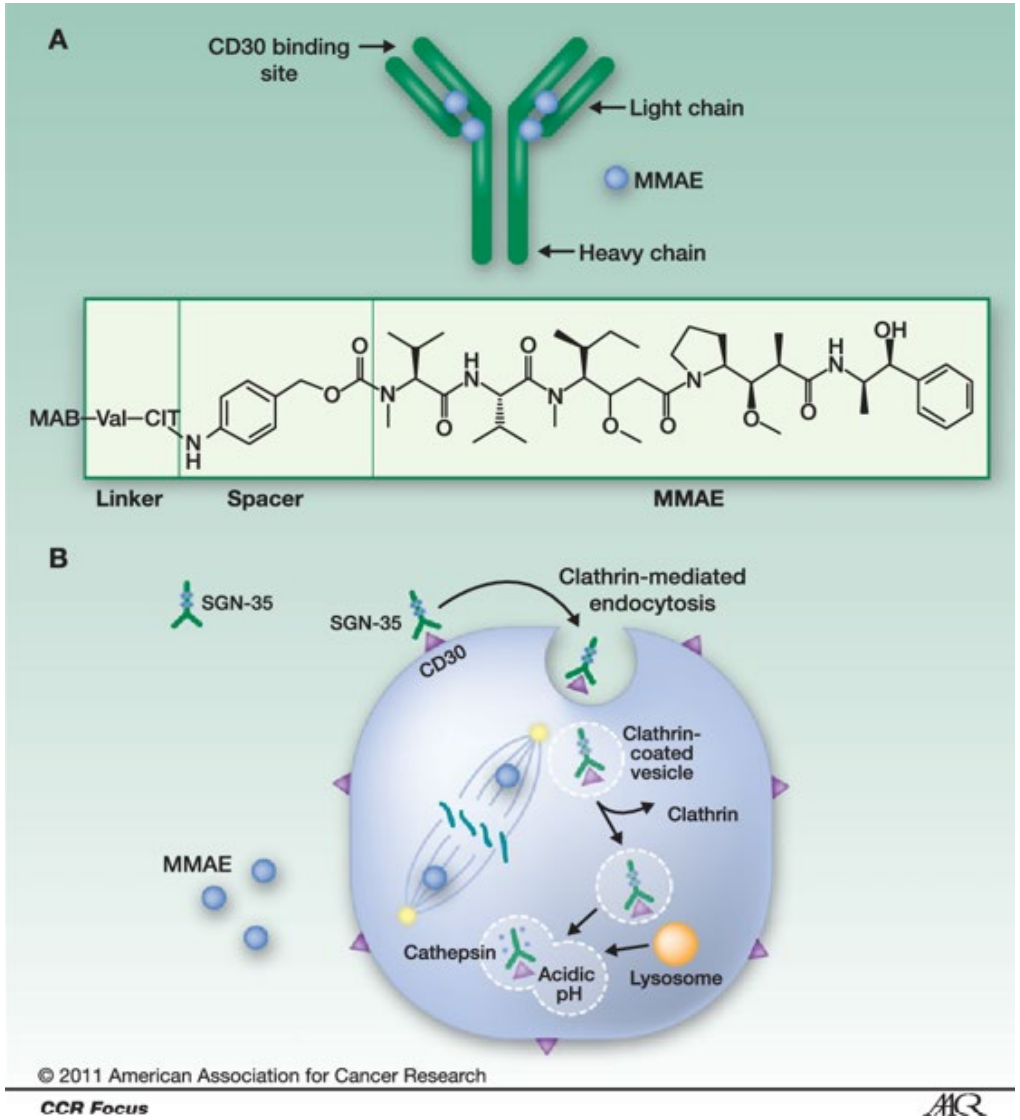
ABC-DLBCL : activated B-cell-DLBCL;
BL : Burkitt lymphoma;
cHL : classical Hodgkin lymphoma; FDC : follicular dendritic cell; FL : follicular lymphoma; GCB-DLBCL, GC B-cell-like diffuse large B-cell lymphoma;
MCL, mantle cell lymphoma;
PMBCL : primary mediastinal B-cell lymphoma;
TFH : T follicular helper cell.

Recurrent gain of function (red) and loss of function (blue) molecular biomarkers of common types of B-cell lymphoma and HLs are summarized. Immunohistochemical biomarkers (green) that are of diagnostic value in B-cell lymphomas are also shown.

Modern Pathology volume 29, pages1118–1142 (2016)

Brentuximab Vedotin (Adcetris): Target: CD30

- Study : ECHELON
  - AVD vs ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) : untreated advanced classical Hodgkin lymphoma.
  - Brentuximab Vedotin plus CHP (cyclophosphamide, doxorubicin, and prednisone) versus CHOP : untreated CD30-positive peripheral T-cell lymphoma (PTCL), including systemic anaplastic large cell lymphoma (sALCL).
- Study : ALCANZA
  - Brentuximab Vedotin versus physician‘s choice (methotrexate or bexarotene) : CD30 (+) cutaneous T-cell lymphoma (CTCL). CD30 (+) mycosis fungoides (MF) or primary cutaneous anaplastic large-cell lymphoma (C-ALCL).



Brentuximab Vedotin	SG035-0003 CD30	AETHERA CD30	ALCANZA CD 30
Indication	Relapsed or refractory Hodgkin lymphoma (HL) (post auto-SCT, phase 2)	HL patients at high risk of relapse post-auto-HSCT (phase 3) consolidation	brentuximab vedotin vs physician's choice in cutaneous T-cell lymphoma (phase 3)
Comparative Regimens	Single-arm study	Brentuximab Vedotin vs. Placebo	Brentuximab Vedotin vs vs physician's choice:
Overall Response Rate (ORR)	75%, CR : 34%		ORR; 54.7% vs 12.5% (P < .001); CR 17.2% vs 1.6% (P = .002)
Median Progression-Free Survival (PFS)	Median 5.6 months	42.9 months vs 24.1 months At 5 yrs : 59% vs 41%	16.7 months vs 3.5 months (P < .001)
Overall Survival (OS)	Durable CR: 2 years		3-y OS, 64.4 months vs 61.9 (HR for OS, P =0.31)
Adverse Reactions	Peripheral neuropathy, fatigue, nausea, neutropenia, diarrhea	Peripheral sensory neuropathy, neutropenia, upper respiratory tract infection	Peripheral sensory neuropathy, fatigue, nausea, diarrhea
Source	Younes, A., et al. J Clin Oncol. 2012. (Link)	Moskowitz, CH., et al. Lancet. 2015. (Link) Blood (2018) 132 (25): 2639–2642	Blood Adv . 2021 Dec 14;5(23):5098-5106

Brentuximab Vedotin	ECHELON-1 CD 30	ECHELON-2 CD 30
Indication	Previously untreated advanced III or IV classical Hodgkin's lymphoma	phase III study of brentuximab vedotin with chemotherapy for CD30-positive peripheral T-cell lymphoma
Comparative Regimens	Brentuximab Vedotin + AVD vs. ABVD	A+CHP vs CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) 6-8 cycles
Overall Response Rate (ORR)		59% vs 50%
Median Progression-Free Survival (PFS)	82.1% vs 77.2% (at 2 yrs) Brentuximab + AVD vs ABVD: longer	5-year PFS rates were 51.4% vs 43.0% (CHOP) (hazard ratio = 0.70),
Overall Survival (OS)	The 6-year overall survival 93.9% (A+AVD) vs 89.4% (ABVD)	5-year OS : 70.1% (A+CHP) vs 61.0%
Adverse Reactions	peripheral neuropathy, febrile neutropenia. fewer second cancers were reported with A+AVD	Peripheral neuropathy was resolved or improved in 72% of patients in the A+CHP arm and 78% in the CHOP arm.
Source	NEJM 2022;387:310-320 NEJM 2018;378:331-344	Ann Oncol . 2022 Mar;33(3):288-298.

Brentuximab Vedotin with Nivolumab was well-tolerated and showed durable remissions as initial salvage therapy in relapsed/refractory classic Hodgkin's Lymphoma

RELAPSED/REFRACTORY CLASSIC HODGKIN'S LYMPHOMA:
WHAT ARE THE EFFICACY AND SAFETY OUTCOMES WITH USING BRENTUXIMAB VEDOTIN WITH NIVOLUMAB IN FIRST SALVAGE THERAPY IN R/R cHL?

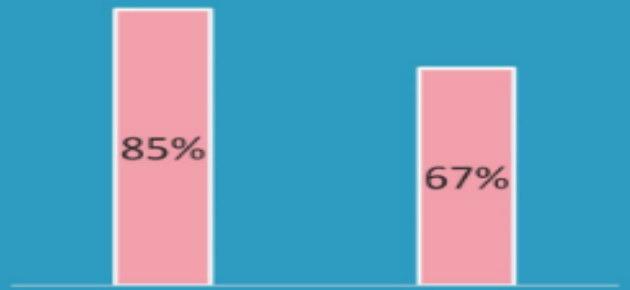
93 patients with r/r cHL

multi-centre, single-arm, phase 1-2 trial

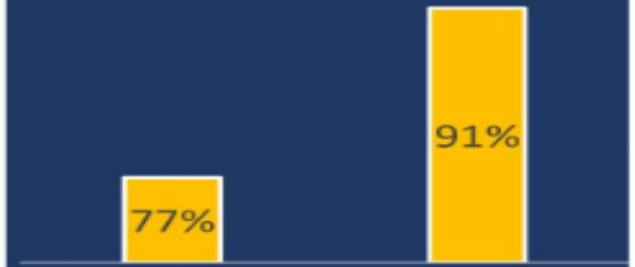
Parts 1 and 2:
staggered dosing of BV and Nivo in cycle 1, same-day dosing in cycles 2-4.

