Antibody Drug Conjugates (ADC) The Current Status

Andrew Zelar, Ph.D.
andrew.zelar@nemo1.com
818 545 7963

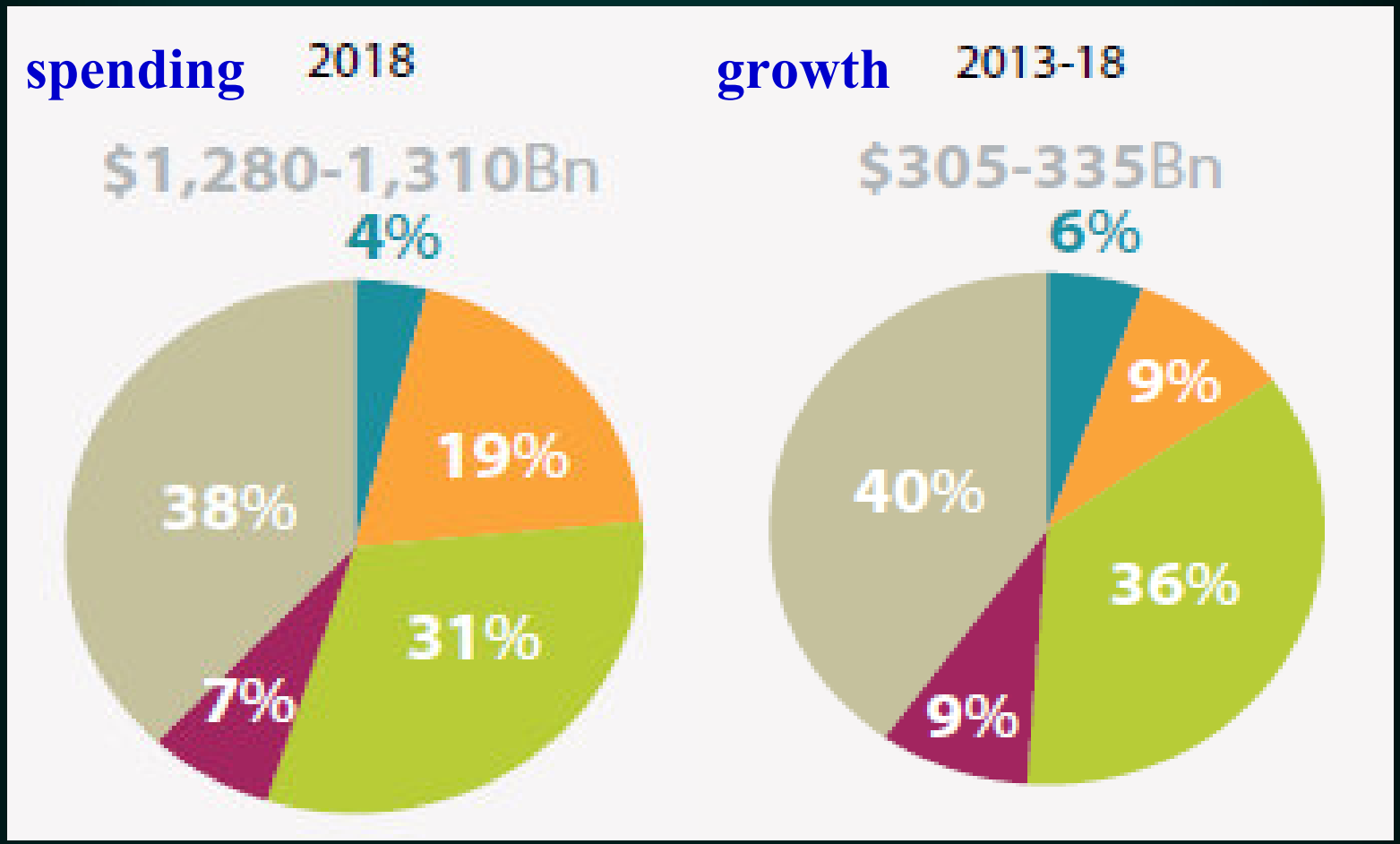
- The field
- ADC on the market
- Conjugation chemistry
- Quality attributes
- Kadcyla, Adcetris, Mylotag, Besponsa, Lumoxiti, Polivy
- Me and ADCs
- Clinical strategy & endpoints
- Accelerated approvals
- Surrogate endpoints - meta view

Global pharmaceutical top markets 2017

Country	Rank	$ Bn	Growth (%)
USA	1	465	4
China	2	121	16
Japan	3	85	-16
Germany	4	47	9
France	5	34	1
Brasil	6	33	5
Italy	7	31	6
UK	8	26	4
Canada	9	21	16
Spain	10	22	4

Association of the British Pharmaceutical Industry - 2017

Geographic distribution of spending & growth



IMS Health -2015

Global cancer medicines

- Global cancer market sales $65 Bn in 2013
- Overall market spending $133 Bn* in 2017
- Global cancer market $200 Bn by 2022
- 10% -13% up globaly next 5 y
- 12% -15% up US next 5 y
- $100 Bn in US by 2022
- Main growth in targeted therapies and biologics

* **Hepatitis C treatments ~ 100Bn not included**

Source: IQVIA 2018

Antibody Drug Conjugates (ADC)

