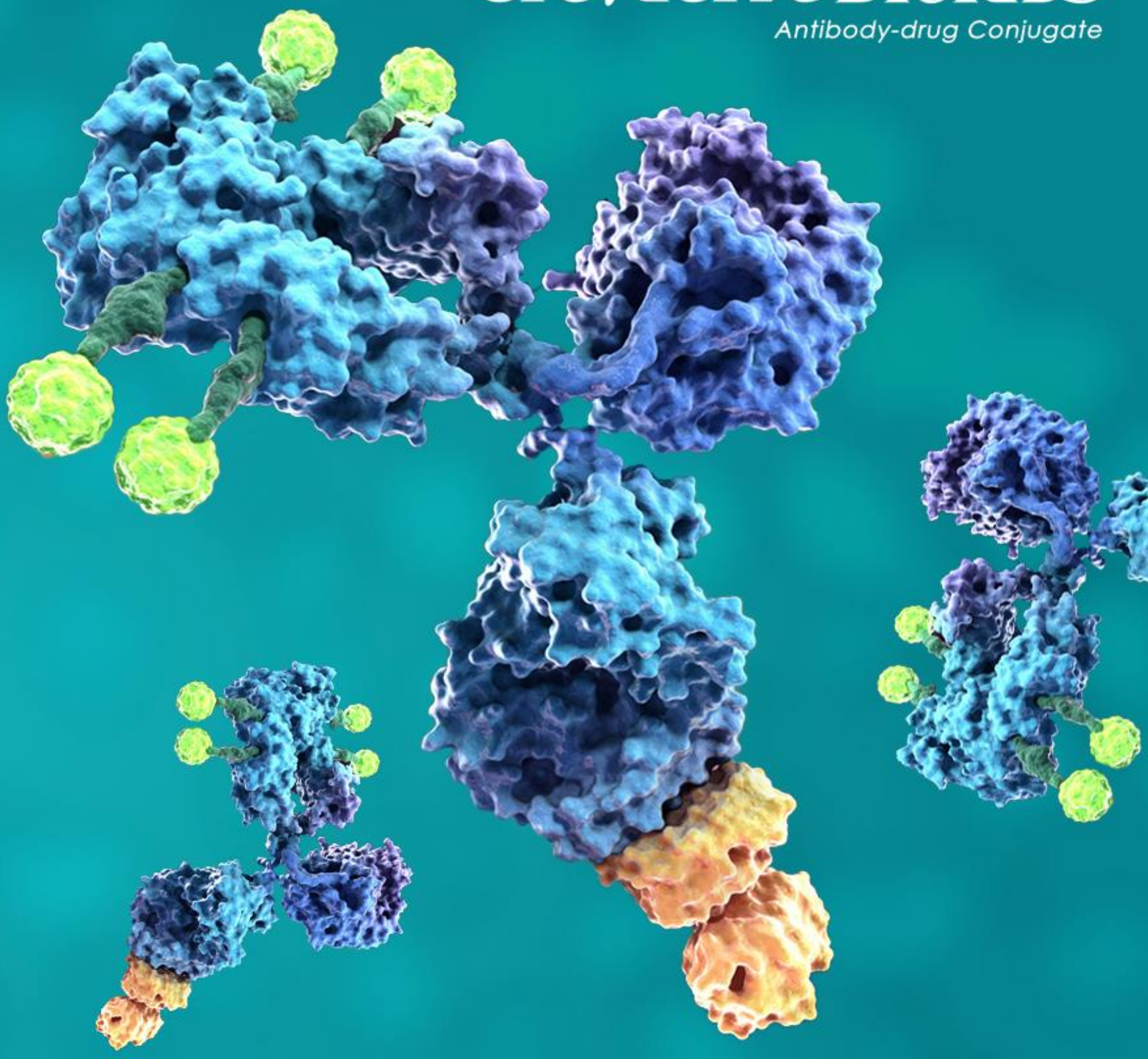
Creative Biolabs®

Antibody-drug Conjugate



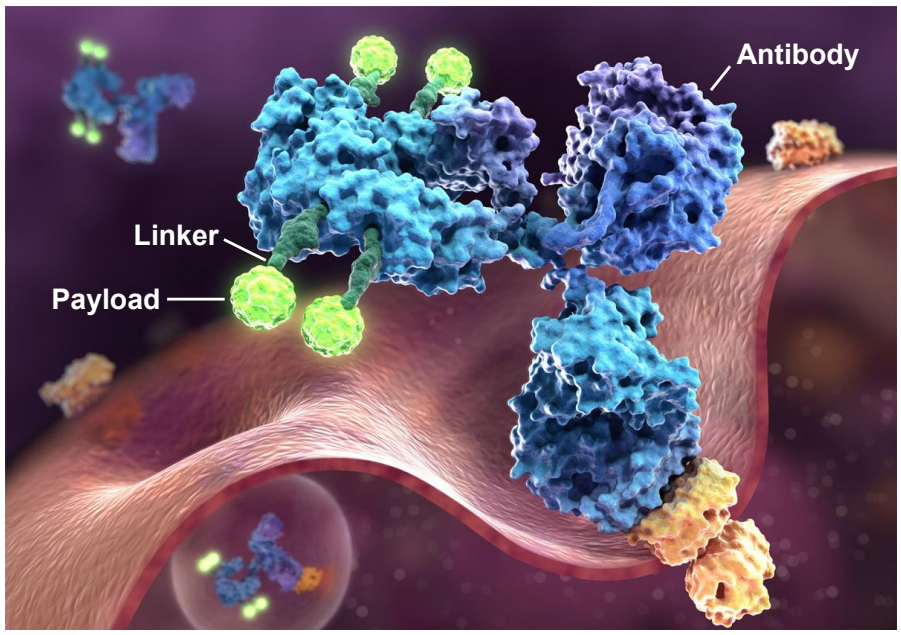
