CRCL CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

Antibody Drug Conjugates
Recent developments and Future Prospects

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Lyon 1

HCL HOSPICES CIVILS DE LYON

Conflicts of interest

Research support

Roche, Servier, Pierre Fabre, Macrogenics

Co-founder

Antineo

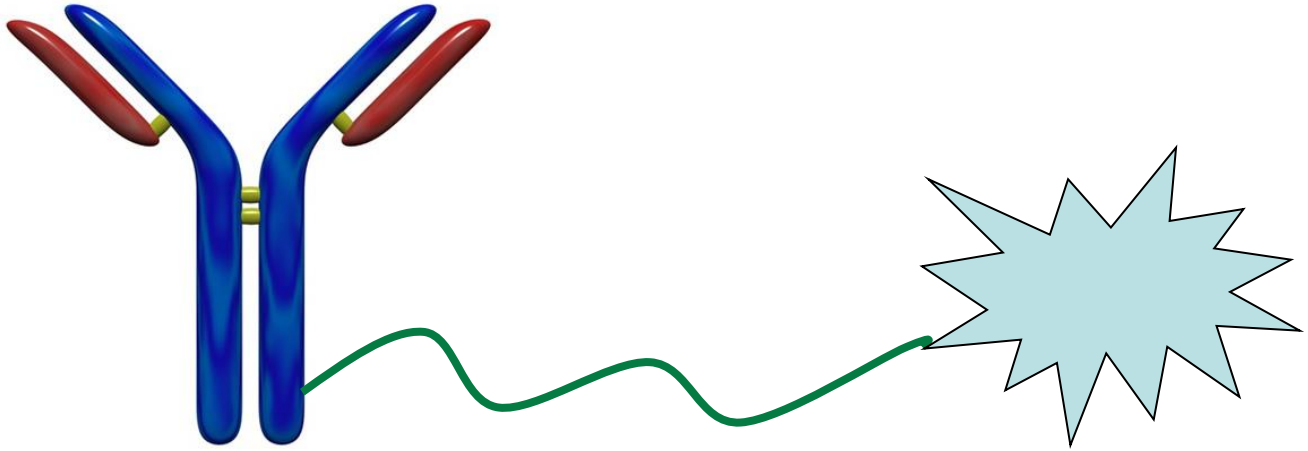
Mablink pharma

Hephaistos pharma

Summary

- What is an ADC ?
- A complicated development
- Recent approvals
- Diversifying conjugates
- Toxicity issues

Antibody Drug Conjugates (ADC)



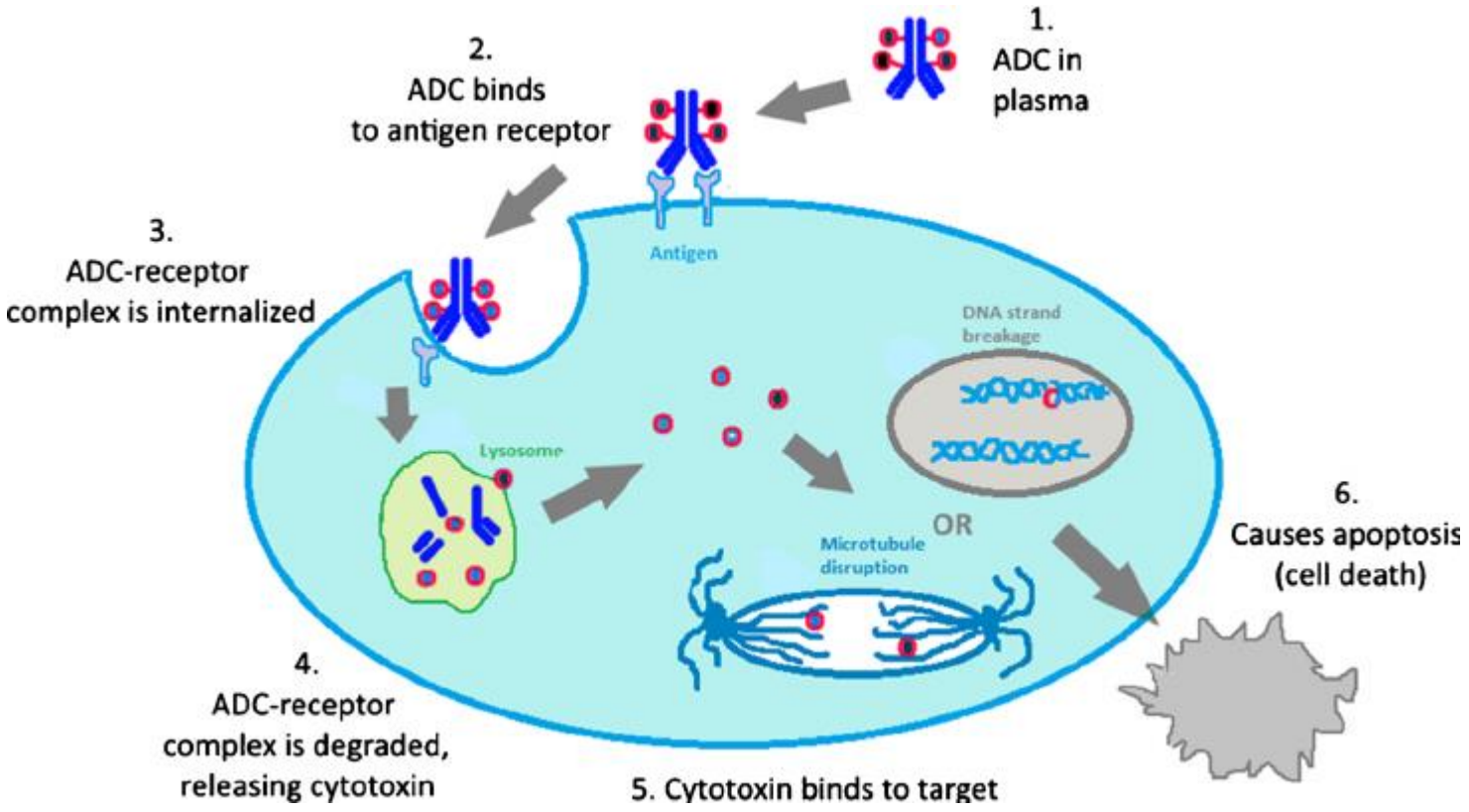
Antibody Linker Conjugate

10-200,000 Ag site per cell -→ expected concentration of conjugate are in the nanomolar range.
The conjugate must be a very potent cytotoxin.

Linker: covalent bond which must be stable in the serum and extracellular environment, cleavable once in the tumor cells

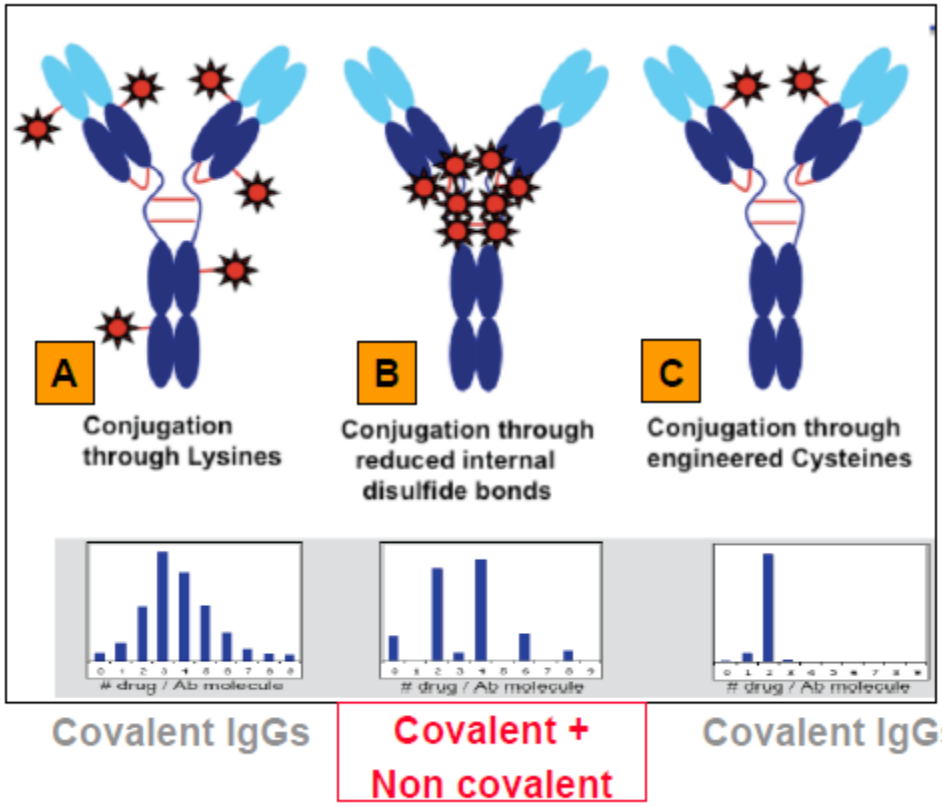
Conjugate must not be released before reaching the tumor +++