global market

$179 million in 2012

$396 million in 2013

$1.57 Bn in 2017

$3.2 Bn by 2023

(CAGR)* of 12.9% -2017-2023

* compound annual growth rate

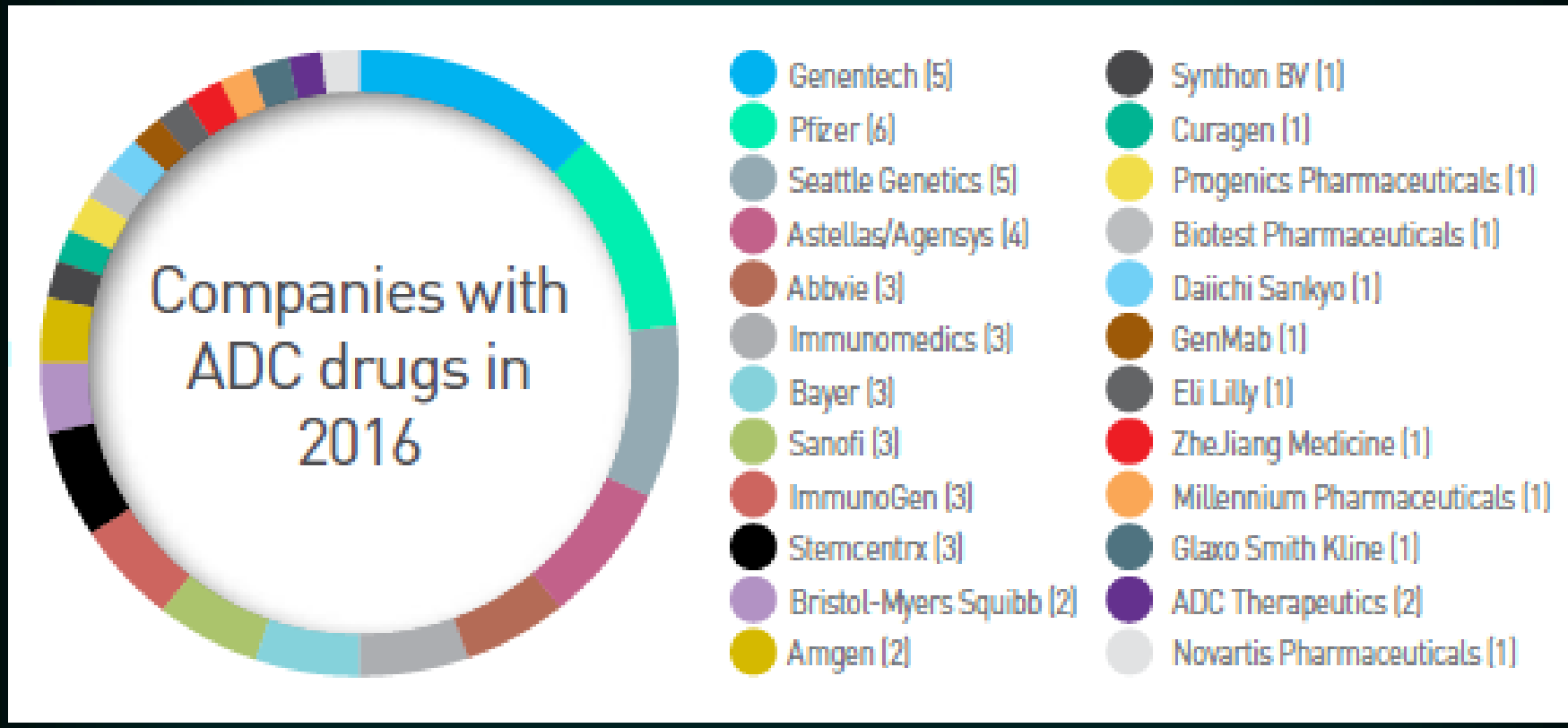
Allied Market Reearch 2019

ADCs in clinic

- 600 total clinical trials with the majority focusing on haematological malignancies.
- 52 open phase I/II studies in solid tumours
- 16 500 Patents in 2019
- 200*unique ADCs under investigation - 35 ADCs investigated in solid tumours

P.Hofland, ADC Review 2018 ADC Market (5th Edition), 2019-2030 ***PRNewswire.com 2019** ***S.Coats et al AACR - 2019***

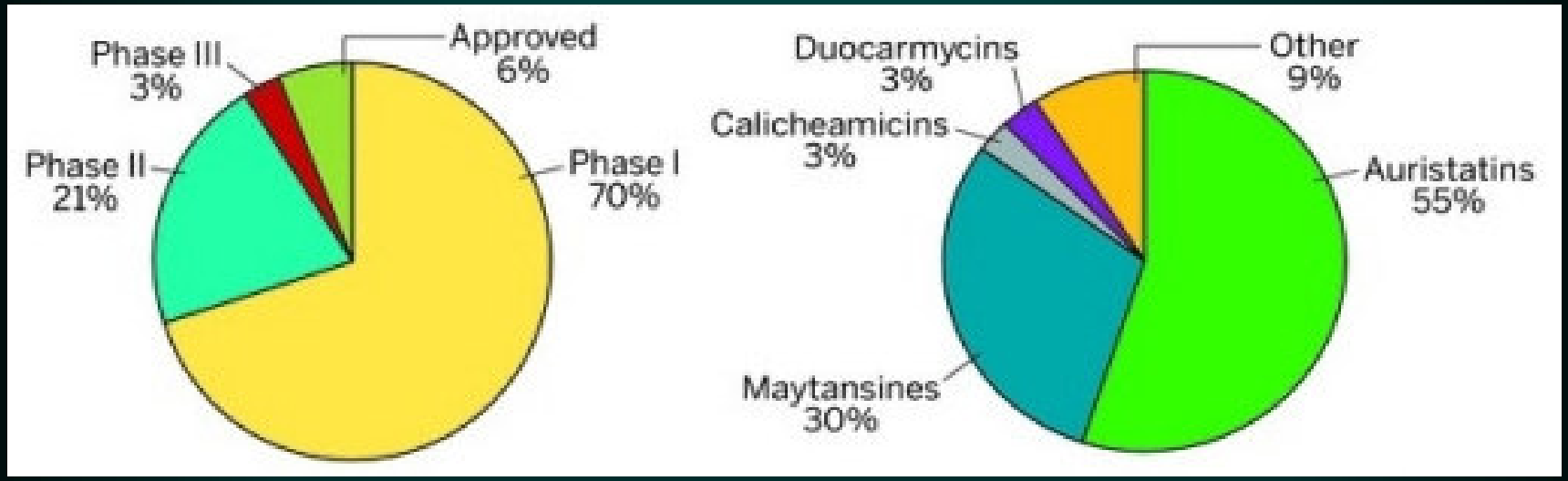
24 companies have ADCs in clinical testing in 2016



http://worldadc-beacon.com

ADC in development

Clinical Phases & cytotoxic payload



Ann M. Thayer C&EN 2019

KEY ANTIGEN TARGETS FOR ADCs

- HER2*
- Nectin-4
- Mesothelin
- GPNMB
- PSMA
- EGFR
- VEGF
- CD19
- CD20
- CD22*
- CD25
- CD30*
- CD33*
- CD40
- CD56
- CD74
- CD79a and CD79b*
- CD138
- CEACAM
- SLITRK6
- LIV-1
- EGP-1
- Mesothelin

** Targets for FDA approved ADC's*

APPROVED ADCs

- **MYLOTARG (GEMTUZUMAB OZOGAMICIN) - Wyeth**

acute myelogenous leukemia from 2000 to 2010
mAb to CD33 + acid-cleavable linker + calicheamicins
Pfizer withdrew Mylotarg 2010, 2017second chance - Pfizer

- **ADCETRIS (BRENTUXIMAB VEDOTIN) - Seattle Genetics**

Hodgkin lymphoma 2011 approved, mAb to CD30
cathepsin-cleavable linker + monomethyl auristatin E

- **KADCYLA (TRASTUZUMAB-DM1) – Genentech**

HER2 positive breast cancer 2013 approved, mAb Herceptin
to HER2 + SMCC linker + maytansinoid (DM1)

- **BESPONSA (INOTUZUMAB OZOGAMYCIN) – Pfizer**

Hematologic cancers 2017 approved, mAb to CD22
+ acid-cleavable linker + calicheamicins

BCC Research LLC &FDA 2019

APPROVED ADCs

- **Lumoxiti (MOXETUMOMAB PASUDOTOX) – AstraZeneca**

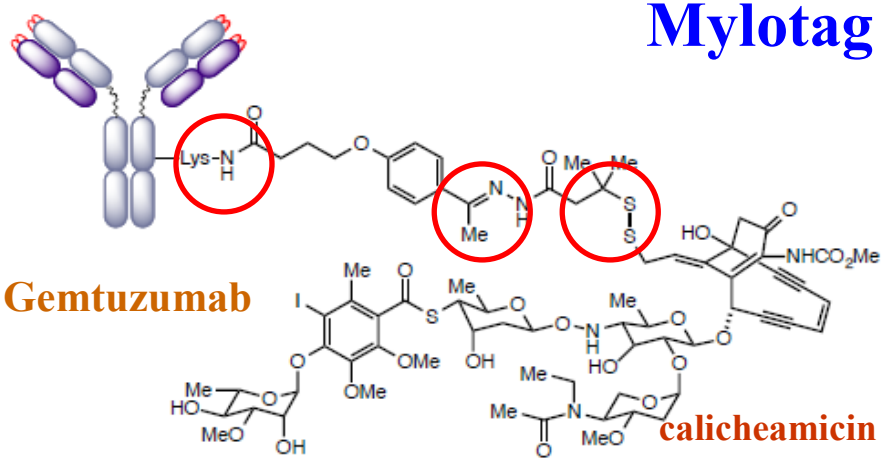
Hematologic cancers 2018 approved, murine Fv to CD22
Fv segment –s-s- fused to the Pseudomonas exotoxin A (PE38)
deleted cell-binding portion