Global Antibody-drug Conjugate (ADC)

Clinical Trial Review

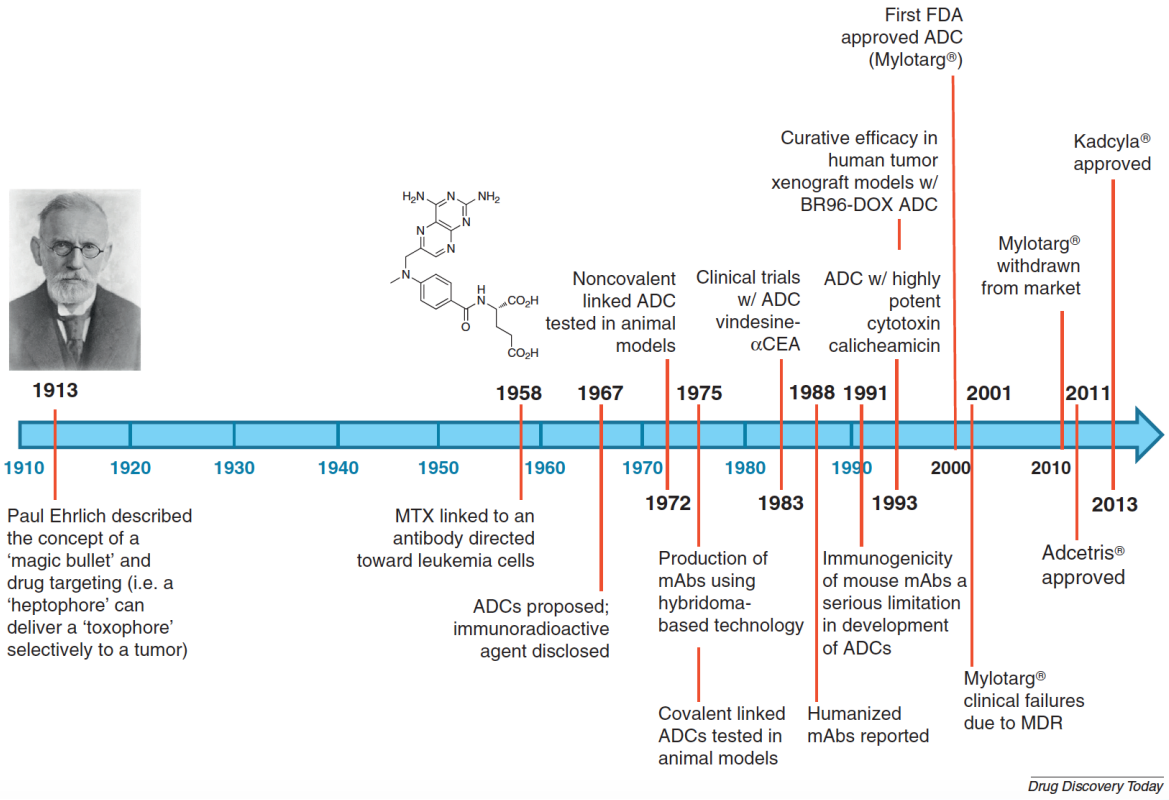
Global Antibody-drug Conjugate (ADC)