Binding, internalization, release



N.B.: not all antigens are internalized once bound by antibody

Conjugation strategies



(A) Lysines conjugation
- Gemtuzumab ozogamicin
- Trastuzumab emtansine

(B) Reduced native cysteines conjugation
- Brentuximab vedotin

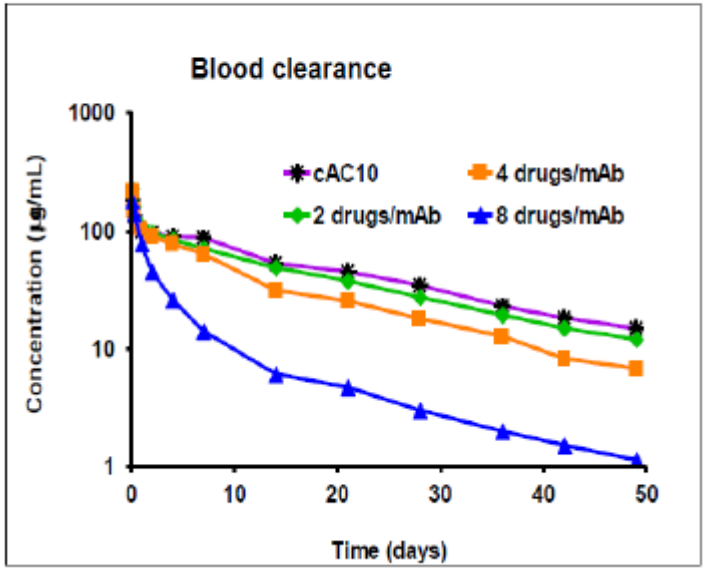
(C) Engineered cysteines conjugation
- Thio-trastuzumab

K. Lin (Genentech), Pharm Res, 2012

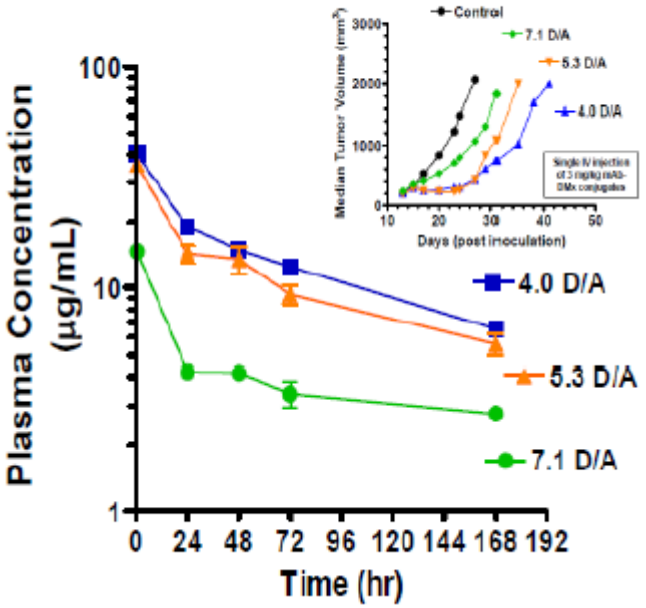
DAR: drug to antibody ratio

Effect of DAR on kinetics

(A) MMAE-Cys-IgG (Seattle Genetics)