- **Polivy (POLATUZUMAB VEDOTIN) – Genentech**

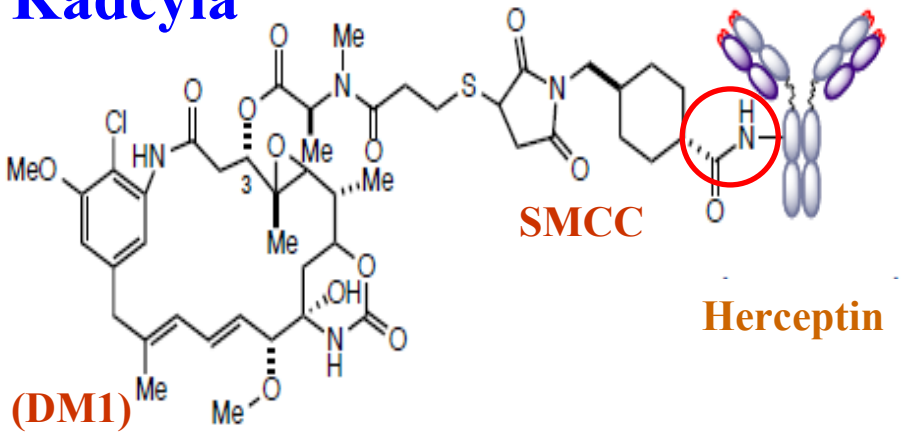
Hematologic cancers in combination with bendamustine & rituximab
2019 approved, humanized murine mab to CD79B conjugated to dolastatin via **(Val–Cit) cathepsin-cleavable linker**