Median Follow-up
34.3 months

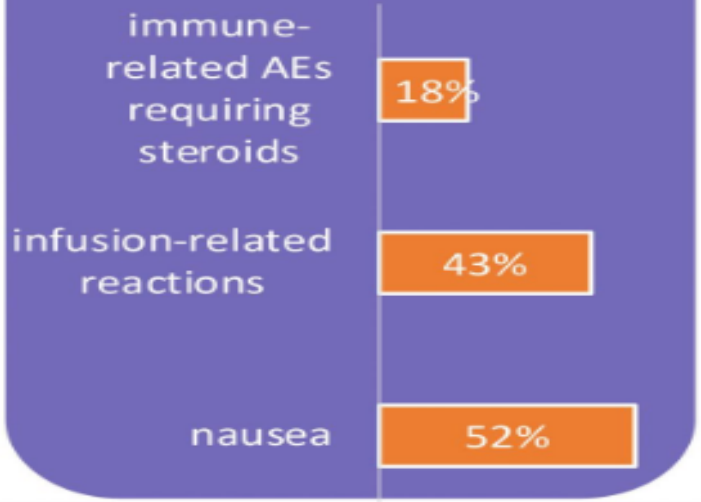
Response Rates



Estimated Progression-Free Survival rate at 3 years



Most common adverse events prior to ASCT



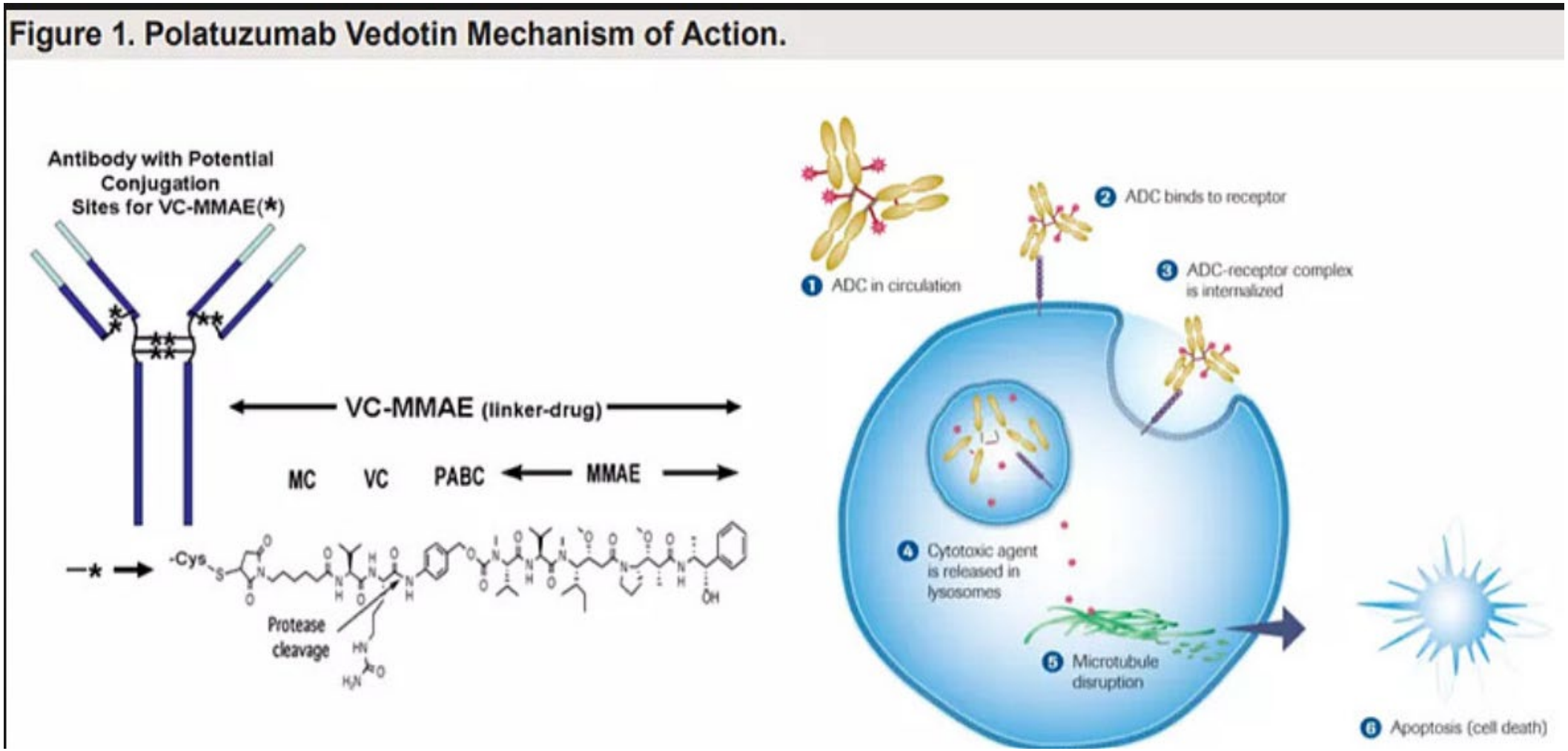
Longer-term follow-up shows combination therapy of brentuximab vedotin with nivolumab have durable efficacy, impressive progression-free survival, and do not add toxicity concerns as a first salvage regimen in relapsed/refractory classic Hodgkin's lymphoma, especially in patients who proceed directly to transplant.

ASCT = autologous stem cell transplantation, BV= brentuximab vedotin, Nivo = nivolumab

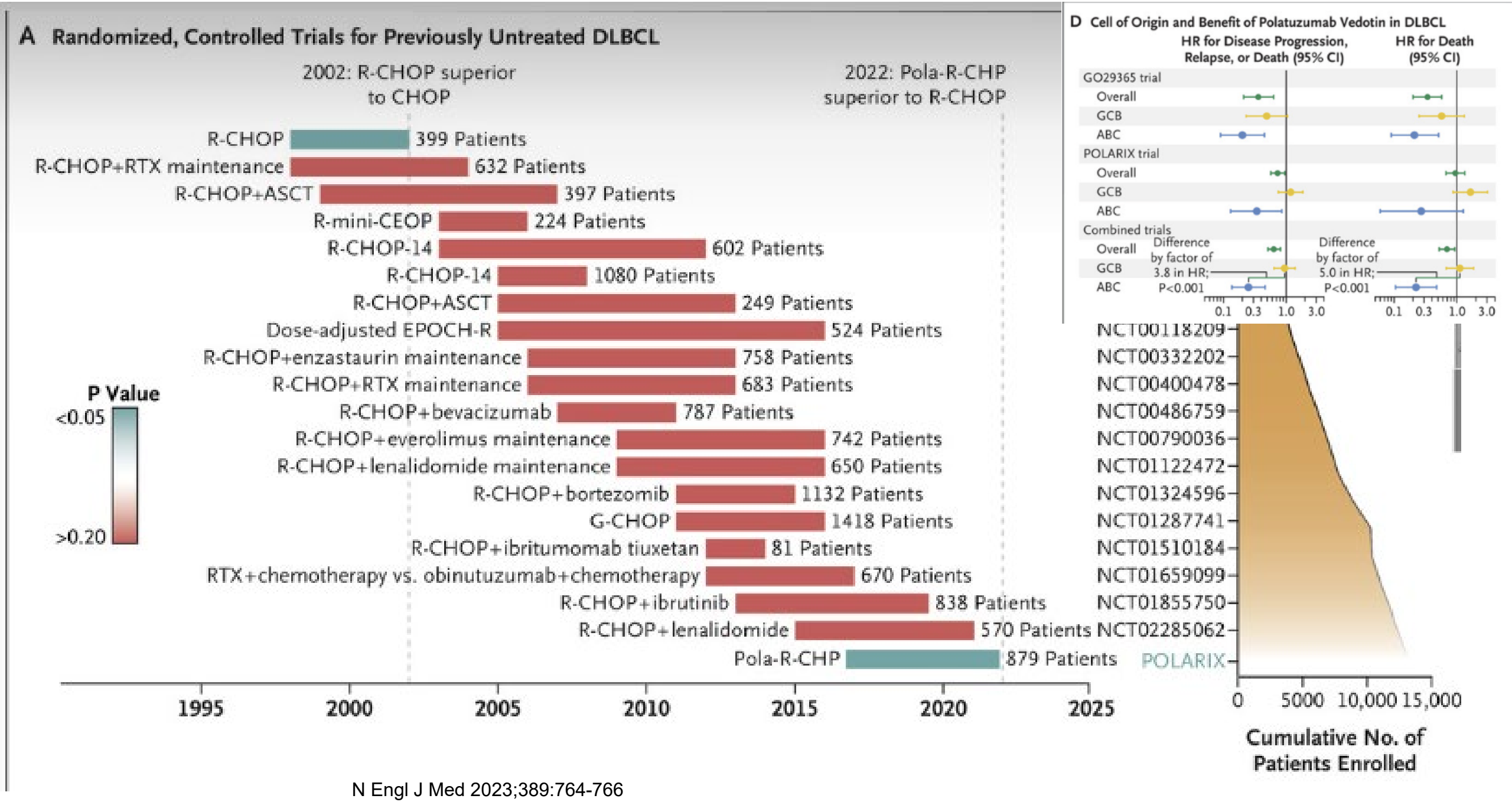
Advani et al. *Blood Cancer Journal*, August 12, 2021.

Polatuzumab Vedotin

Figure 1. Polatuzumab Vedotin Mechanism of Action.