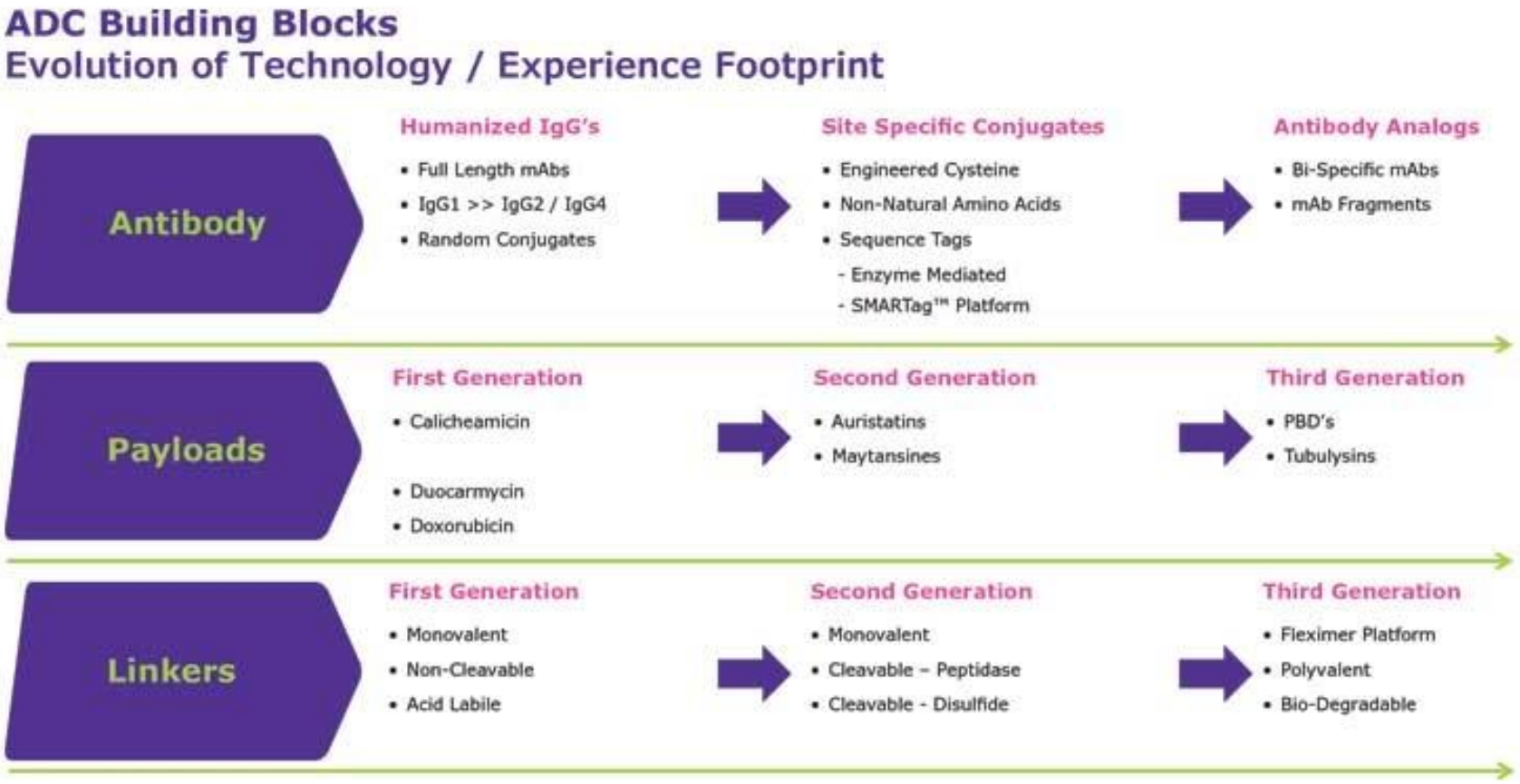


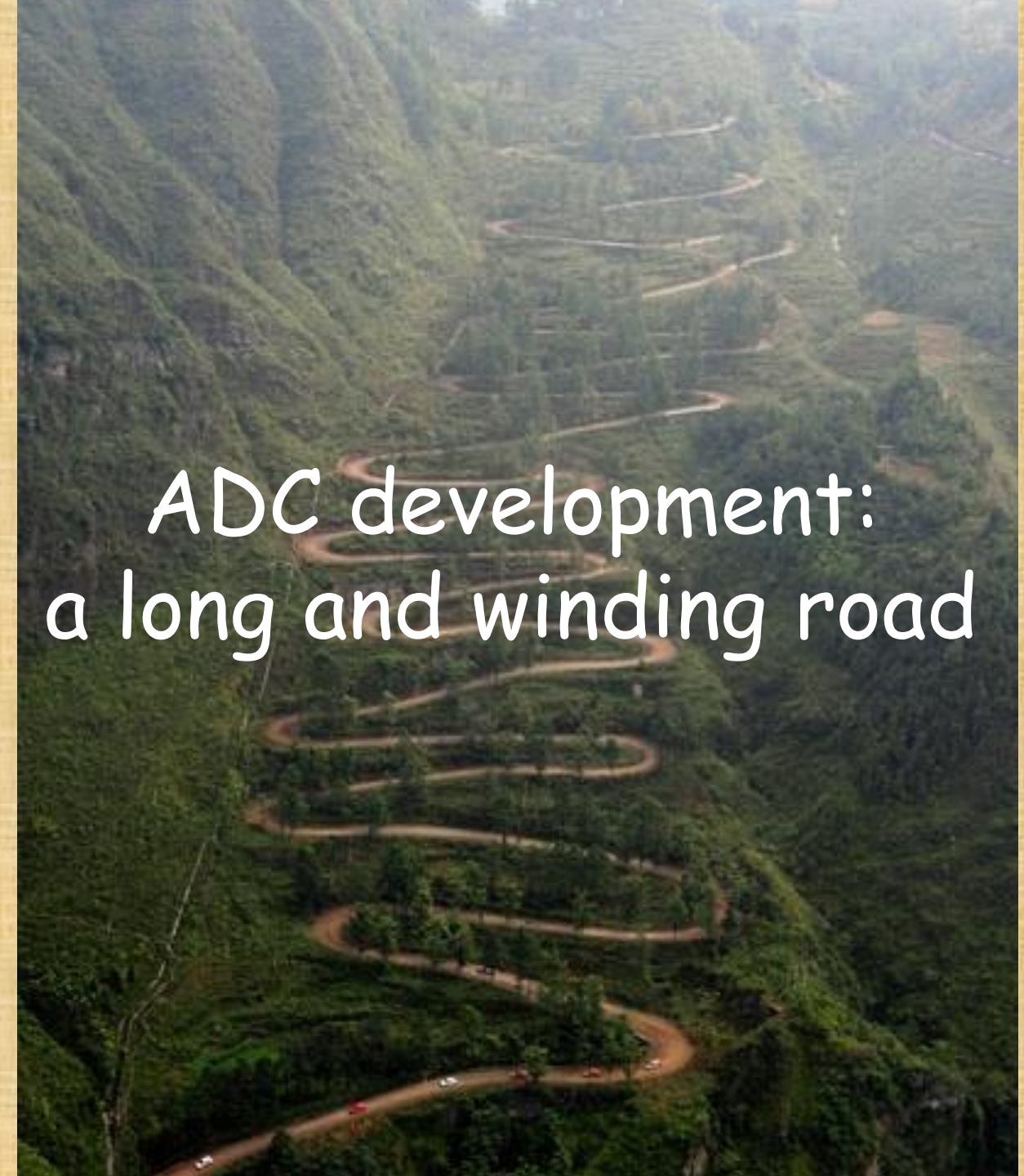
(B) DM1-Lys-IgG (ImmunoGen)



- Hamblett KJ et Al, Clin Cancer Res 2004 & 2006
- McDonagh CF et Al, (Seattle Genetics) Prot Eng Design & Selection 2006

Available technologies




ADC development:
a long and winding road

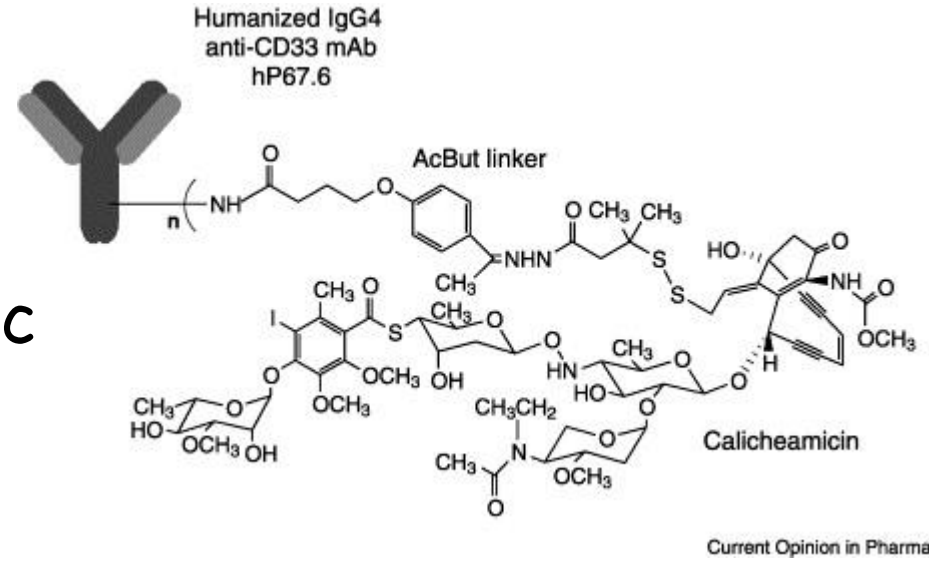
Gemtuzumab ozogamicin

Mylotarg®

Humanized IgG4 coupled to the bacterial toxin calicheamicin

Directed against CD33

Expressed in most leukemic blasts but also in normal hematopoietic cells



Current Opinion in Pharmacology

Gemtuzumab ozogamicin – ADC anti CD33

2000: accelerated-approval process by the FDA
patients >60y
relapsed AML) or unfit for standard chemotherapy

2001: black box warning FDA
increased risk of **veno-occlusive disease** (**VOD**)

2004: A randomized phase 3 trial initiated in 2004
stopped prior to completion due higher fatal toxicity rate in the gemtuzumab combination therapy group vs standard therapy group. (5.7% vs. 1.4%)

2010: Mylotarg withdrawn from the US and EU markets

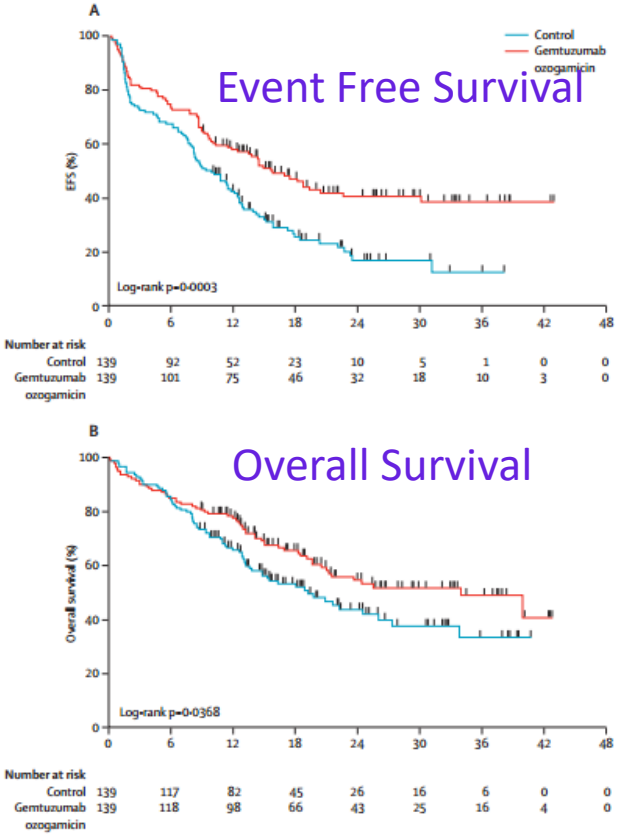
2017: reapproved by FDA

THE LANCET

Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study

Sylvie Castaigne, Cécile Pautas, Christine Terré, Emmanuel Raffoux, Dominique Bordessoule, Jean-Noel Bastie, Ollivier Legrand, Xavier Thomas, Pascal Turlure, Oumedaly Reman, Thierry de Revel, Lauris Gastaud, Noémie de Gunzburg, Nathalie Contentin, Estelle Henry, Jean-Pierre Marolleau, Ahmad Aljijakli, Philippe Rousselot, Pierre Fenaux, Claude Preudhomme, Sylvie Chevret, Hervé Dombret, for the Acute Leukemia French Association