APPROVED ADCs

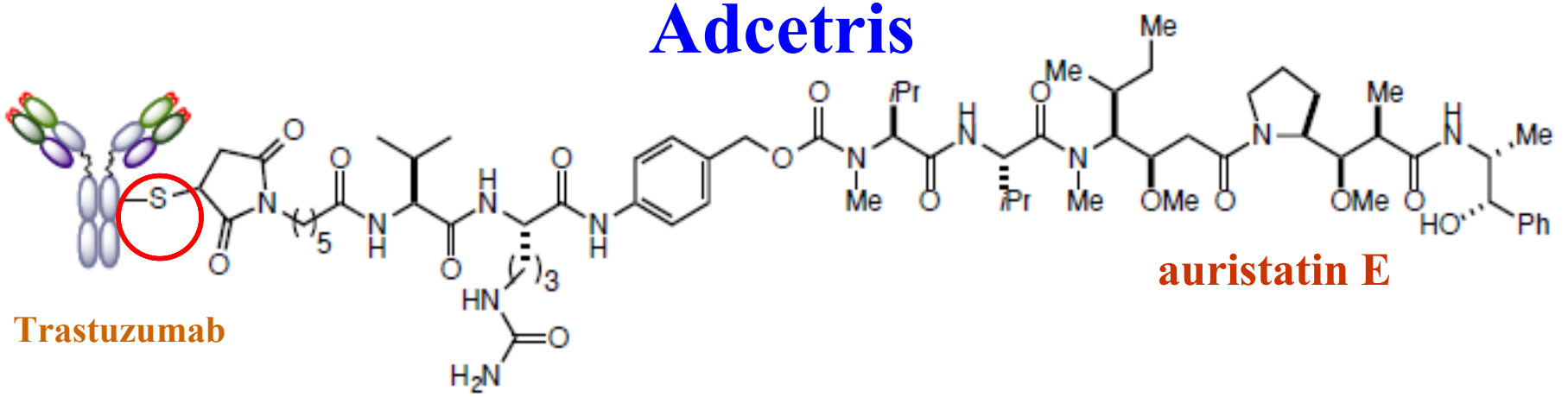
Mylotag



Kadcyla

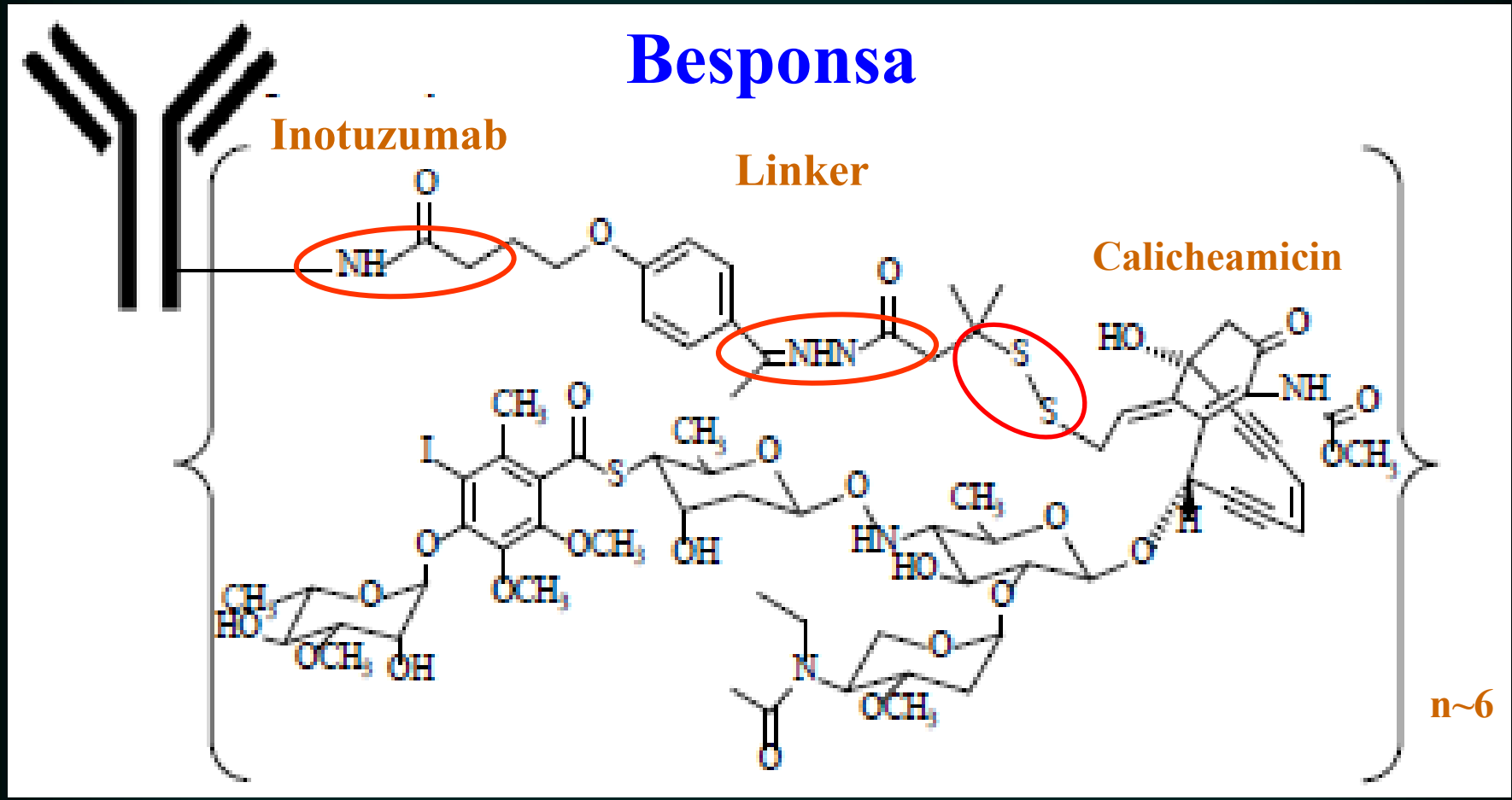


Adcetris



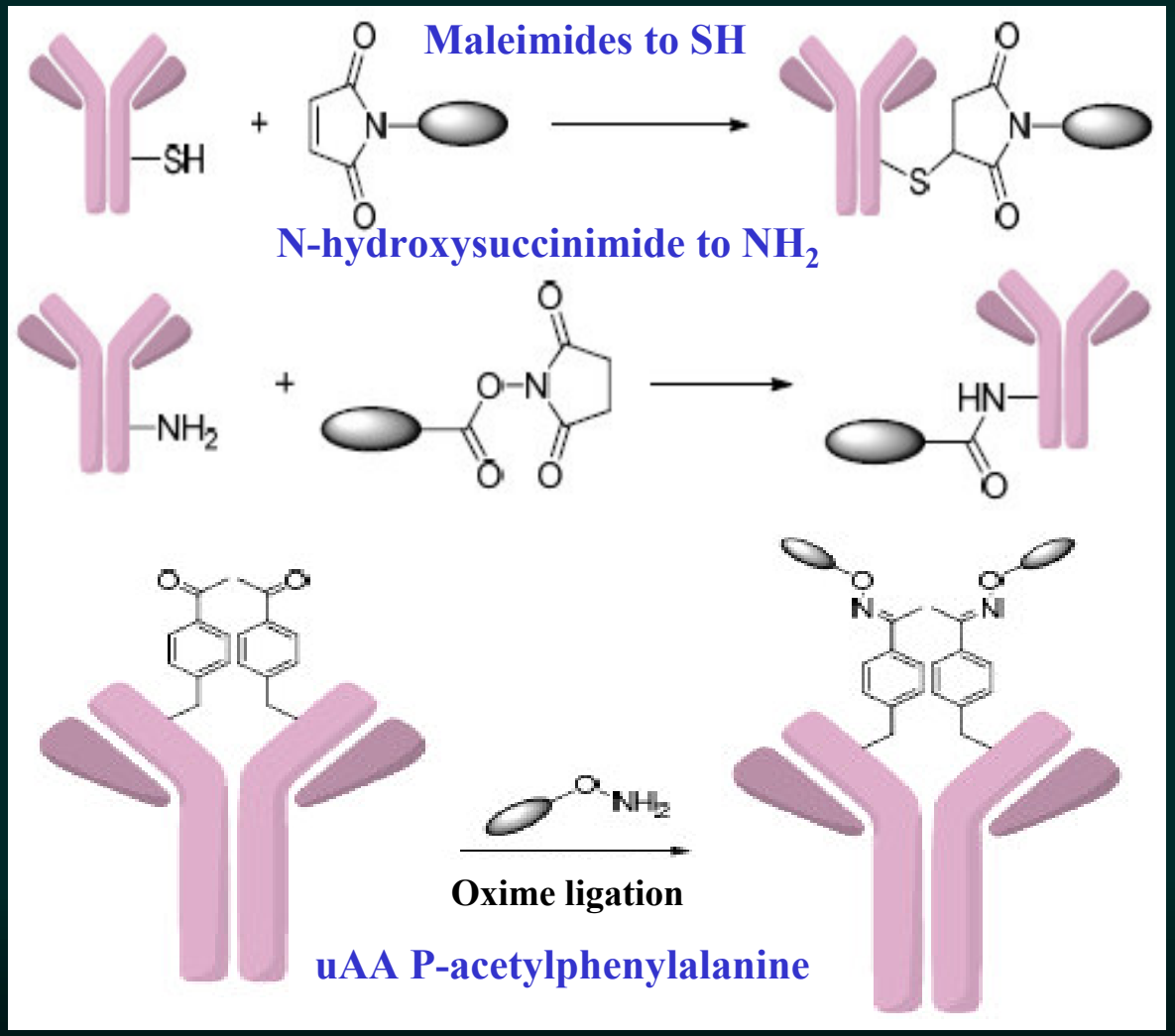
APPROVED ADCs

Besponsa



Besponsa package insert -Pfizer 2017

Examples of conjugation chemistry



H. Yao et al Int. J. Mol. Sci. 2016

Asup et al. Proc. Natl. Acad. Sci. USA 2012,.

Current mAb Conjugation Sites

- **Cysteine (polar)**

4 interchain disulfide bonds in IgG1/IgG4

8 conjugation sites

- **Lysines (basic)**

25/22 lysines in IgG1/IgG4 constant region

8 lysines in κ constant region

Additional lysines in VH or VL regions

DAR – drug : antibody ratio

- ADCs, with Cys & Lys conjugation are heterogeneous, populations with different drug-to-antibody ratios (DARs) and distributions.
- DAR drug-load & distribution are essential to stability and efficacy
- The optimal DAR is undetermined
- Too few drug molecules - decreased efficacy.
- Too many - effect stability, PK, increased plasma clearance, reduced half-life and increased toxicity

A. M. Sochaj et al. Biotechnology Advances 2015

N. Diamantis et. al. British Journal of Cancer (2016)

Hamblett et al. 2004; Teicher and Chari. 2011

Linkers - cleavable and non-cleavable

- Non-cleavable linker - **Kadcyla**
- pH sensitive linkers - hydrazone - **Mylotag**, **Besponsa**
- Glutathione-sensitive linkers -S-S- **Mylotag, Lumoxiti**
- Lysosomal protease-sensitive - cathepsin cleavable (Val-Cit) – **Adcetris, Polivy**
- As 2017 ADC's in development non cleavable ~ **60%**

Groundview research 2019

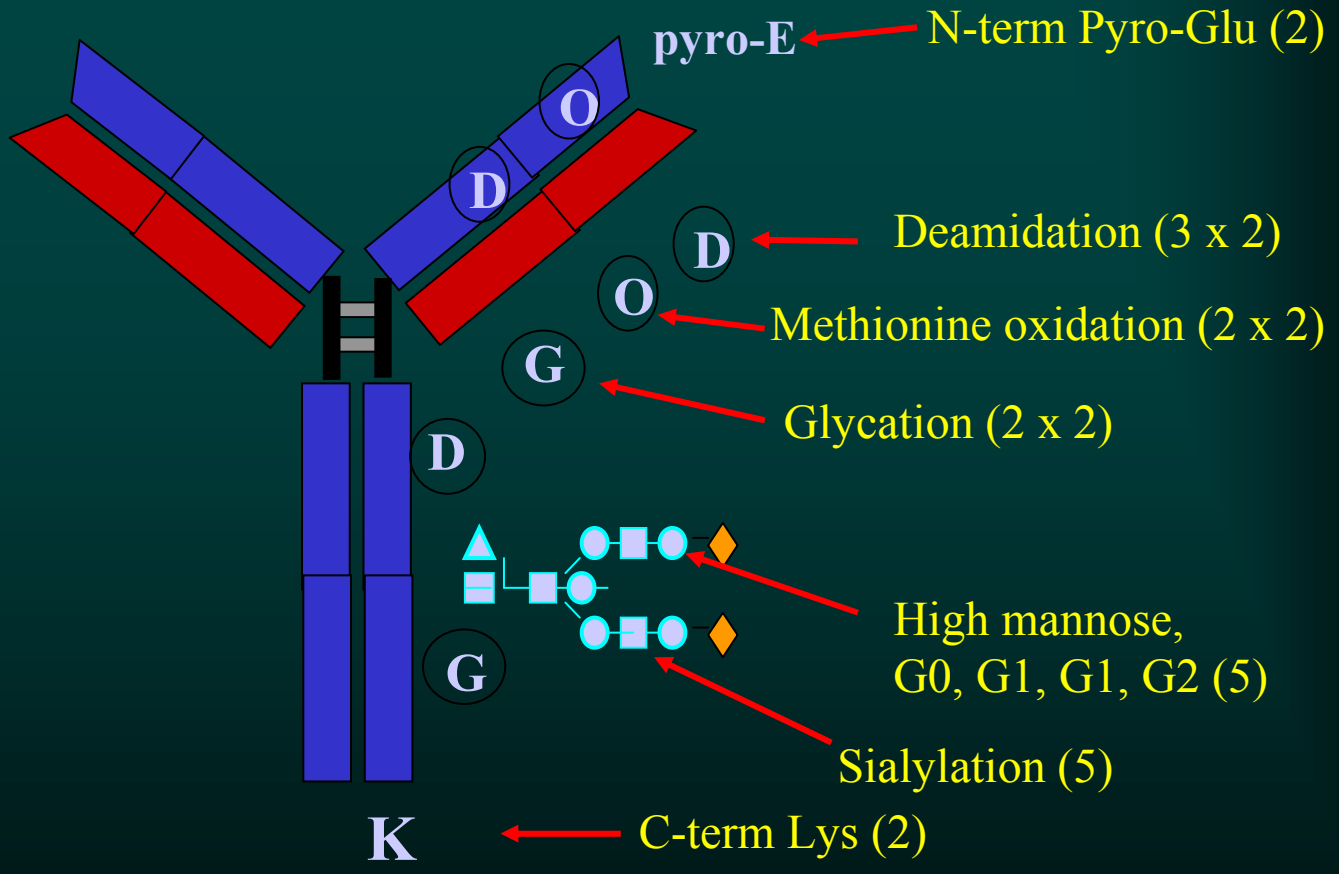
N. Diamantis et. al. British Journal of Cancer (2016)