Category	Polatuzumab Vedotin (Polivy) CD79b	Polatuzumab Vedotin (Polivy) CD79b
Indication	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	phase 3 trial, (untreated intermediate-risk or high-risk DLBCL.
Comparative Drug(s)	Bendamustine and rituximab (BR) vs. Polatuzumab Vedotin with BR (Pola-BR)	modified regimen of pola-R-CHP vs standard R-CHOP
Overall Response Rate (ORR)	CR : Pola-BR: 45%; BR: 18%	
Median Progression-Free Survival (PFS)	Pola-BR : 9.5 months BR: 3. 7 months	76.7% vs. 70.2% (p=0.02) at 2 years;
Median Overall Survival (OS)	Pola-BR: 12.4 months vs BR: 4.7 months	at 2 years did not differ significantly (88.7% pola-R-CHP vs 88.6% R-CHOP ; P = 0.75).
Adverse Effects	Thrombocytopenia, neutropenia, anemia, fatigue, peripheral neuropathy, diarrhea	TThe safety profile was similar in the two groups.
Source	J Clin Onco 2019 38:155-165.	J Clin Onco 2019 38:155-165.



N Engl J Med 2023;389:764-766

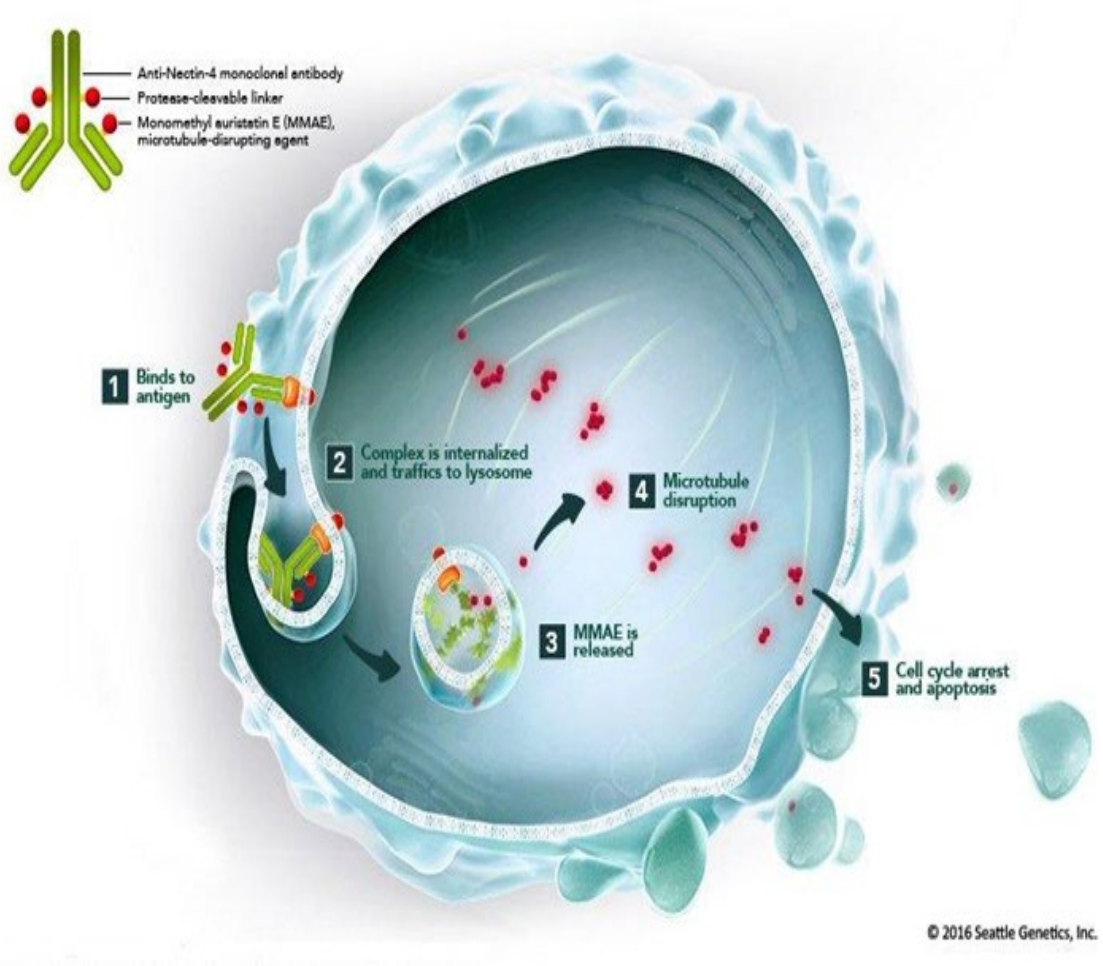
Enfortumab Vedotin: An Antibody–Drug Conjugate Targeting Nectin-4

Nectin-4 是一種I型跨膜蛋白，屬於一個與免疫球蛋白相關的黏附分子家族，這些分子與細胞間的黏附有關。Nectin促進的黏附支持多種生物過程，如免疫調節、宿主與病原體的相互作用及免疫逃逸。Nectin-4 在癌細胞中特別是尿路上皮癌中高度表達，在正常的人類皮膚中則表現適中。Enfortumab vedotin 是一種新型、完全人源化的單克隆抗體-藥物偶聯物，其作用是將一種微管破壞劑MMAE傳送到表達Nectin-4的細胞中。Enfortumab vedotin 選擇性地與表達Nectin-4的細胞結合，啟動ADC-Nectin-4複合物的內化以及偶聯的MMAE的蛋白水解裂解，從而破壞微管網絡，最終導致細胞凋亡。

J Clin Oncol. 2020 Apr 1;38(10):1041-1049.

Enfortumab Vedotin: An Antibody–Drug Conjugate Targeting Nectin-4

- Fully humanized mAb against nectin-4
- Nectin-4 is a transmembrane cell adhesion molecule[1] highly expressed in 97% of mUC patient samples[2]
- Anti-Nectin-4 mAb conjugated with microtubule-disrupting agent (MMAE) by a protease-cleavable linker
  - ADC conjugation occurs on cysteine residues that comprise the interchain disulfide bonds of mAb to yield a drug-to-antibody ratio of approximately 3.8:1
  - MMAE (payload) gets released, binds to tubulin and inhibits its polymerization, resulting in G2/M phase arrest and inducing apoptosis in Nectin-4 overexpressing tumor cells[3]