9 mg/m2 → 3 x 3 mg/m2



Event Free Survival

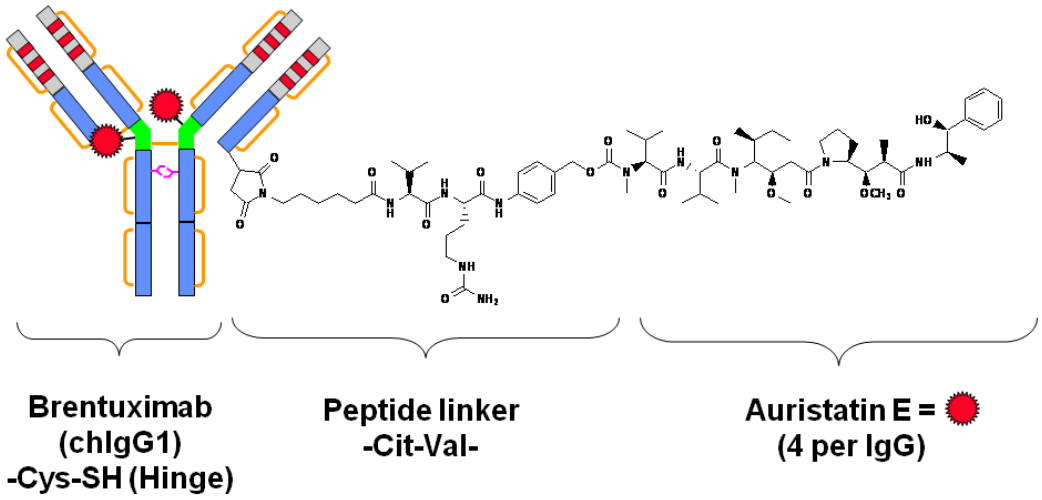
Overall Survival

	Control group (n=139)	Gemtuzumab ozogamicin group (n=139)	Relative risk (95% CI)	p value
Induction death	5/139 (4%)	9/139 (6%)	0·56 (0·20–1·54)	0·41
Transfer to intensive-care unit	17/139 (12%)	20/139 (14%)	0·85 (0·47–1·54)	0·72
Treatment-related death during CR or CRp	8/104* (8%)	2/113 (2%)	4·35 (1·07–17·84)	0·051
Grade 3 and 4 adverse events				
Haemorrhage	4/139 (3%)	12/139 (9%)	0·33 (0·12–0·95)	0·068
Cardiac	9/139 (6%)	11/139 (8%)	0·82 (0·36–1·87)	0·82
Liver	9/139 (6%)	18/139 (13%)	0·50 (0·24–1·05)	0·10
Skin or mucosa	25/139 (18%)	32/139 (23%)	0·11 (0·03–0·42)	0·37
Gastrointestinal	14/139 (10%)	22/139 (16%)	0·64 (0·34–1·18)	0·21
Pulmonary	16/139 (12%)	16/139 (12%)	1·00 (0·53–1·90)	1·00
Grade 3 and 4 infections				
During induction	50/131 (38%)	59/129 (46%)	0·83 (0·62–1·11)	0·26
During first consolidation	38/95 (40%)	48/97 (49%)	0·80 (0·59–1·11)	0·19
During second consolidation	38/82 (46%)	38/81 (47%)	0·99 (0·71–1·37)	0·99

Data are n/N (%), unless otherwise indicated. CR=complete remission. CRp=complete remission with incomplete platelet recovery. *Includes five deaths after stem-cell transplantation.

Table 4: Non-haematological toxicity

Brentuximab vedotin (Adcetris®) anti-CD30



Currently approved:

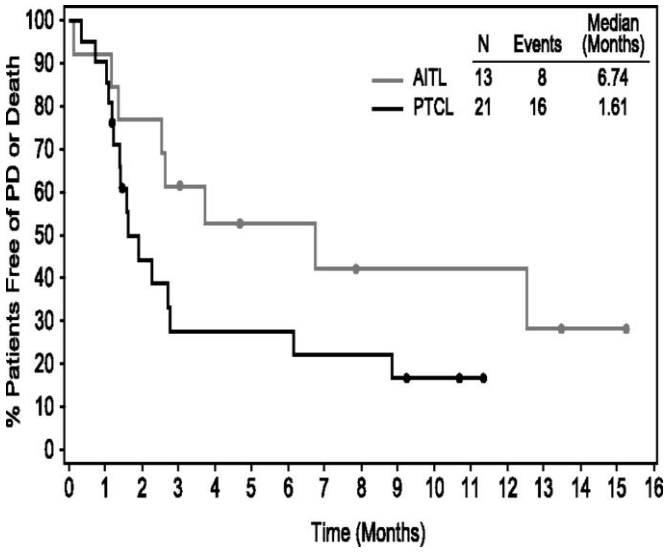
Hodgkin's disease

at high risk of relapse post transplant, after treatment failure, in *previously untreated* stage III/IV in combo with chemotherapy

Systemic Anaplastic large cell lymphoma

Previously untreated in combination or after treatment failure

Primary cutaneous anaplastic or MF lymphoma after prior therapy



T-DM1

T-DM1 = trastuzumab – emtansine

DM1 : highly potent antitubulin agent

Phase I (Krop, 2010) :

Dose limiting toxicity thrombocytopenia

MTD 3,6 mg/kg with 75% clinical benefit

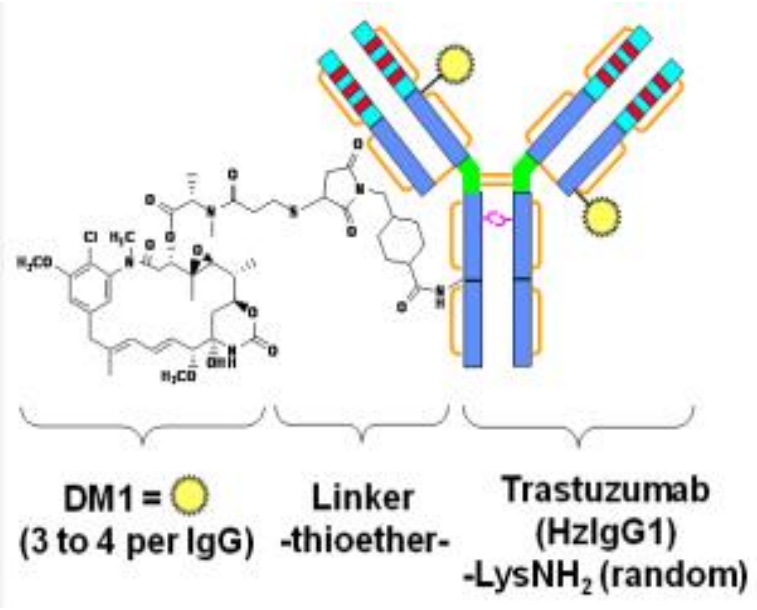
No significant peripheral neuropathy

Phase II (Burris, 2010)