Radioimmunotherapy

- ^{131}I-tositumab (Bexxar® GSK) non-Hodgkin's lymphoma
- ^{90}Y-ibritumomab tiuxetan (Zevalin® Bayer /Spectrum Pharma) non-Hodgkin's lymphoma
- ^{177}Lu and ^{211}At radioimmunoconjugates targeting colon cancer are in works

A.M. Sochaj et al. Biotechnology Advances 2015

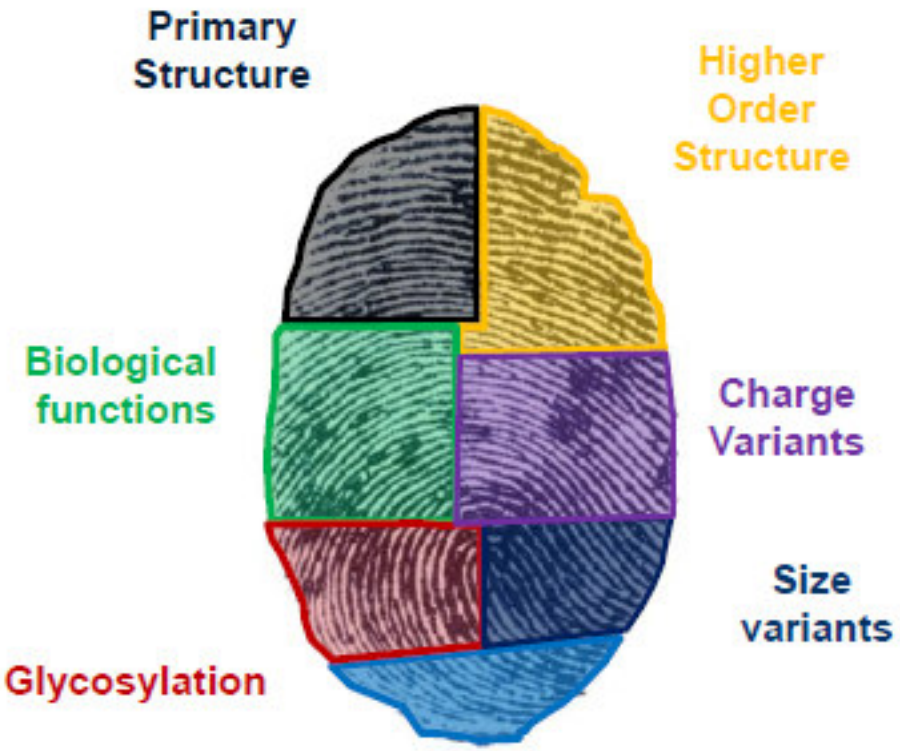
mAb's are a heterogeneous mixtures - the hot spots of change



Quality Attributes analysis

Attributes e.g.:

- Primary structure
  - Mass
- Disulfide bridging
  - Free cysteines
  - Higher order structure
- N- and C-terminal heterogeneity
  - Glycosylation
  - Glycation
- Fragmentation
  - Oxidation
- Deamidation
- Aggregation
  - Particles
- Target-binding
  - Fc effector functions



Methods e.g.:

- MS
- Peptide mapping
  - Ellman's
  - CGE
  - SDS-PAGE
  - CD, FT-IR
- H-D exchange
- NMR, X-ray
  - HPLC
  - HPAEC
  - IEF
- 2AB NP-HPLC
- SE-HPLC
  - FFF
  - AUC
  - DLS
- MALLS
- Bioassays
  - SPR

Jan Visser, ***CMC Strategy Forum Europe 2014, Sorrento, Italy***

Orthogonality & redundancy is the key

- Redundancy
- Orthogonality
  - 50–60 methods to analyze structure
  - 15 methods to test function

For mAbs an array of binding assays to assess both :

- Fab/antigen interaction
- Fc/Fc receptor interaction, binding kinetics, -- surface plasmon resonance (SPR; e.g., Biacore) or biolayer interferometry (BLI, e.g., Octet).

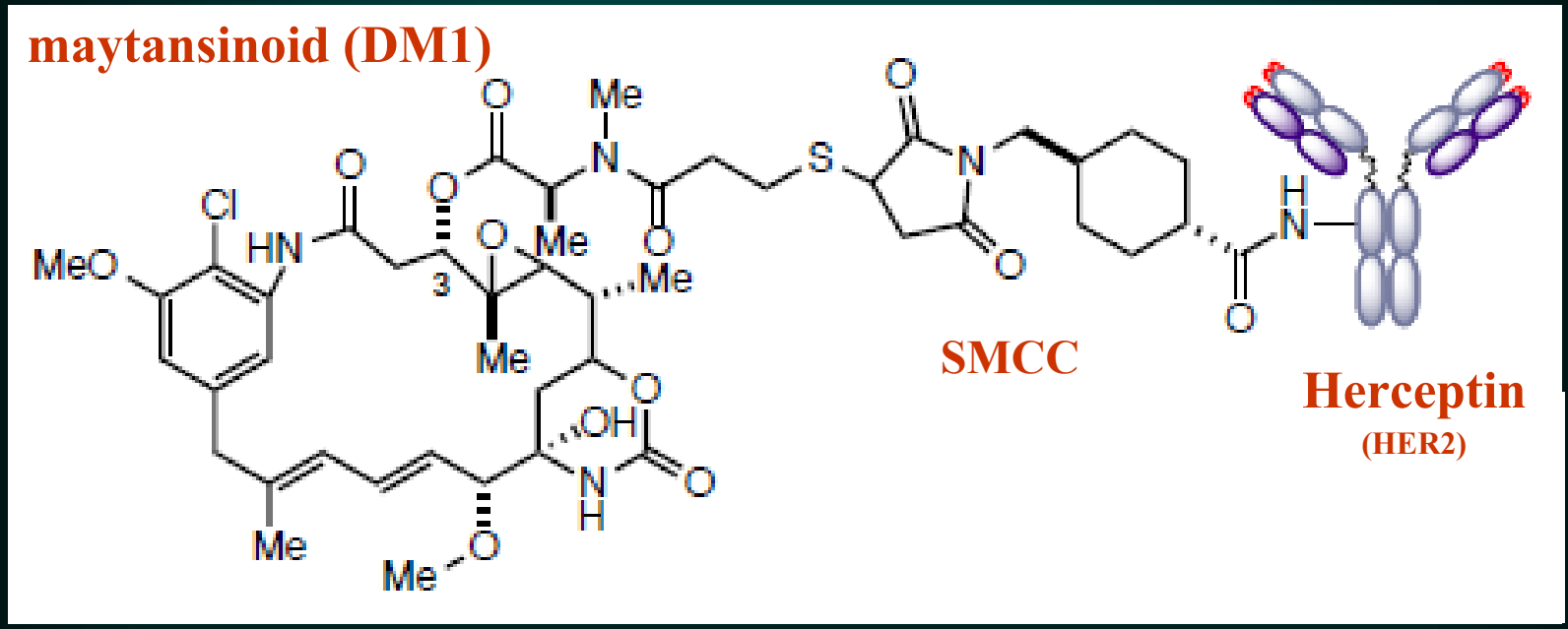
Impact of CQAs on safety and efficacy- (Herceptin)