As innovative next-generation immunotherapeutic agents, antibody-drug conjugates (ADCs) are being developed worldwide as a major strategy to combat cancer and other immunological disorders. With the combination of a monoclonal antibody and extremely toxic chemical payloads, these bio-macromolecule “warheads” are by far one of the most powerful weapons in the immunotherapy arsenal, bearing the hope as “the beginning of the end” to the battle against cancer.

An ADC is formulated by conjugating a toxic payload with a monoclonal antibody via a small chemical linker. The antibody portion of an ADC serves as a molecular guidance system that accurately delivers the toxic payload to the tumor site for target elimination with minimum collateral damage to the healthy tissues. The payloads used in ADCs interrupt crucial intracellular pathways (microtubule dynamics, DNA structure and integrity, as well as gene transcription and translation…) and often exert extreme toxicity. The chemical conjugation of the payload to the antibody expands the therapeutic window of the payloads and enables the usage of these otherwise lethal compounds into tumor therapy for highly efficient tumor cell elimination by both ADC and bystander killing effects from the cycling free payloads. Linkers are another important component in an ADC that serve as a bridge to covalently connect the antibody and the payload. In the meantime, a linker also dictates the payload release mechanism.



The basic concept of ADC was proposed by German physician Dr. Paul Ehrlich well-known as the “magic bullets” back in 1913. By far, with four FDA-approved ADCs (Mylotarg, Adcetris, Kadcyla, and the newly approved Besponsa) and over 70 new ADCs under clinical evaluation, this concept has become a reality and Dr. Ehrlich’s vision and legacy continues to shape the new era of modern immunology, hematology, and medicine.



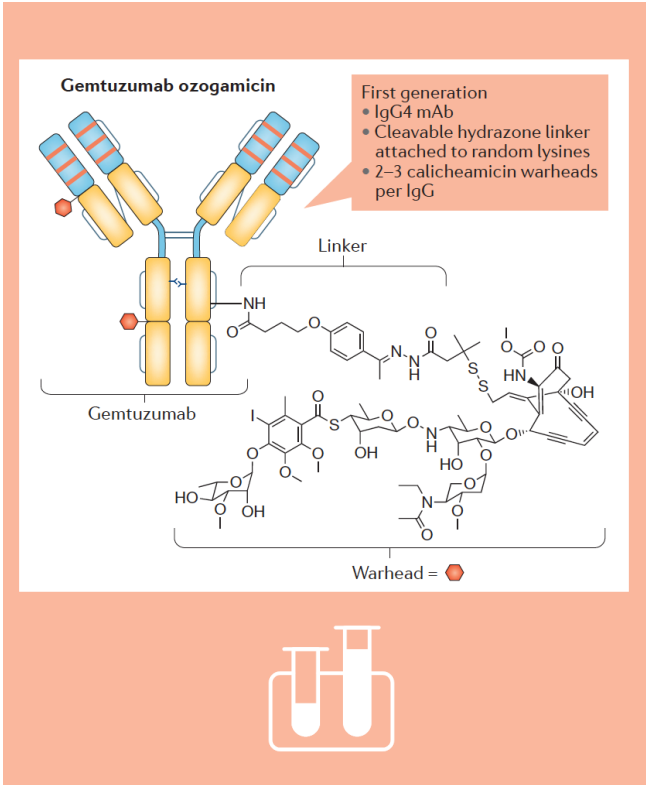
As an interdisciplinary product of protein biochemistry, synthetic organic chemistry, and bio-conjugation chemistry, ADC development has gained worldwide attention and we are in an age of “ADC boom” with a large number of emerging ADCs in the clinical trial pipeline. To formulate an ADC is quite challenging and the major challenges include selecting a suitable target, develop an antibody with high affinity and internalization capability upon binding, using a suitable linker that enables proper drug release and retains ADC serum stability, and lastly, optimization of the conjugation strategy to facilitate adequate payload loading for desired efficacy. After the successful demonstration of high efficacy in the pre-clinical settings, an ADC is interrogated in the clinical trials for a thorough evaluation of the expected drug efficacy and safety. This document offers a comprehensive review of the global ADC clinical trials and our outlooks on the trends in future ADC developments.