112 patients relapsing after Her2 targetted therapy

26% response rate,

Disease free survival 5 months



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2012 VOL. 367 NO. 19

Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

Phase III study

991 patients with advanced Her 2 + breast cancer

Previously been treated with trastuzumab and a taxane

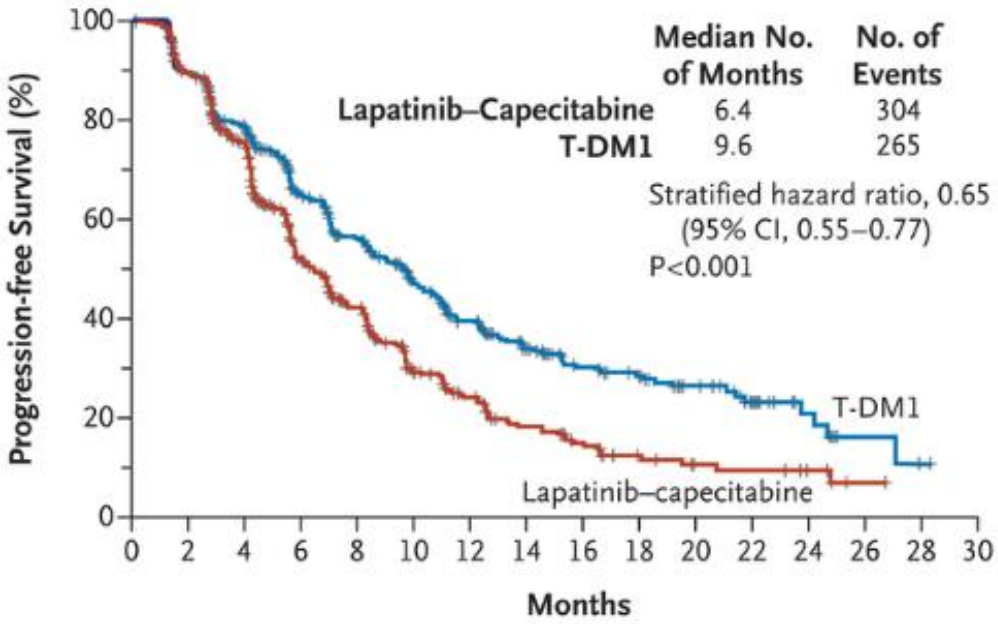
Randomly assigned to T-DM1 or lapatinib plus capecitabine

Primary end points were progression-free survival, overall survival, and response

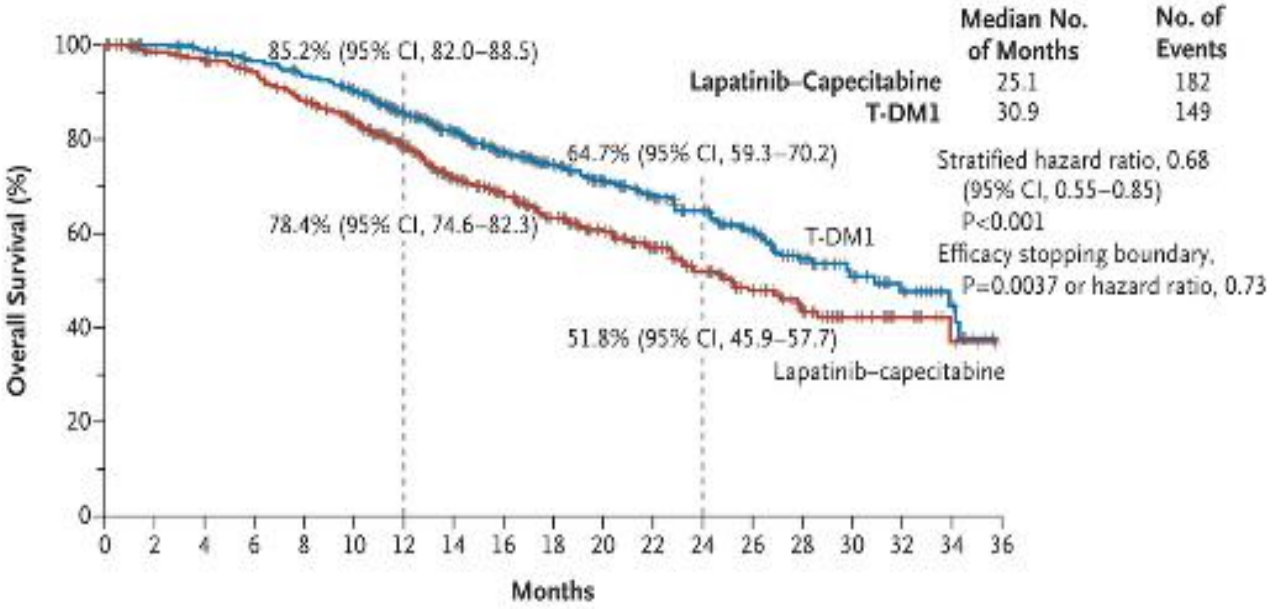
T-DM1 efficacy data

	lapatinib + capecitabine	T DM1	p value
Median Progression free survival (months)	6.4	9.6	< 0.001
Median Overall survival (months)	25.1	30.9	< 0.001
Overall response rate (%)	30.8	43.6	< 0.001