Attribute	PD	PK	Immunogenicity
Sequence	Nonspecific	Nonspecific	Different response due to sequence modifications
Higher order structure	Nonspecific	Nonspecific	Determined by MW & structure complexity
Glycosylation	Fucosylated, highly mannosylated, and sialylated variants could alter efficacy	Highly mannosylated => higher clearance Highly Sialylated => lower clearance	Sialic acid can hide Antigenic determinants. Highly mannosylated & nonglycosylated variants => up immunogenicity
Charge heterogeneity	Altered if pI differences are >1 unit	Major Δ alter volume of distribution and clearance	Acidic variants are prone to elicit immunogenicity
Aggregates	Lower biological activity	Lower absorption & bioavailability	ADAs presence
FcγRI affinity FcγRII affinity FcγRIII affinity	Affects endocytosis, phagocytosis, antigen presentation ADCC,	Not determined	Not determined
FcRn affinity	Not determined	Lower affinity to acidic & oxidized methionine variants No Δ in variants with 3- to 4-fold changes in FcRn Affinity	Not determined

C. A. López-Morales, et al, BioMed Research International, 2015

Kadcyla

Trastuzumab emtansine



Kadcyla

FDA 2013

65 total 39 recruiting studies - https://clinicaltrials.gov

- Approval was based on the phase III trial Kadcyla vs Xeloda + Tykerb in 991 people with unresectable, locally advanced or metastatic HER2-positive breast cancer previously treated with Herceptin + taxane.

- Improved PFS in patients treated with trastuzumab emtansine (median 9.6 vs. 6.4 months), along with improved OS (median 30.9 vs. 25.1 months) and safety

- Cost - $9,800 /mo, typically $94,000 for a course

Verma S, Miles D, Gianni L, et al. (2012). N. Engl. J. Med. ***367 (19): 1783–91***

Adverse effects

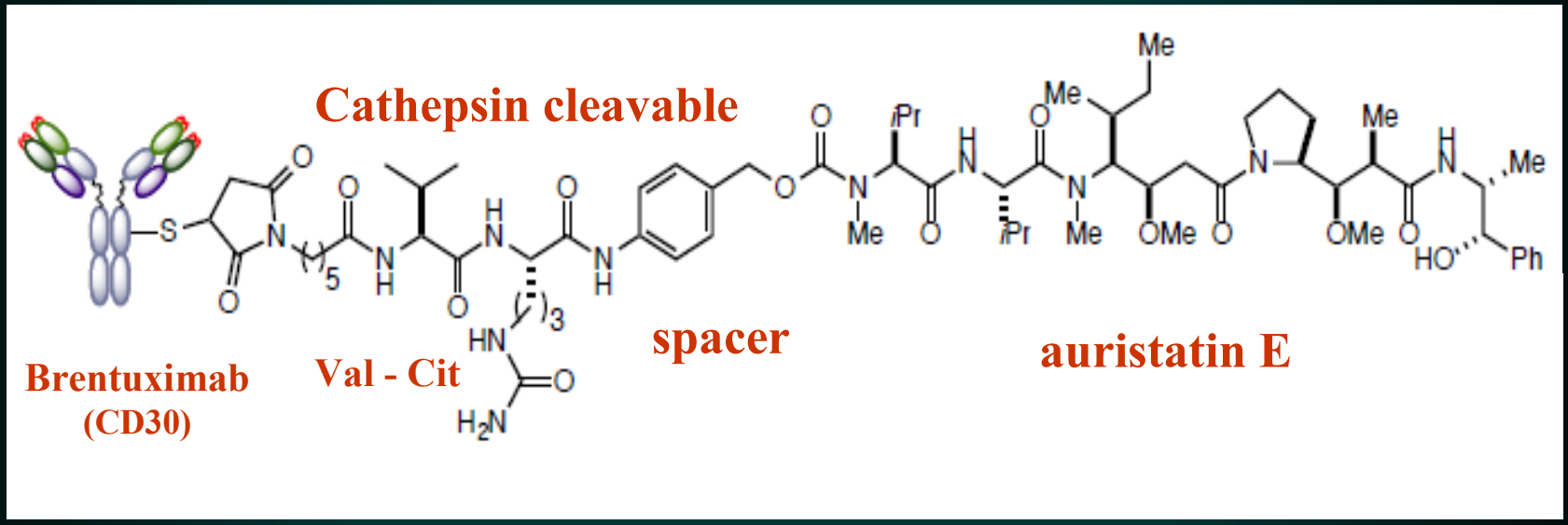
Kadcyla carries black box warings for:

- Liver toxicity
- Heart damage
- Fetal harm if given to pregnant women.

Verma S, Miles D, Gianni L, et al. (2012). N. Engl. J. Med. ***367 (19): 1783–91***

Adcetris

Brentuximab vedotin



Adcetris – indications

Brentuximab vedotin

107 Clin studies 64 active recruiting

- 2011 Seattle Genetics - FDA accelerated approval - *relapsed or refractory Hodgkin's lymphoma* (HL) and *relapsed or refractory systemic anaplastic large cell lymphoma (*ALCL)

- Conditional marketing authorization from the EMEA - 2012 for relapsed or refractory HL and relapsed or refractory ALCL.

J Clin Oncol 30:2183-2189. © 2012

Adcetris – Approval

Hodgkin's lymphoma (HL)

- The accelerated approval for Hodgkin's lymphoma (HL) - single-arm phase II trial, where there was a 75% ORR , 34% CR
- 102 patients 1.8 mg/kg iv every 3 weeks maximum of 16 cycles. The primary end point - (ORR)
- Median progression-free survival (PFS) for all patients was 5.6 months,
- Median duration of response for those in CR was 20.5 months.