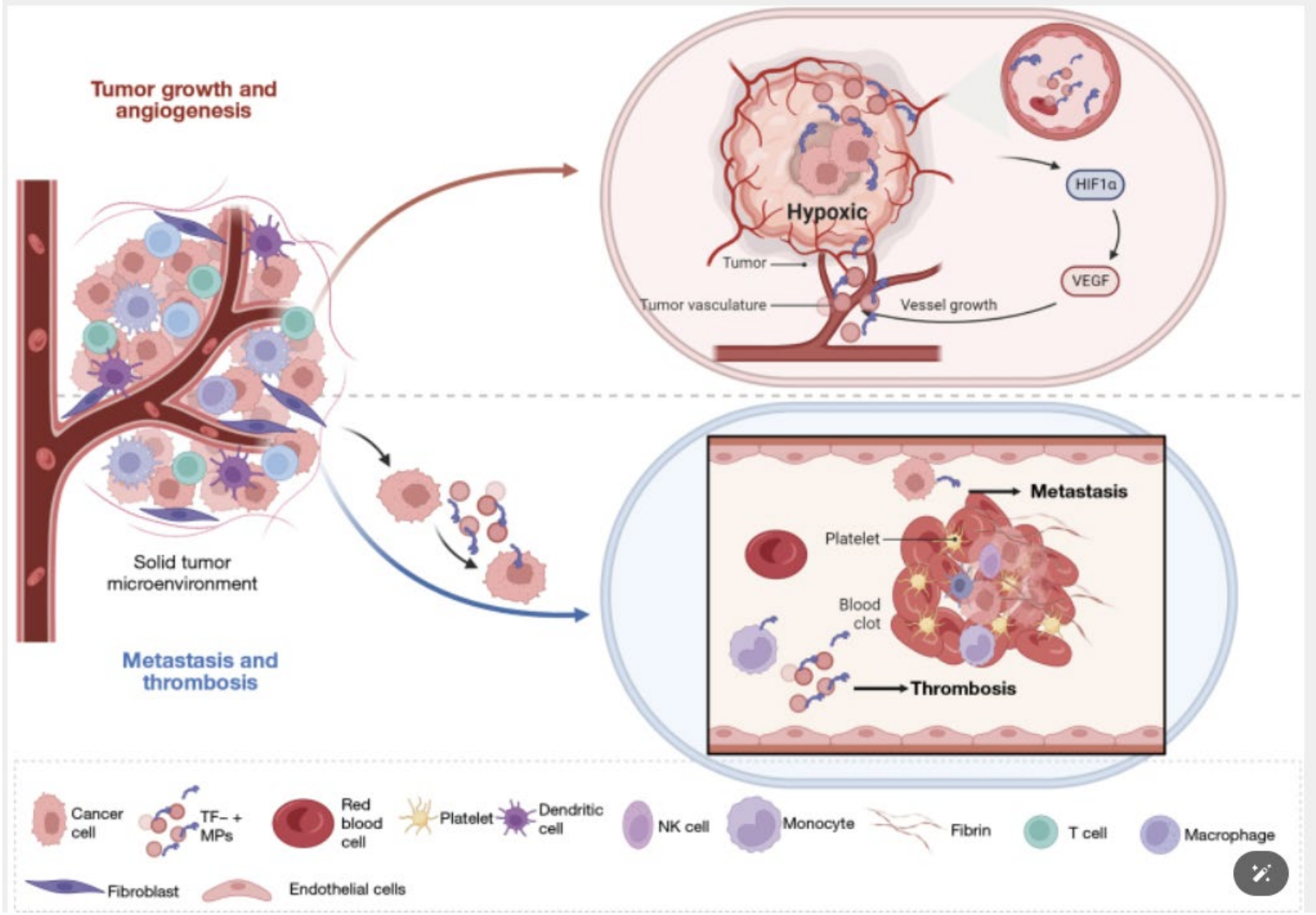


1. Samanta. Cell Mol Life Sci. 2015;72:645. 2. Petrylak. J Clin Oncol. 2017;35:106.

Category	**Enfortumab Vedotin (Padcev) Nectin-4** EV-301 (**second line**)	**Enfortumab Vedotin (Padcev) Nectin-4** EV-302 (**front line**)
Indication	Locally advanced or metastatic urothelial cancer (previously treated with platinum and (PD-1/L1) EV: 301 pts, TPC: pts	**Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer** EV+P (Enfortumab vedotin/pembrolizumab) : 442 G+P (chemotherapy group) : 444 pts
Comparative Drug(s) : Dose modifications for toxicities: First dose reduction → 1 mg/kg → 0.75/kg → 0.5 mg/kg, max dose 50 mg	Enfortumab vedotin (1.25 mg/kg on days 1, 8, 15 of a 28-day cycle) vs chemotherapy (standard docetaxel, paclitaxel, or vinflunine), administered on day 1 of a 21-day cycle.	Enfortumab vedotin (1.25 mg/kg on days 1 and 8 of 21-day cycle) and pembrolizumab (200 mg IV on day 1): (EV+P) VS gemcitabine/cisplatin or carboplatin
Overall Response Rate (ORR)	ORR 40.6% vs. 17.9%,	
Median Progression-Free Survival	mPFS 5.6 vs. 3.7 months,	12.5 months vs. 6.3 months
Median Overall Survival (mOS)	mOS 12.9 vs. 9.0 months.	31.5 months vs. 16.1 months (hazard ratio for death P<0.001)
Adverse Effects	ADR ≧ grade 3 or higher was also similar in the two groups (51.4% and 49.8%, respectively) skin reactions, peripheral neuropathy, and hyperglycemia (11%)	ADR ≧ grade 3 or higher occurred in 55.9% vs 69.5% (the chemotherapy group) . Peripheral sensory neuropathy (55.6%), fatigue (51.1%), alopecia (48.9%)
Source	NEJM 2021, 384, 1125–1135.	NEJM 2024 Mar 7;390(10):875-888

Tissue factors

pancreatic cancer, acute lymphocytic leukemia, sarcomas, lung cancer, triple-negative breast cancer (TNBC) and glioma



Coagulation disorder and tumor progression based on the TF-mediated process.

TF-associated signaling and increased TF expression promote tumor angiogenesis and progression.

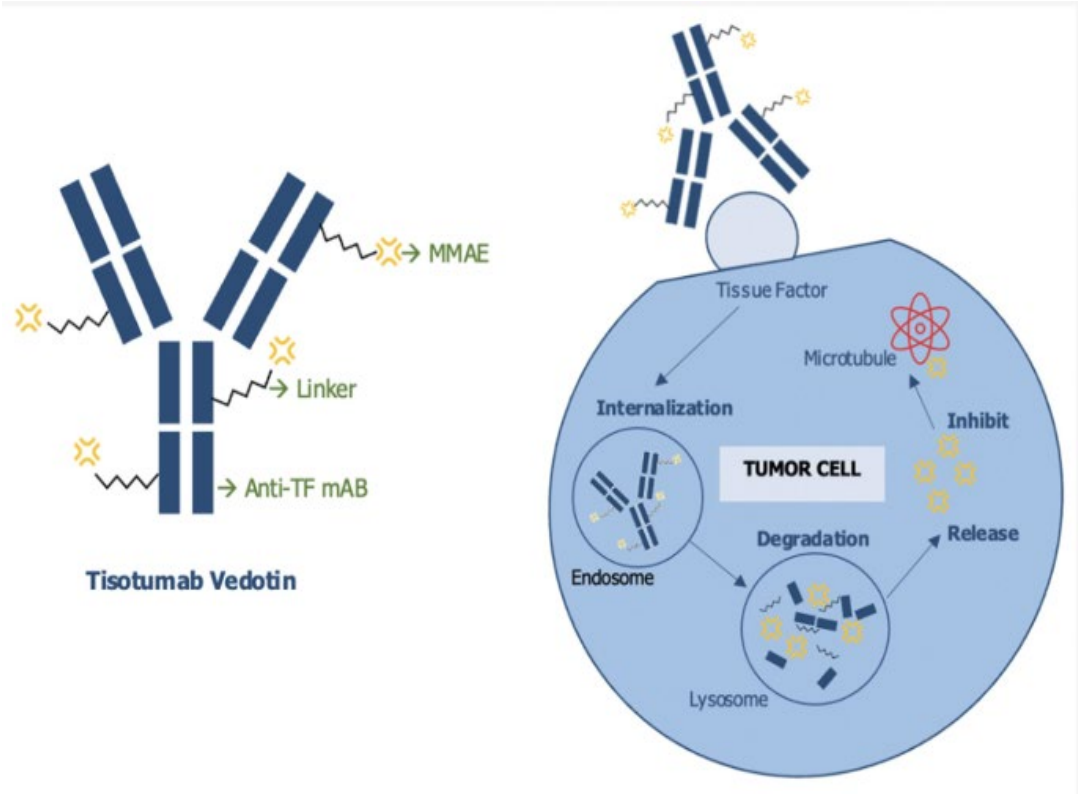
TF via TF(+) microvesicle motility facilitates metastasis and cancer-associated thrombosis.

TF: tissue factor;
MPs : microparticles;
VEGF : vascular endothelial growth factor;
HIF1α: hypoxia-inducible factor 1α.

Ann Transl Med 2022;10(22):1250

Category	Tisotumab Vedotin (Tivdak) Target : Tissue factor)
Indication	Recurrent or metastatic cervical cancer who had received one or two prior regimens
Comparative Regimens	tisotumab vedotin vs investigator's choice of single-agent chemotherapy in 502 pts
Overall Response Rate (ORR)	17.8% vs 5.2%; P < .0001), CR : 2.4% . The disease control rate was 75.9%(tisotumab vedotin) vs 58.2%,
Median Progression-Free Survival (PFS)	4.2 months vs 2.9 months, (P < .0001), with 30.4% vs 18.9%, respectively, progression-free at 6 months.
Overall Survival (OS)	11.5 months (tisotumab vedotin) vs 9.5 months (P = .0038), OS : 48.7% vs 35.3% (in a 12-month)
Adverse Reactions	Grade ≥ 3 toxicities was lower with tisotumab vedotin (29.2% vs 45.2%). Peripheral neuropathy (5.2%), ocular toxicities (3.2%), and bleeding (0.8%).
Source	ESMO Congress 2023. Abstract LBA9, Lancet Oncol . 2021 May;22(5):609-619

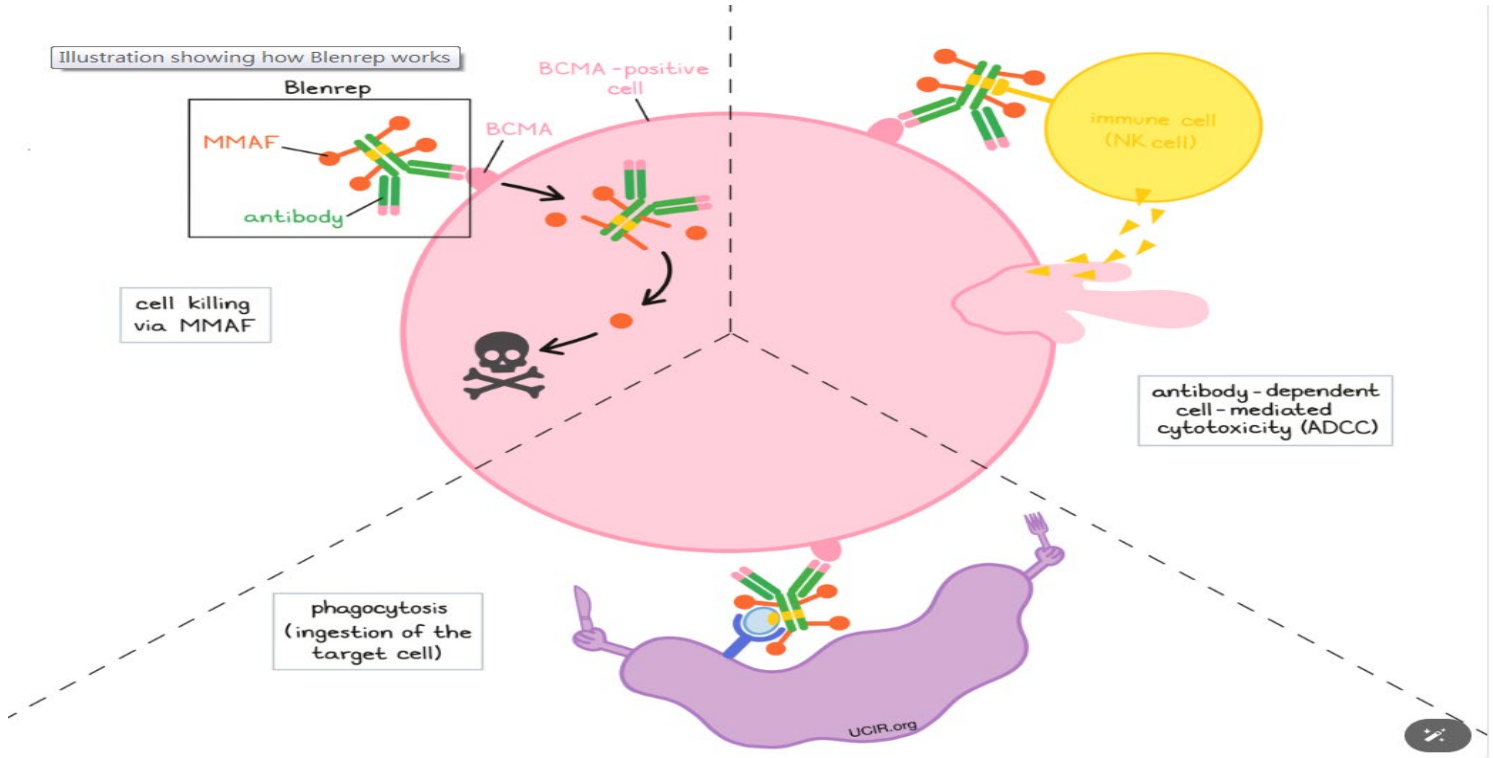
High expression of TF : in several solid tumors, including CC, correlating to poor prognosis