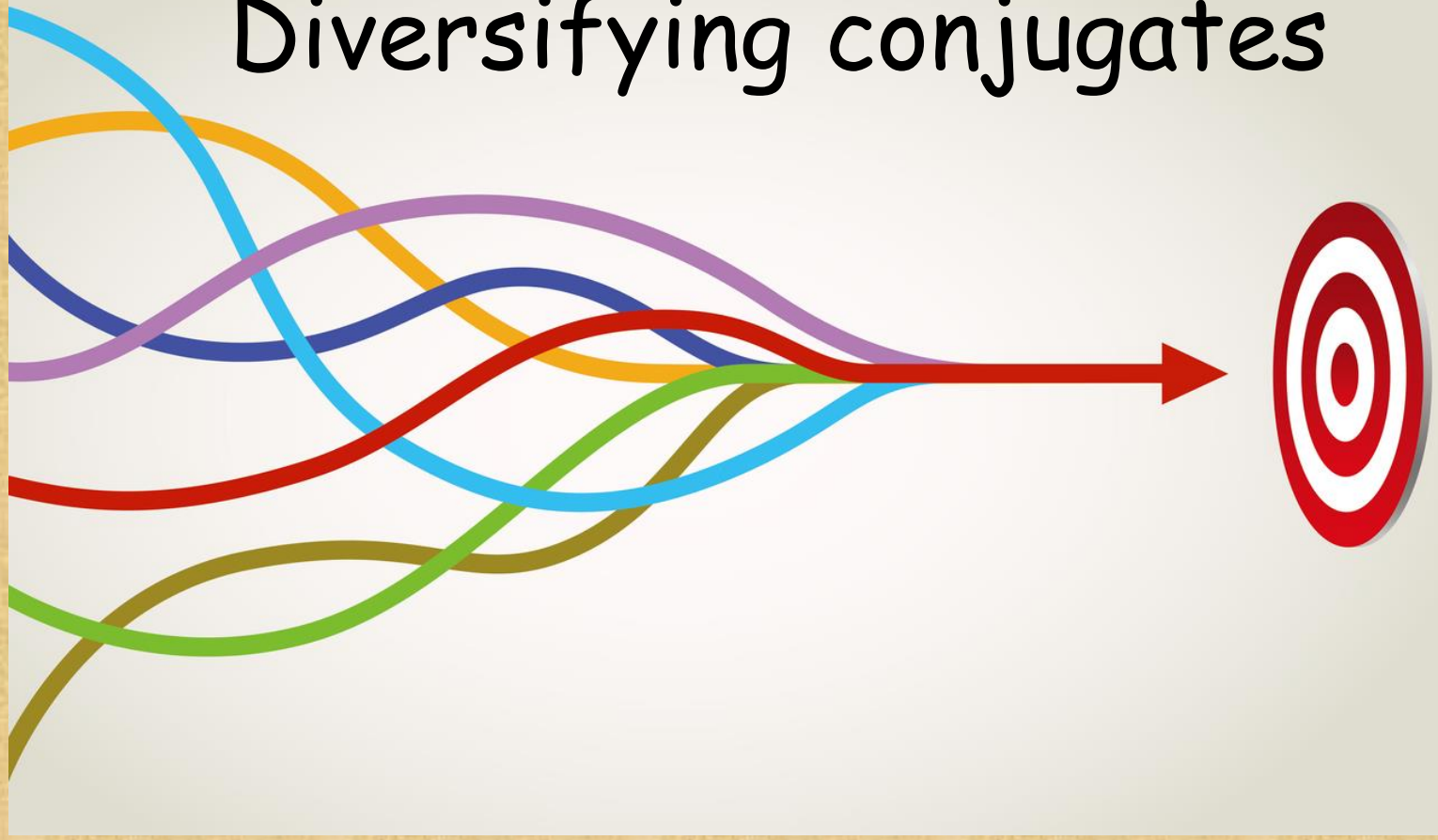
Progression Free Survival



Overall Survival

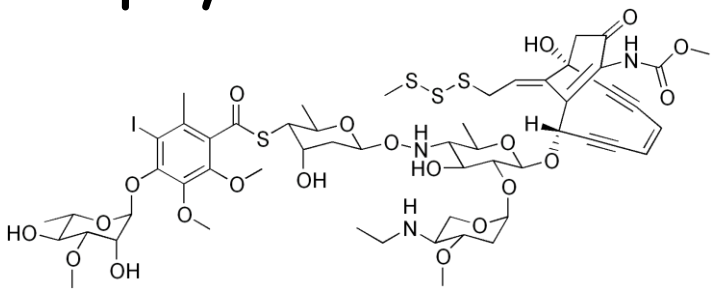


Diversifying conjugates

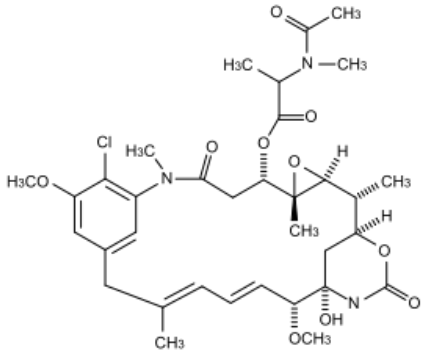


Currently approved payloads

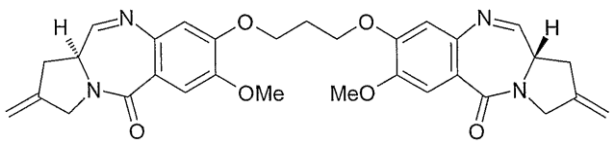
Gemtuzumab Ozogamicin
Calicheamycin
DNA binders



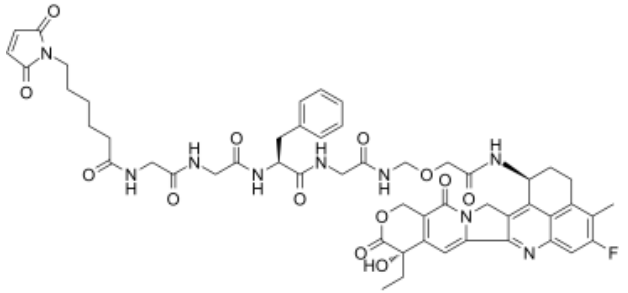
Maytansinoids, auristatin
Tubulin binders



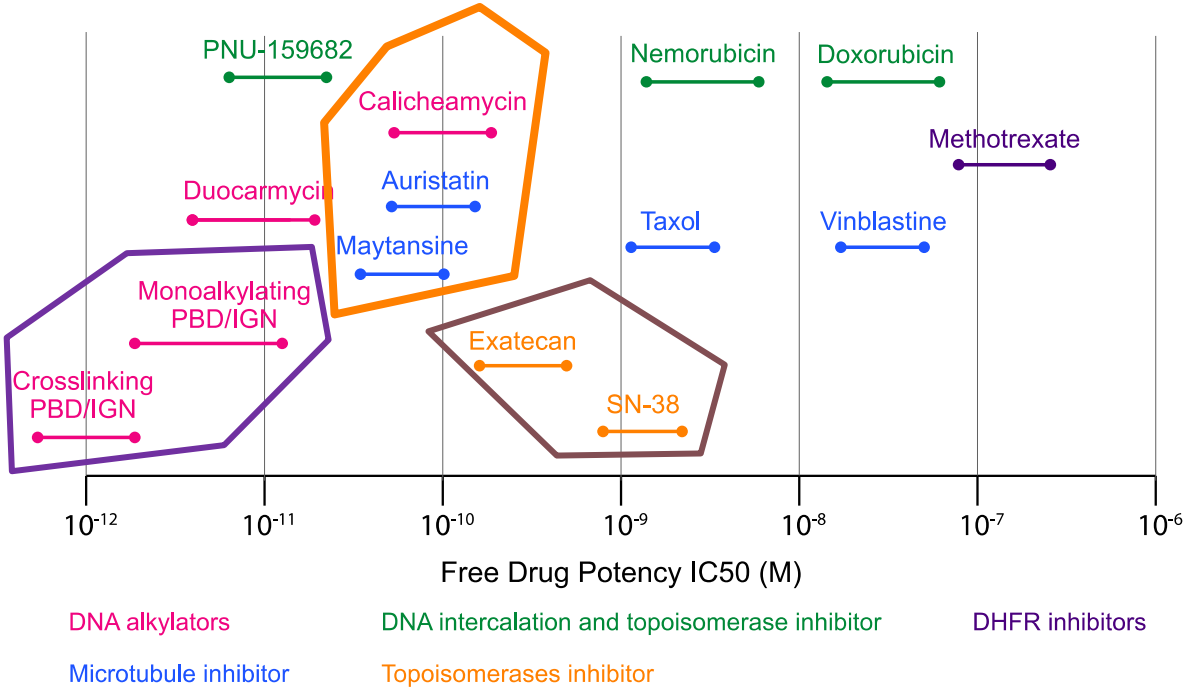
PBD: pyrrolobenzodiazepine
DNA alkylators



Deruxtecan, SN38
Topoisomerase 1 inhibitor



Next generation antibody-drug conjugates



Microtubules inhibitors

DNA-alkilating agents

New ADC target: Topoisomerase I

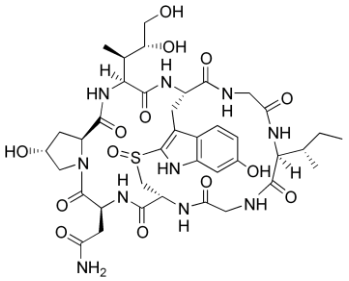
- Enhertu: Trastuzumab-Dxd (2019)
- Trodelvy: anti-TROP2-SN-38

Future payloads ?

Novel cytotoxicity mechanims +++

Bioproteins and small molecules

Ricinus communis (castor bean)