J Clin Oncol 30:2183-2189. © 2012

Adcetris – Approval

anaplastic large cell lymphoma ALCL

- The indication for ALCL
  - ORR 86%
  - CR 54%

J Clin Oncol 30:2183-2189. © 2012

Adcetris - serious adverse events

Peripheral neuropathy
Neuropenia
Anemia
Upper respiratory tract infection

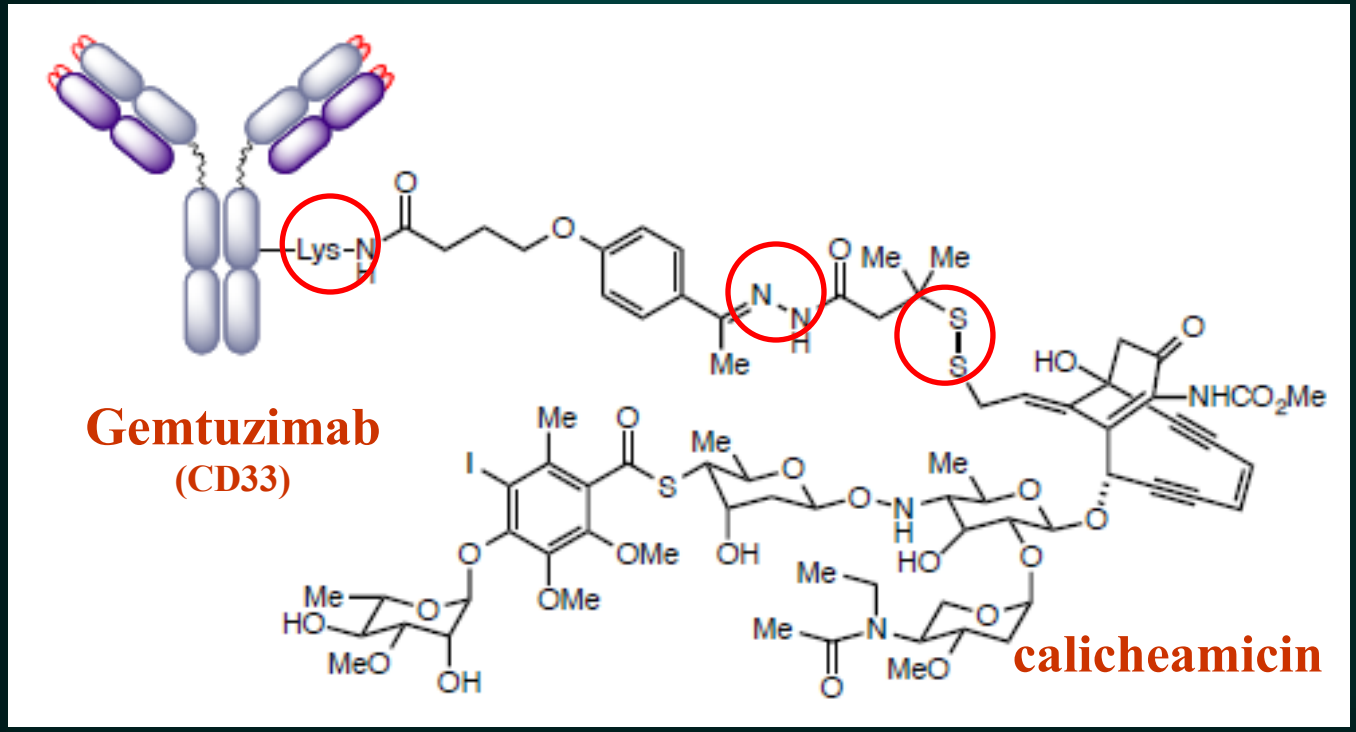
Black box warning

Progressive multifocal leucoencephalopathy

J Clin Oncol 30:2183-2189. © 2012

MYLOTARG

Gemtuzimab Ozogamicin



Tracy Liu, MacMillan Group Meeting 2015, Princeton .edu

Mylotarg - 2000

Gemtuzumab ozogamicin

acute myelogenous leukemia (AML)

- FDA in 2000 accelerated-approval for patients 60 y & older with relapsed acute myelogenous leukemia (AML) – three single arm trials, 142 patients, surrogate endpoint – ORR
- ORR 30% median time to remission was 60 days
- Median relapse-free survival was 6.8 mo

Mylotarg- 2000

acute myelogenous leukemia (AML)

- The post marketing clinical phase 3 trial (2004) was discontinued early - no improvement in clinical benefit in the randomized study

- Test arm - Mylotag 6 mg/m^2 + 3-day anthracycline + 7-day cytarabine in untreated patients age < 60 years.

- Control arm - 3-day anthracycline +7-day cytarabine

adcreview.com 2015

Mylotarg - side effects

- Severe myelosuppression in 98% of patients
- Disorder of the respiratory system
- Tumor lysis syndrome
- Type III hypersensitivity

Black box warning :

- Venous occlusion, and death

adcreview.com 2015

Mylotarg - 2017

acute myelogenous leukemia (AML)

Combination therapy

- The safety & efficacy in combination with chemo daunorubicin and cytarabine (DA) 271 patients newly diagnosed CD33-positive AML

- Test arm --131 patients Mylotarg (3 mg/m^2 Day 1, 4 and 7 in combination with (DA)
- Control arm -- 137 patients treated with DA alone

- Median, event-free survival 17.3 months vs. 9.5 months

FDA - Mylotarg 2017

Mylotarg - 2017

acute myelogenous leukemia (AML)

monotherapy

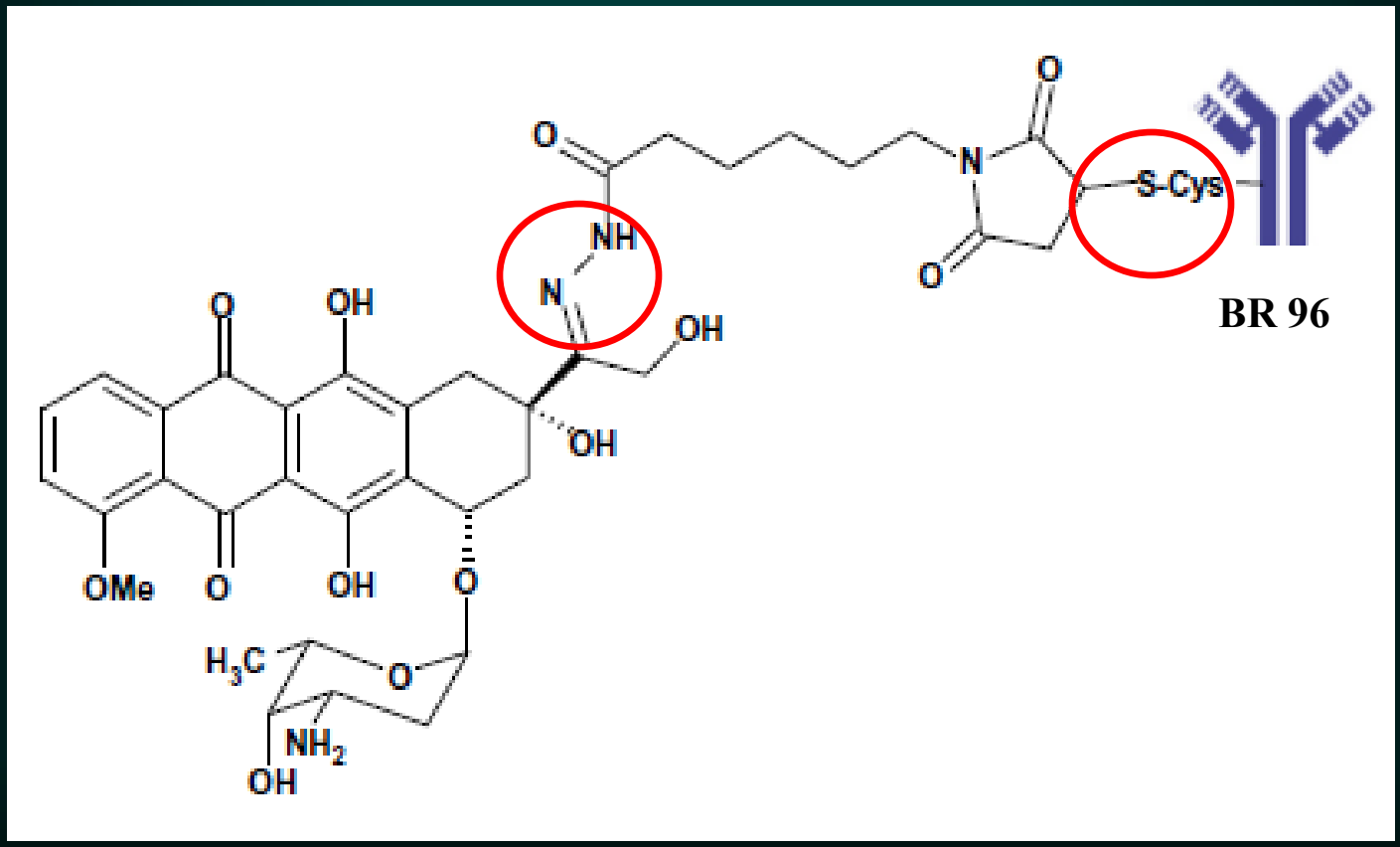
- Test arm - Phase 3 trial (N=118) for Newly-Diagnosed CD33-positive AML. Mylotarg (6 mg/m^2 day-1, 3 mg/m^2 day-7) versus
- Control arm - best supportive care (BSC) (N=119) - Median overall survival 4.9 months vs. 3.6 months

- Single arm (N=57) Relapsed CD33-positive AML, 3 mg/m^2 on Days 1, 4 and 7, 26 % complete remission that lasted a median 11.6 months.