Int. J. Mol. Sci. 2022, 23(7), 3559

Belantamab mafodotin : target (B-Cell Maturation antigen)

Belantamab mafodotin's accelerated approval was withdrawn in 2023 following a confirmatory Phase 3 study (DREAMM-3) that did not demonstrate a statistically significant improvement in OS. The FDA decided to withdraw the drug from the market.



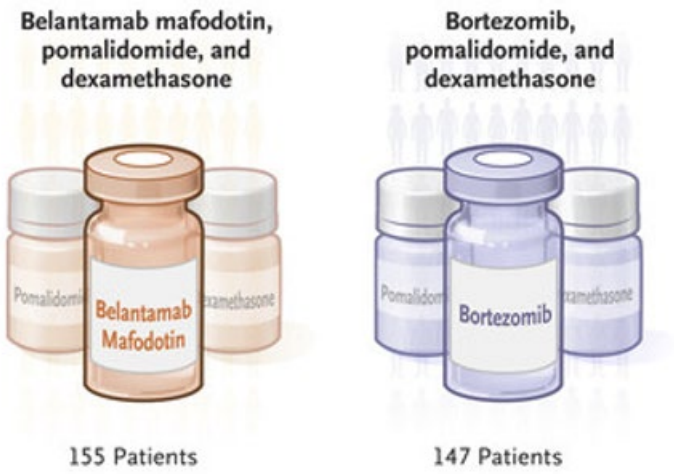
Trial Name	Indication	Comparative Protocol	ORR	PFS	Overall Survival	Adverse Events	Source of Journal
DREAMM-3 Pts :320	Relapsed/Refractory Multiple Myeloma	Belantamab mafodotin vs. Pomalidomide + Low-dose Dexamethasone	41% (Belantamab) vs. 36%	11.2 months (Belantamab) vs. 7.6 months	Not reached (data still maturing)	Keratopathy (72%), thrombocytopenia (25%), anemia (20%)	Lancet Oncology, 2022
DREAMM-2 Pts :196	Relapsed/Refractory Multiple Myeloma	Single-arm study, no comparator	31%	2.8 months	Not reached	Keratopathy (72%), thrombocytopenia (25%), anemia (20%)	Lancet Oncology, 2020

Belantamab Mafodotin, Pomalidomide, and Dexamethasone in Multiple Myeloma

(DREAMM-8)

Background : Triplet or quadruplet therapies incorporating proteasome inhibitors, immunomodulators, and anti-CD38 antibodies have led to prolonged survival among patients with newly diagnosed multiple myeloma.

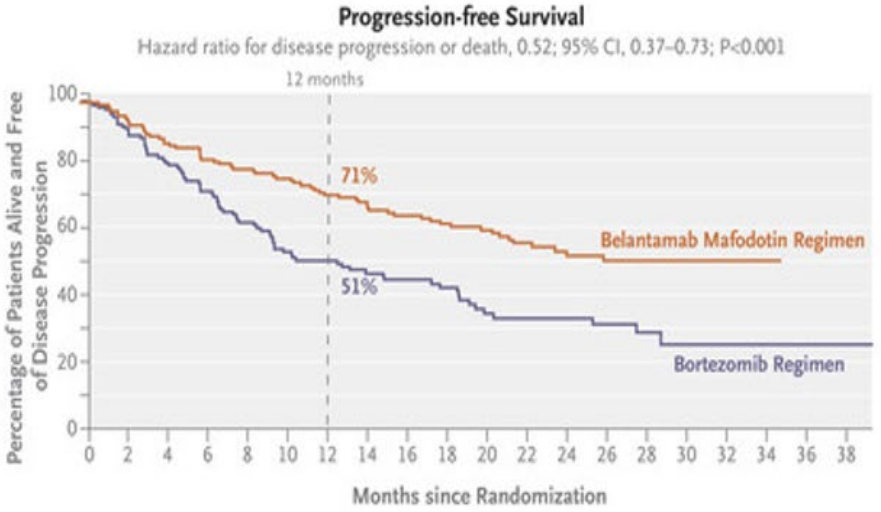
Belantamab mafodotin, pomalidomide, and dexamethasone (BPd) vs pomalidomide, bortezomib, and dexamethasone (PVd), in lenalidomide-exposed patients who had relapsed or refractory myeloma after at least one line of therapy.



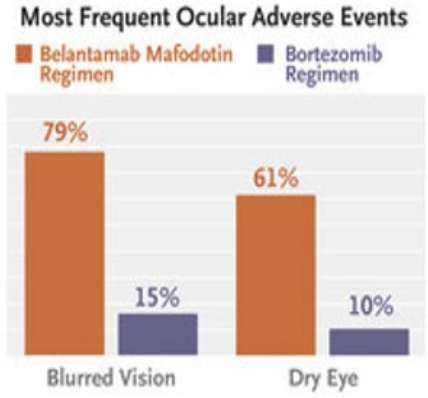
N Engl J Med 2024;391:408-421

RESULTS

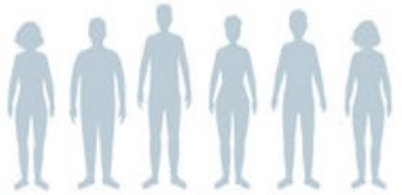
The therapy that included belantamab mafodotin resulted in a significantly lower risk of disease progression or death than the therapy that included bortezomib.



Adverse events were more common with belantamab mafodotin, especially ocular events, which led to treatment discontinuation in 9% of patients assigned to that regimen.

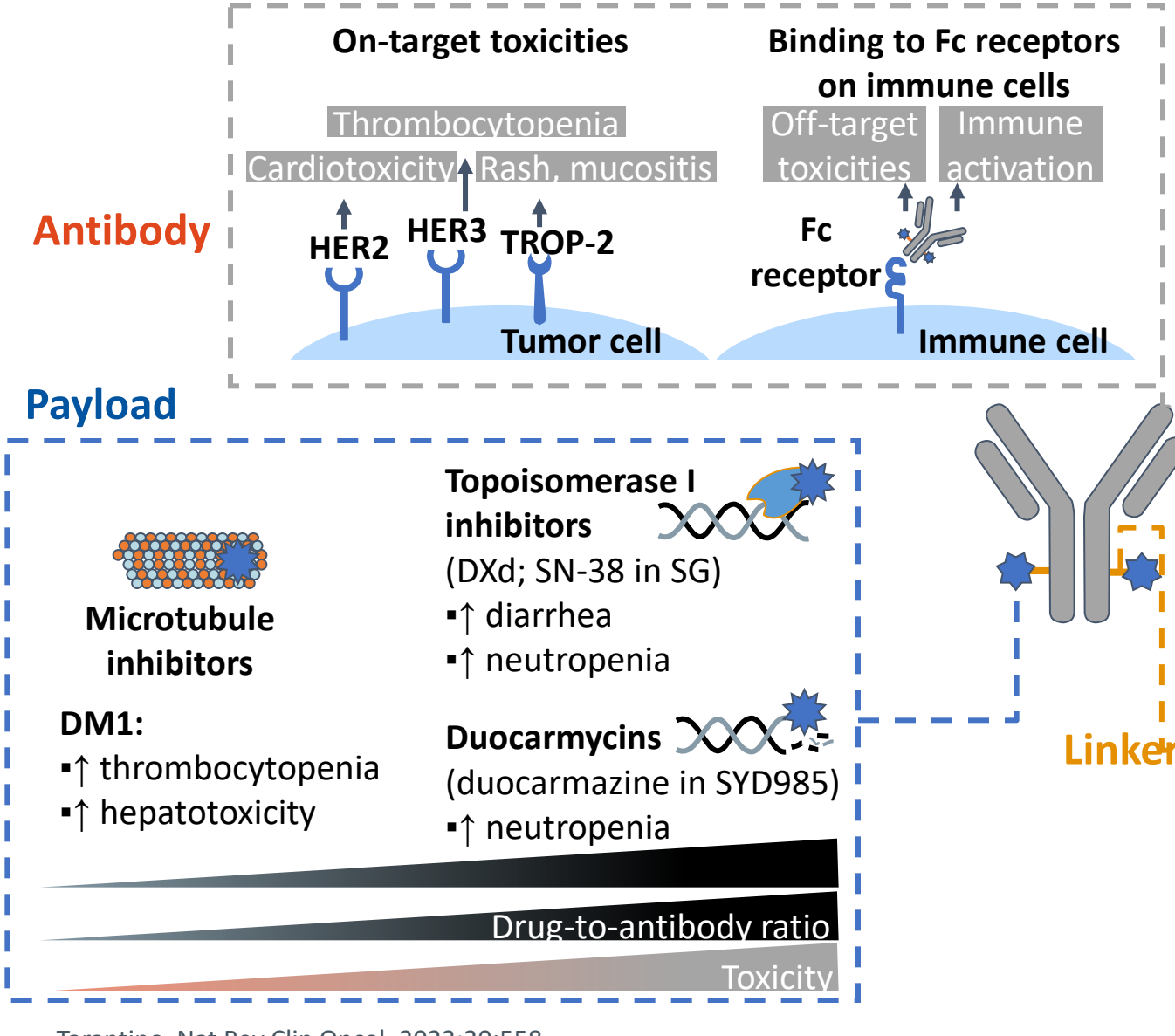


ONGOING FOLLOW-UP



This was an interim analysis. Follow-up for overall survival is ongoing, and assessment of this outcome is planned for future interim and final analyses.