Amanitin

Toxicity and immunogenicity issues


Managing
side-effects

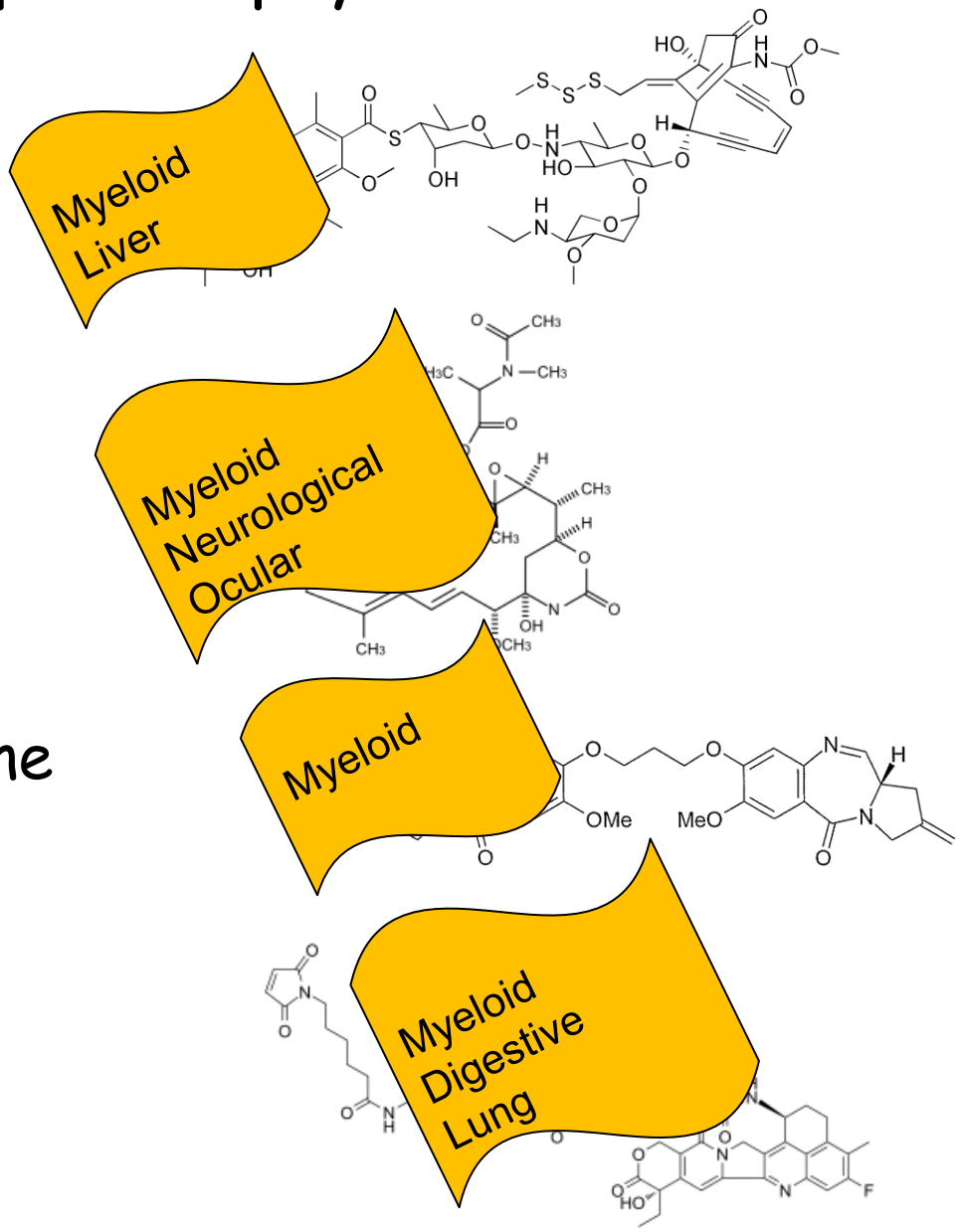
Currently approved payloads

Gemtuzumab Ozogamicin
Calicheamycin
DNA binders

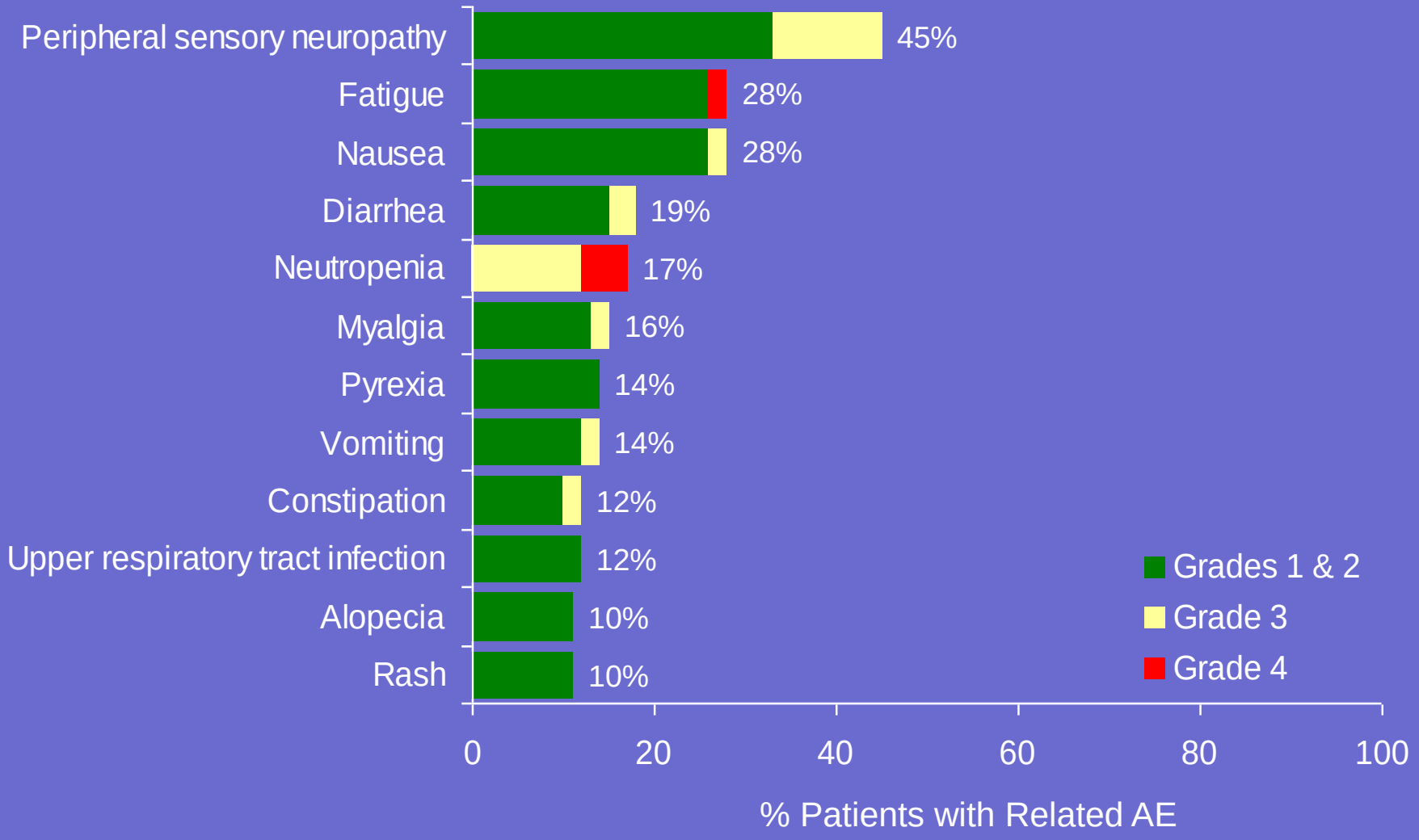
Maytansinoids, auristatin
Tubulin binders

PBD: pyrrolobenzodiazepine
DNA alkylators

Deruxtecan, SN38
Topoisomerase 1 inhibitor



Brentuximab vedotin : most Common Related Adverse Events (≥10%)



Serious adverse events (SAEs) were reported in 31 % of patients. The most common (more than 2 percent) SAEs reported were peripheral motor neuropathy, urinary tract infection, and abdominal pain.

2012: the FDA notified two additional cases of progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection that can result in death, resulting in a new *Boxed Warning* highlighting this risk has been added to the drug label.

Phase I Data for Brentuximab Vedotin Plus ABVD or AVD in Hodgkins Lymphoma[a]

	ABVD arm	AVD arm
Complete Remission (%)	95	96
Pulmonary Toxic Effects (%)	44	0

A new Contraindication warning against use of brentuximab vedotin in *combination with the cancer drug bleomycin* due to increased risk pulmonary toxicity has been added to the drug label.

What is « acceptable toxicity » ?