FDA - Mylotarg 2017

BR 96

The chimeric anti-Lewis^y cBR96 mAb conjugated with doxorubicin
The acid-labile hydrazone linker. Blood pH 7.4–7.5 endosomes (pH 5.5–6.2) lysosomes (pH 4.5–5.0) release the active drug after internalisation

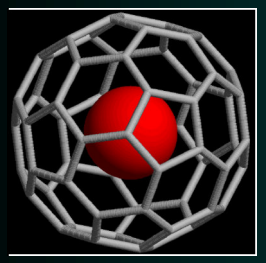


BR 96

H.Bouchard et al. Bioorganic & Medicinal Chemistry Letters 24 (2014)

BR 96 conjugated to :

metal doped Fullerenes & ^{131}I



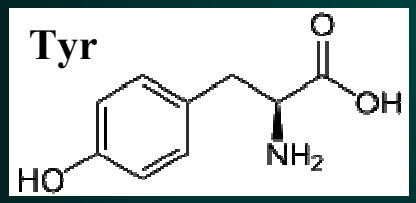
C 60

+ H_2N—NH_2 +

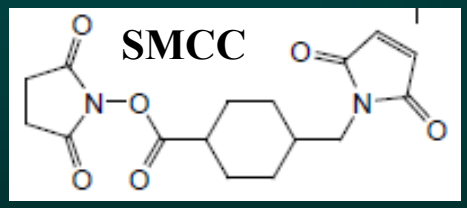
+

BR 96

^{131}I +



+



+

BR 96

● = ^{90}Y, ^{111}In

Strategy - which way ?

(expedited programs - FDA 2014)

	2017	2018
Fast Track	39%	73%
Breakthrough Therapy	37%	73%
Accelerated Approval	13%	73%
Priority Review	61%	73%

FDA Guide Expediated programs for serious conditions 2014

Fast Track

- Serious condition + nonclinical or clinical data demonstrate the potential to address unmet medical need
- Submission with IND no later than the pre-BLA or pre-NDA meeting
- FDA response - 60 calendar days

FDA Guide Expediated programs for serious conditions 2014

Breakthrough Therapy

- Serious condition + preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies
- Submission with IND no later than end-of-phase 2 meeting
- FDA response - 60 calendar days

FDA Guide Expediated programs for serious conditions 2014

Accelerated Approval

- Serious condition + generally provides a meaningful advantage over available therapies + demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
- Possibility + endpoints to be discussed with FDA case by case
- FDA response – not specified

FDA Guide Expediated programs for serious conditions 2014

Priority Review

- Serious condition + significant improvement in safety or effectiveness
- Submission with BLA/NDA
- Six months vs ten months
- FDA response - 60 calendar days

FDA Guide Expediated programs for serious conditions 2014

The aims of a Phase I oncology trial are:

- To identify the appropriate drug dose, dosing interval, route of drug delivery, PK/PD characteristics, safety, toxicity and carcinogenicity
- Endpoints of a Phase I trial include evaluating dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD)
- Phase Ib trials test an anti-cancer agent in combination with other anti-cancer agents
- Oncology Phase 1 trials enroll cancer patients

R.Ananthakrishnan Critical Reviews in Oncology/Hematology (2013)

Phase II Oncology trial

- Test the safety and efficacy of a fixed dose on patients with one specific cancer type
- Phase II oncology trials have traditionally been single arm, open-labeled trials
- Phase II randomized trial provide a better estimate of treatment effect for an endpoint for Phase III

R.Ananthakrishnan Critical Reviews in Oncology/Hematology (2013)

Phase III Oncology designs

- **Double-blinded and randomized** typically. In the two arm parallel arm design, patients are randomized to either the study drug or the standard of care (SOC).
- **Superiority trials** commonly (i.e. to test if the study drug is superior to the standard of care in terms of the primary efficacy endpoint and not worse in terms of safety).
- **Equivalence trials** to test if the study drug and the standard of care are the same within an equivalence margin
- **Non-inferiority** trials to test if the study drug is not worse than the standard of care within a margin, commonly used in biosimilar trials/studies

R.Ananthakrishnan Critical Reviews in Oncology/Hematology (2013)

Oncology clinical Trial Endpoints

- **Overall Survival (OS) –** The time between treatment and death (from any cause)
- **Disease Free Survival (DFS) –** The length of time between treatment and relapse or death generally used in adjuvant.
- **Progression Free Survival (PFS) –** The length of time between treatment and measurable worsening of the disease or death (**TTP** does not include deaths)
- **Objective Response Rate (ORR) –**The percentage **(CR + PR)** of patients whose cancer shrinks or disappears after treatment. Frequently used in single-arm trials

Clinical Trial Endpoints FDA 2007

End Points – Oncology

Surrogate End Points vs Marketing Approval

End Points	Example	Type of approval
Established Surrogate	Response Rate (RR) in brest cancer with hormonal treatment	Regular approval
Reasonably likely surrogate	Response Rate in refractory solid tumors	Accelerated approval
Not reasonably likely surrogate	Tumor markers	Not approvable

"Oncology endpoints.." J.R. Johnson, G. Williams, R. Pazdur - J Clin Oncol 2003

End Points – Oncology

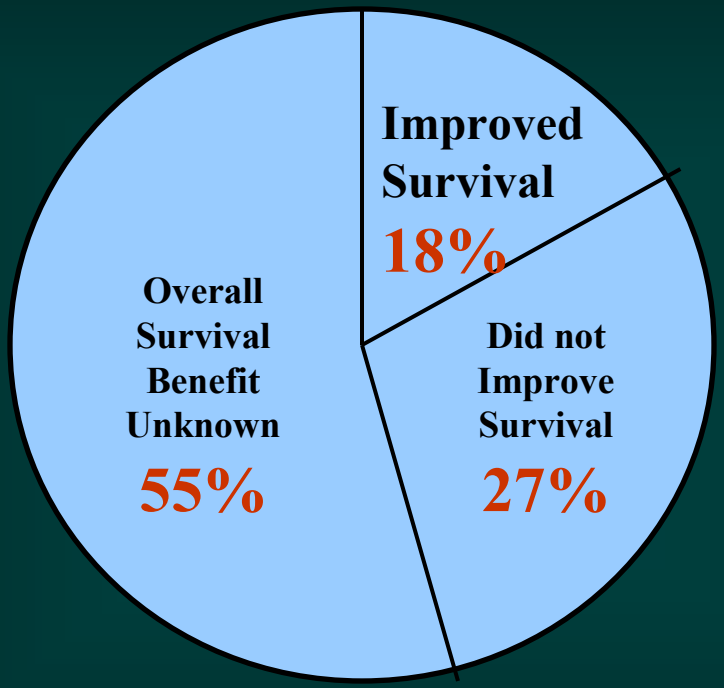
1990 to 2002

Surrogate End Points were basis for:

- 68% (39 of 57) – of regular approvals
- 25% (14 of 57) – of accelerated approvals

"Oncology endpoints.." J.R. Johnson, G. Williams, R. Pazdur - J Clin Oncol 2003

Accelerated approval vs Improved survival



Among 55 cancer drugs recently approved on the basis of a surrogate endpoint, less than one-fifth have been shown to improve survival in follow-up clinical trials.

C. Kim & V. Prasad, Mayo Clinic Proceedings (2016)

Accelerated approval vs validation trials

- Out of eight products approved with accelerated approval (AA) 1995 – 2000 the average time between the granting of marketing through AA and the completion of ongoing validation trials for these eight products was projected to be ten years.
- After receiving authorization to market the product, the sponsor often has a loss of the sense of urgency

T.R. Fleming Health Affairs 24, (2005)

The End