Factors Influencing the Toxicity of ADCs



Patient-Related Factors:

- Comorbidities
- Organ function
- Pharmacogenomic polymorphisms
- Body composition
- Ethnicity

Tarantino. Nat Rev Clin Oncol. 2023;20:558.

Common (in ≥30%) and Dose-Limiting Toxicities Associated With T-DM1 and T-DXd

T-DM1

Fatigue: 36-50%

Musculoskeletal pain: 30-36%

IRR: <2%

ILD/pneumonitis: 1%

LVEF dysfunction: <2%

Hepatotoxicity
Increased AST/ALT: 29-32%
Hyperbilirubinemia: 17%
Nodular regenerative hyperplasia: <1%

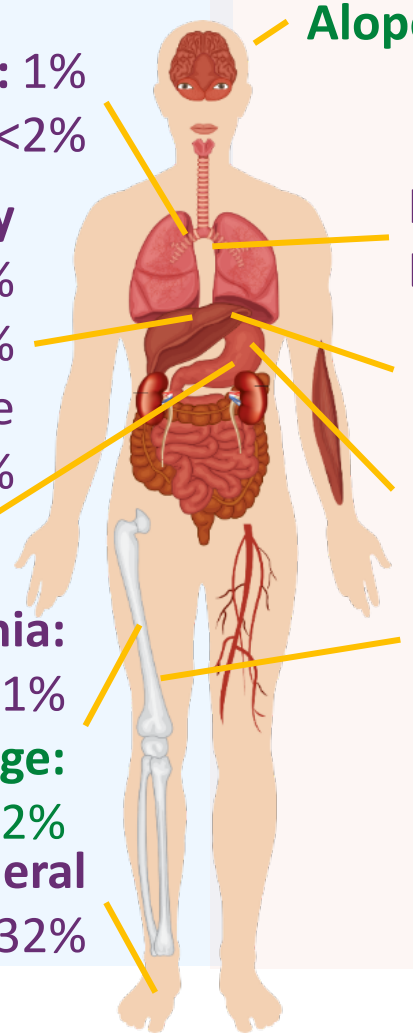
Nausea: 40-42%

Thrombocytopenia: 29-31%

Hemorrhage: 29-32%

Peripheral neuropathy: 21-32%

Black Box Warnings:
- Hepatotoxicity
- Cardiac toxicity
- Embryo–fetal toxicity



T-DXd

Alopecia: 21-46%

Fatigue: 32-59%

ILD/pneumonitis: 10-12%

LVEF decrease: 4-8%

Increased AST/ALT: 42-48%

Nausea: 61-79%

Neutropenia: 65-72%

Thrombocytopenia: 24-28%

Black Box Warnings:
- ILD/pneumonitis
- Embryo–fetal toxicity

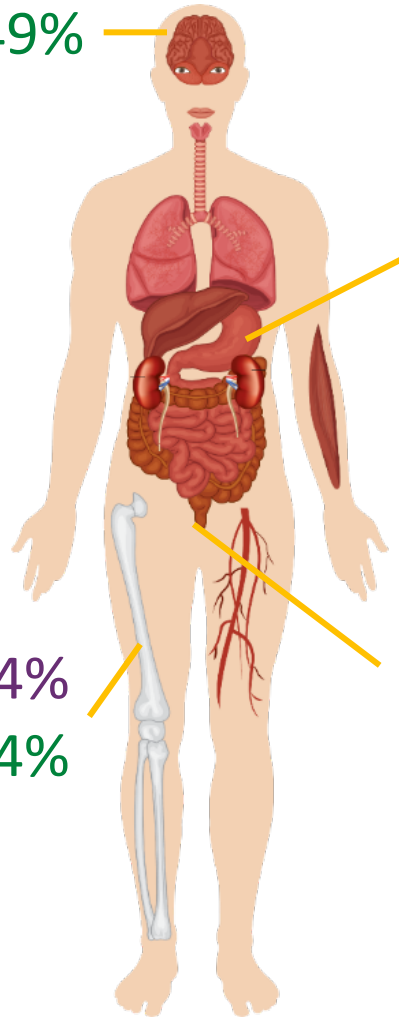
Trastuzumab emtansine PI. Trastuzumab deruxtecan PI. Modi. NEJM. 2022;387:9. Goto. JCO. 2023;41:4852.

Common (in ≥30%) and Dose-Limiting Toxicities Associated With Sacituzumab Govitecan

Alopecia: 38-49%

Fatigue: 51-68%

Hypersensitivity/IRR: 35%



Nausea: 57-69%

Vomiting: 23-49%

Diarrhea: 59-72%

Constipation: 34-37%

Neutropenia: 64%

Anemia: 34%

Black Box Warnings:
- Neutropenia
- Diarrhea

Also listed in Warnings and Precautions:
Embryo–fetal toxicity

Sacituzumab govitecan PI. Rugo. JCO. 2022;40:3365.
Bardia. NEJM. 2021;384:1529.

Managing Diarrhea With Sacituzumab Govitecan

Grade 1: <4 stools/day over BL

Grade 2: 4-6 stools/day over BL; limiting iADLs

Onset During/Shortly After Infusion
- **Atropine** 0.2 mg IV every 15 min x 2 doses
- Subsequent 0.2-mg atropine doses (1 mg total)
- **Atropine prophylaxis** during future infusions
- **Continue SG at same dose**

Early/acute diarrhea due to cholinergic syndrome

Delayed Onset
- Standard loperamide (4 mg + 2 mg/each loose stool, up to 16 mg/d)
- Dietary management

Resolution
- Discontinue loperamide 12 hr after last episode
- Continue dietary management

No Resolution
- High-dose loperamide (4 mg + 2 mg every 2 hr)

If Not Resolved After 24 Hr
- Octreotide 100-150 µg SC 3x/d
- Fluid/electrolyte replacement

Grade 3: ≥7 stools/day over BL; hospitalization indicated; limiting self-care

Grade 4: life-threatening; urgent intervention indicated

- Consider hospital admission
- Consider IV fluids
- Octreotide 100-150 µg SC 3x/d
- Consider antibiotic therapy

Dose reduce when:
- Grade 4
- Not controlled with antiemetics/antidiarrheals
- Recovery to grade ≤1 takes 2-3 wk

Discontinue when:
- Meet criteria for a third dose reduction
- Recovery to grade ≤1 takes 3 wk

Spring. Oncologist. 2021;26:827. Sacituzumab govitecan PI.

New Chemo , New Corneal Disease

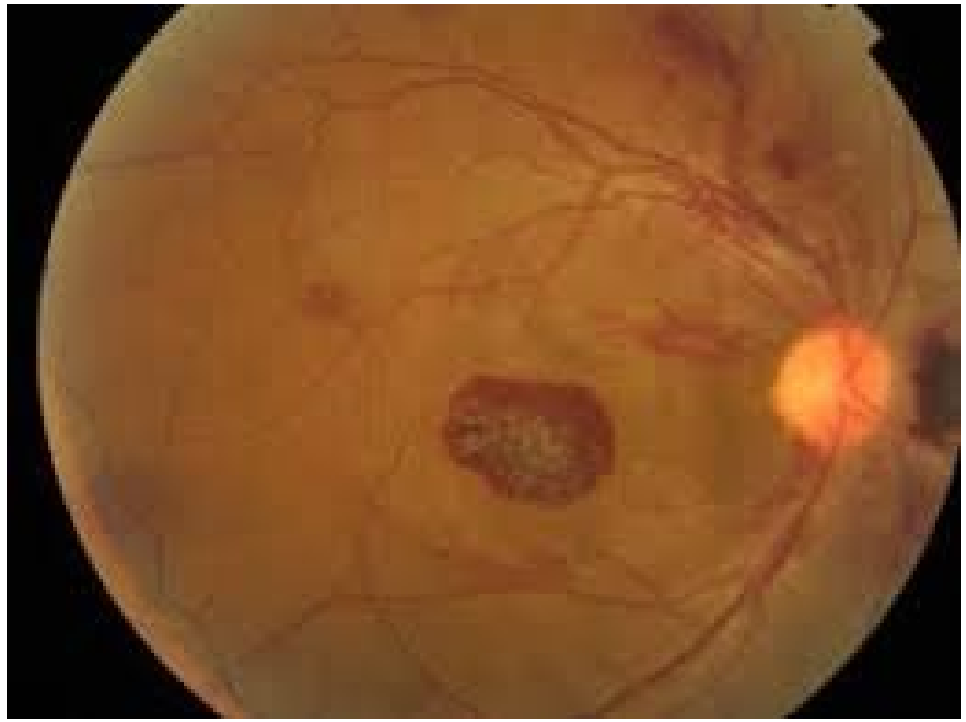
- Corneal findings have been reported in numerous patients receiving ADCs
- **New chemotherapeutic drug class , new corneal disease**
- Corneal findings have been commonly described as "**corneal epithelial microcysts**"