Is highly dependent on the context and the prognosis

Maximal myeloid toxicity in hematology: induction therapy of acute myeloid leukemia with curative intent

Reversible vs irreversible toxicities

Minimal toxicity expected
- in the adjuvant setting
- in the maintenance setting
- in the palliative setting
- in elderly patients with solid tumors

Toxicity and combos

Catch 22 : *MTD identified as single agent often not applicable to combos*

Issues of overlapping toxicities +++

*calicheamycin, PBDs → **myeloid** toxicity*
cumulative toxicities with cytotoxic agents
***neurotoxic** agents : taxanes, vinca alcaloids, cisplatin, bortezomib, IMIDs, …*

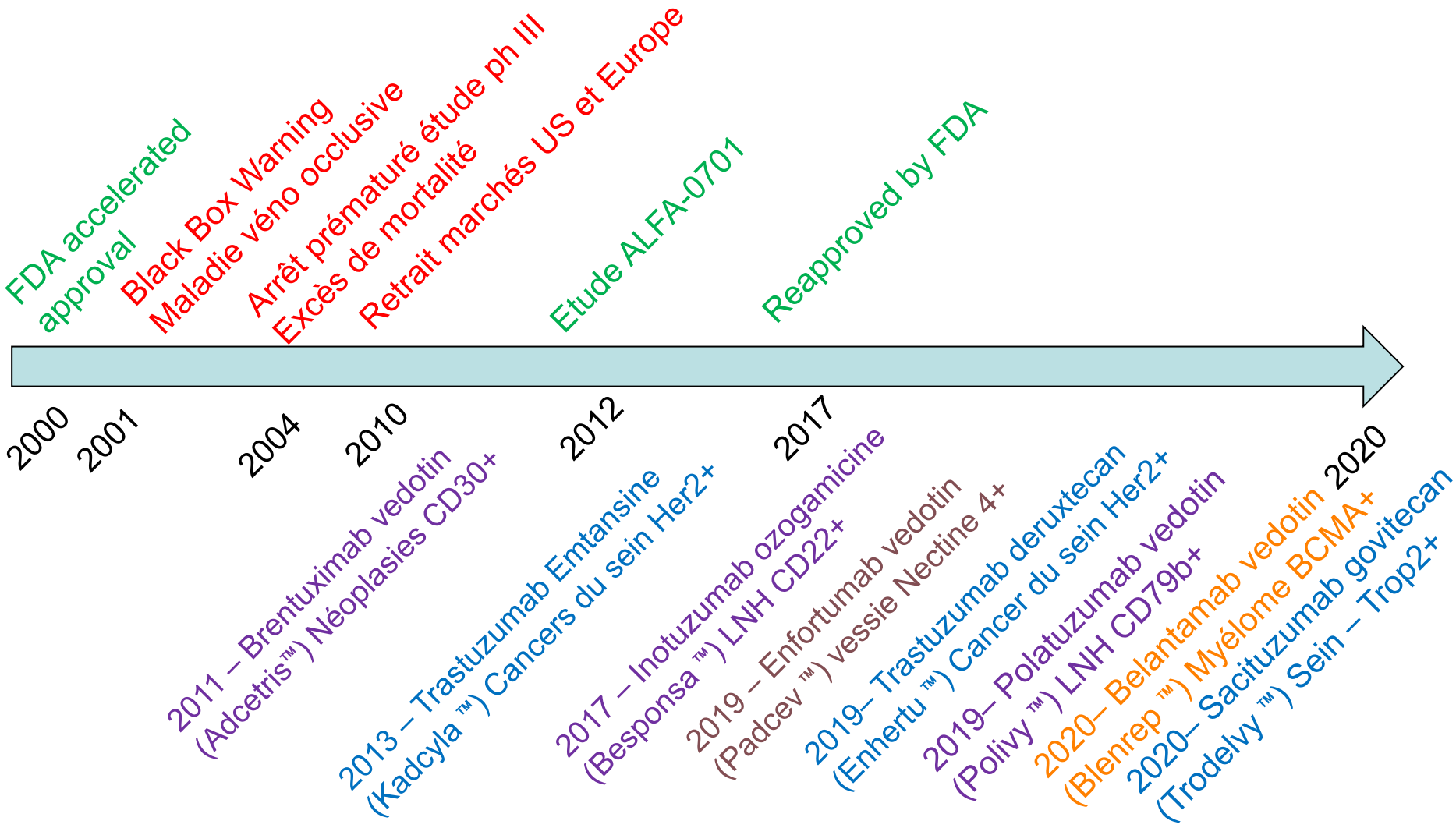
Issues of unexpected toxicities

*brentuximab vedotin and bleomycin → **pulmonary** toxicity in Hodgkin's disease)*

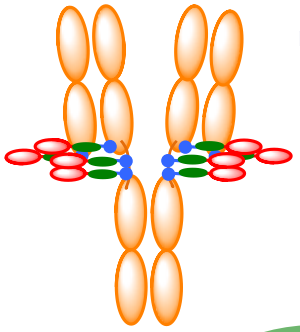
Approved agents
&
Future developments

Currently approved ADCs

Gemtuzumab ozogamicin
anti CD33 coupled to calicheamycin



Non-internalizing ADCs



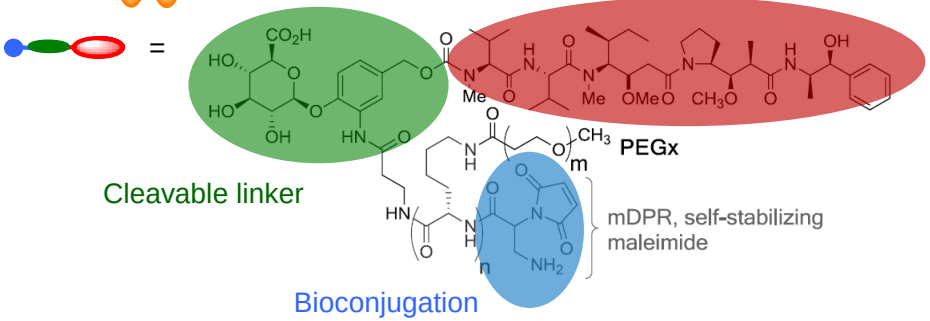
mAb anti-CD19

Large Molecule Therapeutics

Molecular Cancer Therapeutics

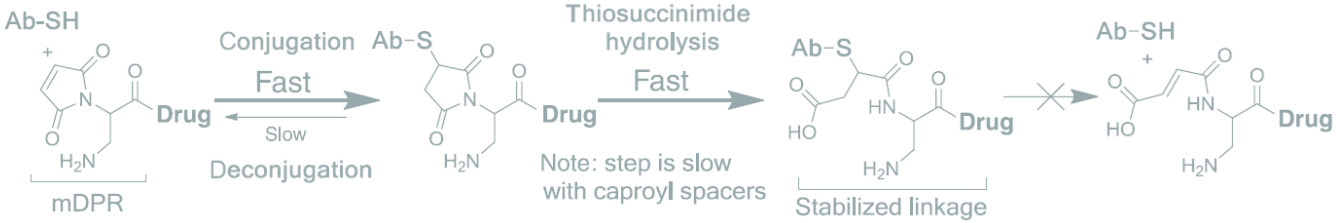
Optimization of a PEGylated Glucuronide-Monomethylauristatin E Linker for Antibody–Drug Conjugates

Patrick J. Burke, Joseph Z. Hamilton, Scott C. Jeffrey, Joshua H. Hunter, Svetlana O. Doronina, Nicole M. Okeley, Jamie B. Miyamoto, Martha E. Anderson, Ivan J. Stone, Michelle L. Ulrich, Jessica K. Simmons, Erica E. McKinney, Peter D. Senter, and Robert P. Lyon



β-Glucuronidase

accumulates in greater concentrations within the **extracellular matrix of solid tumors** following lysosomal release from necrotic or apoptotic cells and tumor-infiltrating monocytes and neutrophils.



SWOT

S

Enhanced efficacy/ toxicity ratio vs. chemo

O

Exploits targets unaccessible to naked Mabs (CD30)

Combos possible

W

Enhanced / toxicity vs. naked Mabs

Intravenous administration

T

Conjugate-specific toxicities (liver, ocular)

Unexpected toxicities in combos (bleomycin)

Future developments

- No paradigm shift yet
- Explore various regimens and combinations
  avoid overlapping toxicities
  combination with immune checkpoint inhibitors
- Favor substitutions of conventional agents with the same mechanisms of action
  example: tubulin binding agents and auristatins or maytansines vs. taxanes anc vinca alcaloids
- Aim for a different target at relapse and at diagnosis:
  example B NHL CD20 then CD19, 22, 79 ?

Aim for payloads with original mechanisms of action +++

Thank you for your attention

Approved antibodies coupled to cytotoxic agent