Chemotherapy and the Eye

- A range of ocular adverse events have been described in patients undergoing chemotherapy, including:
  - Dry eye
  - Meibomian gland dysfunction/meibomitis
  - Corneal deposits
  - Cataract
  - Uveitis

Cancer and the Eye

- Ocular findings can include:
  - Amorphous corneal stromal deposits 無定形角膜基質沉積物 (multiple myeloma)
  - Retinal hemorrhages (leukemia)
  - Ocular/orbital invasion (skin/brain tumors)
  - Ocular/orbital metastasis



eyewiki.aao.org/Retinal_Manifestations_of_Leukemia_-_Leukemic_Retinopathy

Slide credit: clinicaloptions.com

FDA Approved ADCs with Reported Ocular Toxicity

Antibody–Drug Conjugate	Tumor Type	Antibody Target	Chemotherapy Payload	Findings
Belantamab mafodotin	Multiple myeloma	BCMA	Auristatin F/MMAF	72%-77% of patients reported microcyst-like epithelial changes[1]
Tisotumab vedotin	Cervical cancer	Tissue factor (TF)	Auristatin E/MMAE	Ocular events: 60%, including conjunctival AEs, dry eye, corneal AEs, blepharitis[2]
Enfortumab vedotin	Urothelial cancer	Nectin-4	Auristatin E/MMAE	Ocular events: 40%, including dry eye, keratitis, blurred vision[3]
Trastuzumab deruxtecan	HER2+ breast cancer	HER2	Topoisomerase I inhibitor	11% of patients reported dry eye[4]
Trastuzumab emtansine	HER2+ breast cancer	HER2	Maytansine/DM1	Conjunctivitis, photophobia, dry eye, increased lacrimation, blurred or impaired vision reported in <10% of patients[5]
Gemtuzumab ozogamicin	CD33+ AML	CD33	Calicheamicin	1 reported case of ocular bleeding in elderly patient with AML[6]
Polatuzumab vedotin	DLBCL	CD79b	Auristatin E/MMAE	1.2% of patients reported blurred vision[7]

1. Belantamab mafodotin PI. 2. Tisotumab vedotin PI. 3. Enfortumab vedotin PI. 4. Trastuzumab deruxtecan PI. 5. Trastuzumab emtansine PI. 6. Piccaluga. Leuk Res. 2004;28:987. 7. Polatuzumab vedotin PI.

Slide credit: clinicaloptions.com

Approved ADCs With Prescribing Information Warnings on Ocular Toxicity

Belantamab Mafodotin[1]	Tisotumab Vedotin[2]
Treatment with belantamab mafodotin can cause changes in corneal epithelium resulting in changes in vision, including severe vision loss and corneal ulcer Symptoms include blurred vision and dry eye	Treatment with tisotumab vedotin can cause changes in corneal epithelium and conjunctiva resulting in changes in vision, including severe vision loss and corneal ulceration
Perform eye exams at baseline and prior to each dose or for worsening symptoms	Perform eye exams at baseline and as clinically indicated

1. Belantamab mafodotin PI. 2. Tisotumab vedotin PI.

Slide credit: clinicaloptions.com

On-Target Toxicity or Off-Target Toxicity of ADCs

On-Target

- Cytotoxic effect on (noncancer) cells that **express the target antigen**
- Mechanism of action is likely **related to/may be the same** as effect on cancer cells

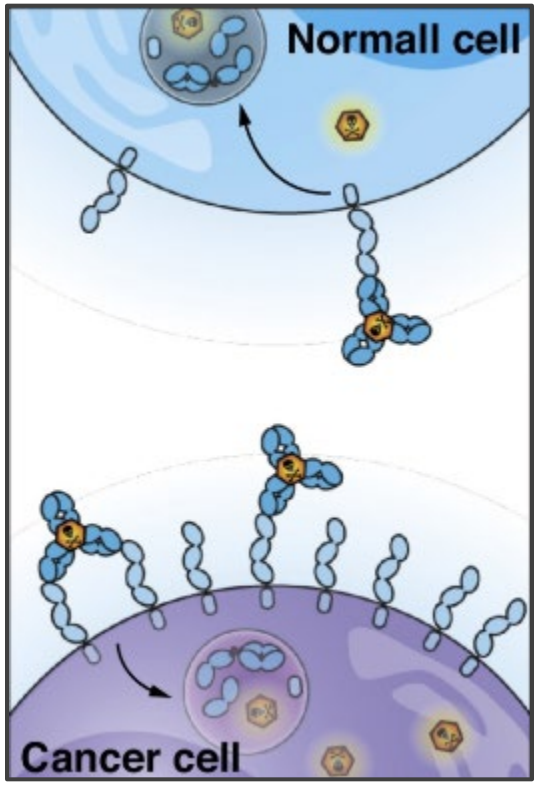
Off-Target

- Cytotoxic effect on (noncancer) cells that **do NOT express the target antigen** (or have minimal expression)
- A few potential mechanisms of off-target toxicity have been described

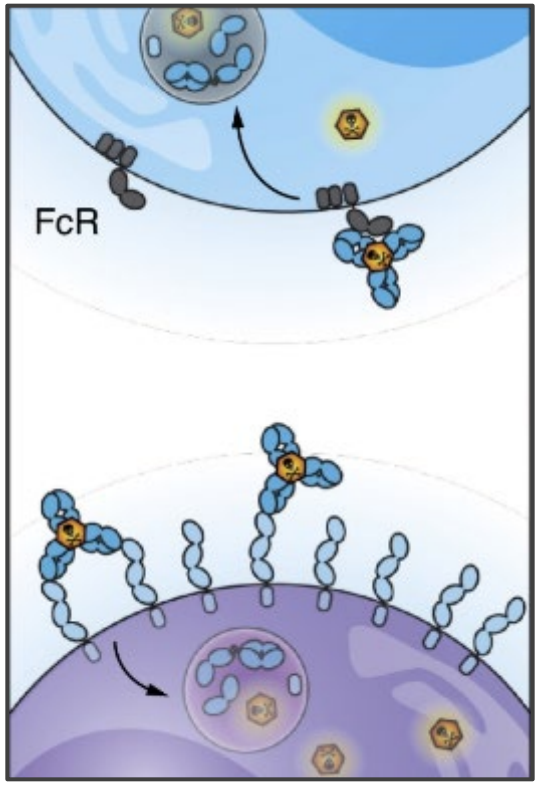
Slide credit: clinicaloptions.com

Mechanisms of ADC Toxicity

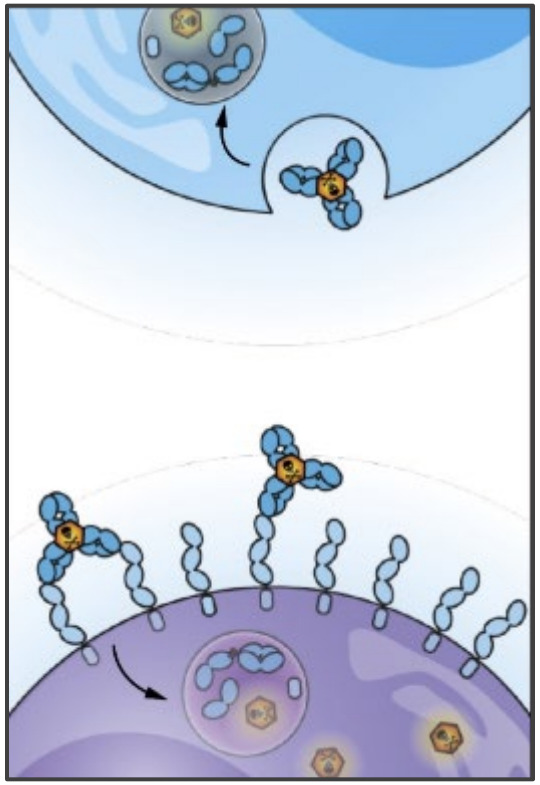
Target-Induced Toxicity



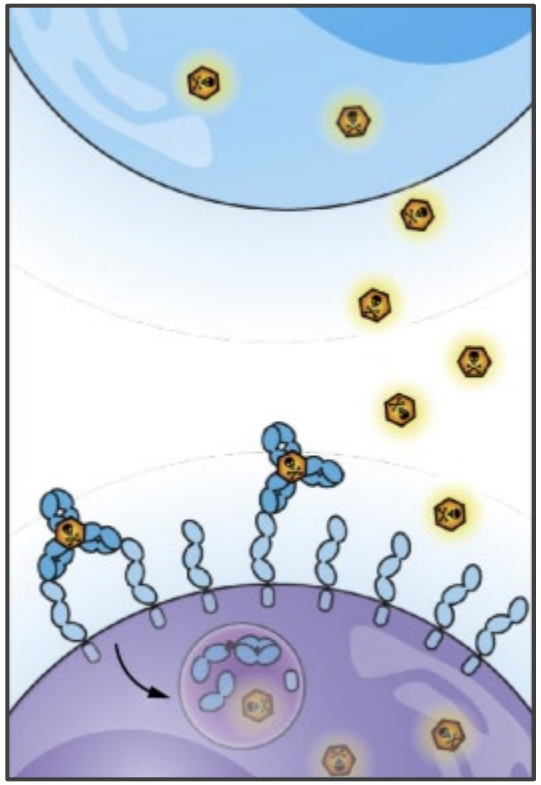
FcR-Driven Toxicity



Pinocytosis-Driven Toxicity



Bystander Toxicity



Goeij. Curr Opin Immunol. 2016;40:14. Available under Creative Commons 4.0. Zhao. Cancer Res. 2018;78:2115.

Slide credit: clinicaloptions.com

On-Target or Off-Target Corneal Toxicity?

- Other ADCs target antigens that are not expressed in the cornea (off-target toxicity)
- However, there is evidence that macropinocytosis (a form of nonspecific cellular uptake, ie, “cell drinking”) may be implicated in off-target toxicity of some ADCs

- It may **depend on the drug**
- For example, **trastuzumab emtansine** is an ADC used against **HER2**-positive breast cancer that was reported to cause corneal epithelial toxicity[1]
- Because **corneal epithelial cells express HER2**, this may potentially represent an “**on-target**” toxicity

1. Tsuda. Cornea 2016;35:1378.

Slide credit: clinicaloptions.com

Vision Changes and Importance

- These changes may affect visual acuity/quality of vision in 2 ways
  - Corneal epithelial changes **within the visual axis**
  - **Topographic/refractive changes (地形/屈光變化)**
- This may impact a patient's ability to **stay in a clinical trial** or their **compliance/desire to continue treatment**, which may otherwise be lifesaving

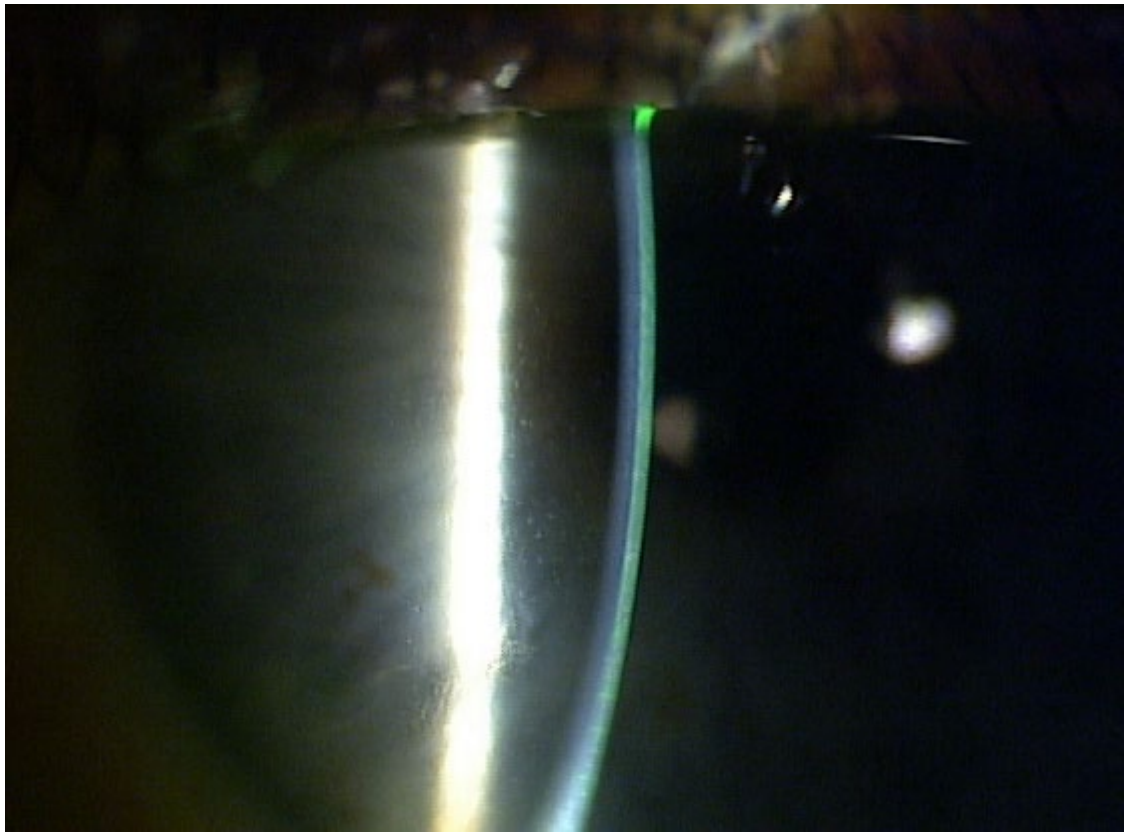
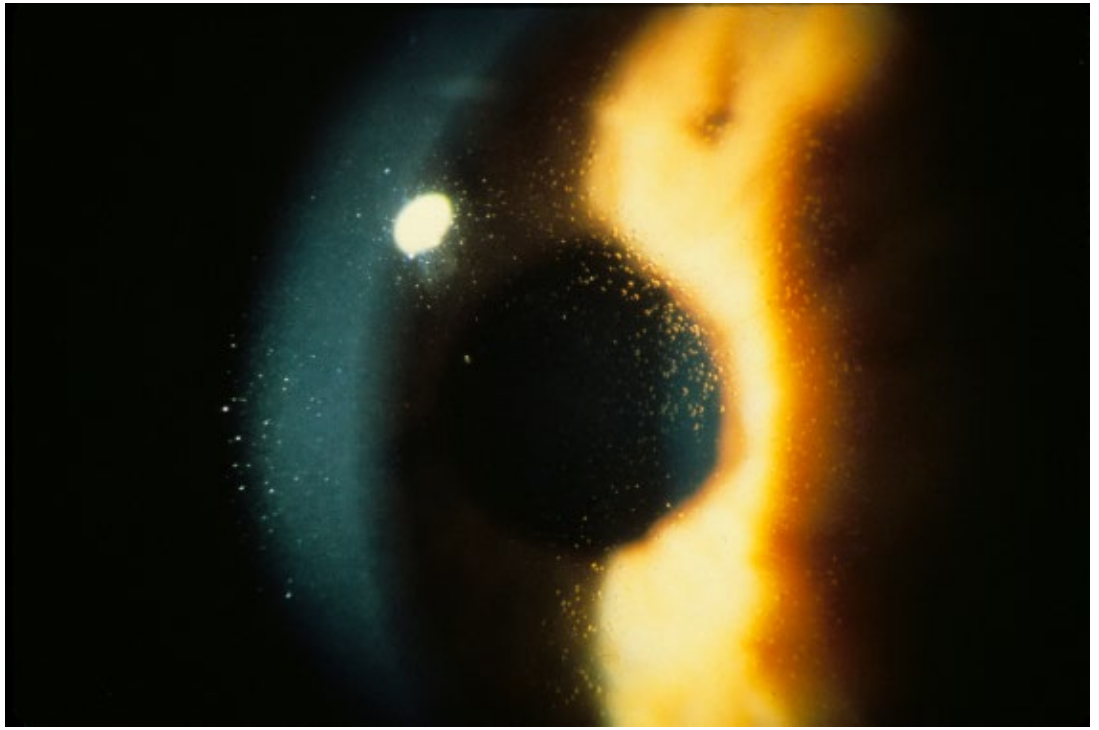


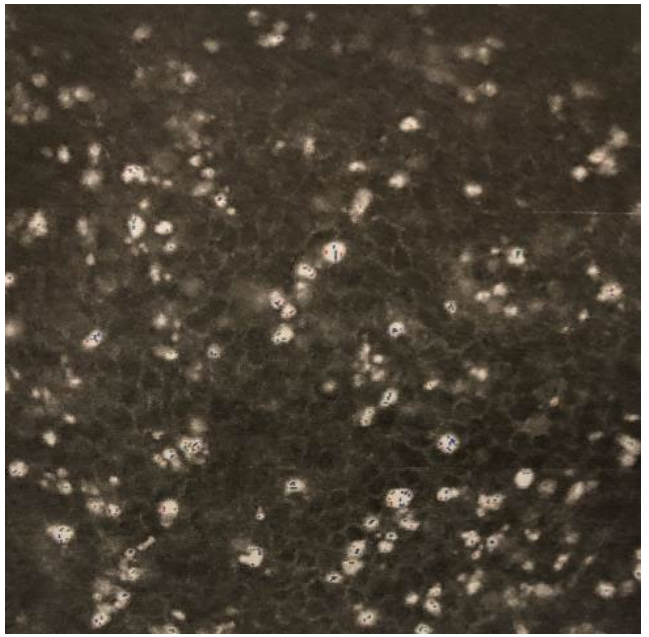
Image courtesy of Asim V. Farooq, MD.

Slide credit: clinicaloptions.com

What Are We Seeing?

- Are these **corneal epithelial microcysts**, as has been suggested?
- Corneal epithelial microcysts: microcystic corneal edema, Meesmann corneal dystrophy (米斯曼角膜營養不良)
- **Confocal microscopy (**共焦顯微鏡**)**may be revealing...





slit lamp examination is an intracellular deposition of the drug (or a drug metabolite)

https://disorders.eyes.arizona.edu/disorders/corneal-dystrophy-meesmann

Slide credit: clinicaloptions.com

Conclusion

- ADCs are now approved across various solid tumors, and despite their ideally targeted mechanism of action, most ADCs still confer frequent and sometimes life-threatening toxicities.
- The mechanisms of ADC toxicity include on-target, off-tumor toxicity predominantly related to the payload and the linker, and target-independent ADC uptake with non-specific endocytosis.

- Awareness, education, prophylaxis, early detection, and multidisciplinary management of adverse events (AEs) are crucial.

- Ongoing strategies to optimize the safety of ADCs include dose-optimization and design optimization, such as probody-drug conjugates, bispecific ADCs, new linker and conjugation technologies, and new classes of payloads

Thank you for listening