Part 1: Overview of the FDA-approved ADCs

2017 is highlighted with the approval of Besponsa (inotuzumab ozogamicin) by the FDA in August. This is by far the fourth ADC therapeutic that have acquired FDA approval. Prior to Besponsa, three other antibody-drug conjugates have gained FDA approval during the most recent course of 10 years. This section reviews general information regarding these ADCs and their market revenues.

Mylotarg

Developed by Wyeth and later Pfizer, Mylotarg, with a generic name of gemtuzumabozogamicin, was the first ever antibody-drug conjugate (ADC) to be granted with FDA approval to treat patients with acute myeloid leukaemia (AML). This ADC is comprised of an anti-CD33 monoclonal antibody, gemtuzumab, coupled with calicheamicin via an acid-labile linker. The antibody portion of Mylotarg, Gemtuzumab is a humanized IgG4 monoclonal antibody while the payload portion, calicheamicin, is a highly toxic DNA cleavage agent that binds to double stranded DNA molecules in the minor groove and cause strand scission. The linker use for Mylotarg is a bi-functional 4-(4-acetylphenoxy)butanoic acid linker and the calicheamicin is conjugated to gemtuzumab via antibody Lys residues. The linker contains a hydrazine module that enables the release of the payload upon internalization and the encounter of the acidic environment in lysosome.

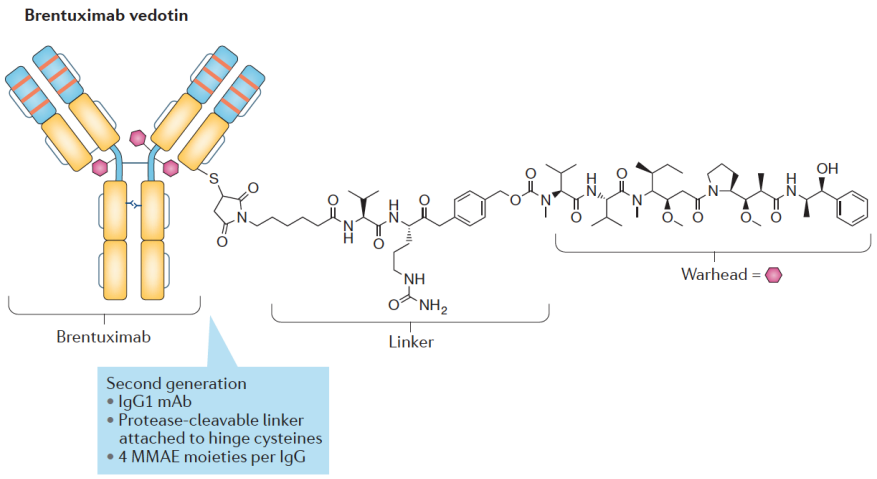


Mylotarg was launched in 2001 but was withdrawn from the market in 2010 after the failure to demonstrate improved survival in combination with chemotherapy and the result of a higher rate of fatal toxicity than chemotherapy alone. The original ADC was released as a mixture containing 50% ADC and 50% naked antibody. The high heterogeneity of the formulation and the instability of the hydrazone linker both contributed to the undesired side effect of this ADC and it was considered as a set-back for ADC developments. However, with extensive improvement made to the ADC and its dosing regimen, it has been validated that the benefits of this treatment outweigh the risk. Mylotarg gained FDA approval once again in 2017 for the treatment of adults with newly diagnosed acute myeloid leukemia (CD33-positive AML). The FDA also approved Mylotarg for the treatment of patients aged 2 years and older with CD33-positive AML who have experienced a relapse or who have not responded to initial treatment (refractory).

Adcetris

Since the approval of Mylotarg, the second ADC that gained FDA approval is Adcetris, developed by Seattle Genetics. Adcetris, with the generic name of brentuximab vedotin, is approved in the United States 2011 for the treatment of Hodgkin lymphoma and one type of non-Hodgkin lymphoma: anaplastic large cell lymphoma (ALCL). Since then, it has gained approval in more than 65 countries, including Brazil, Japan, and countries in the European Union.

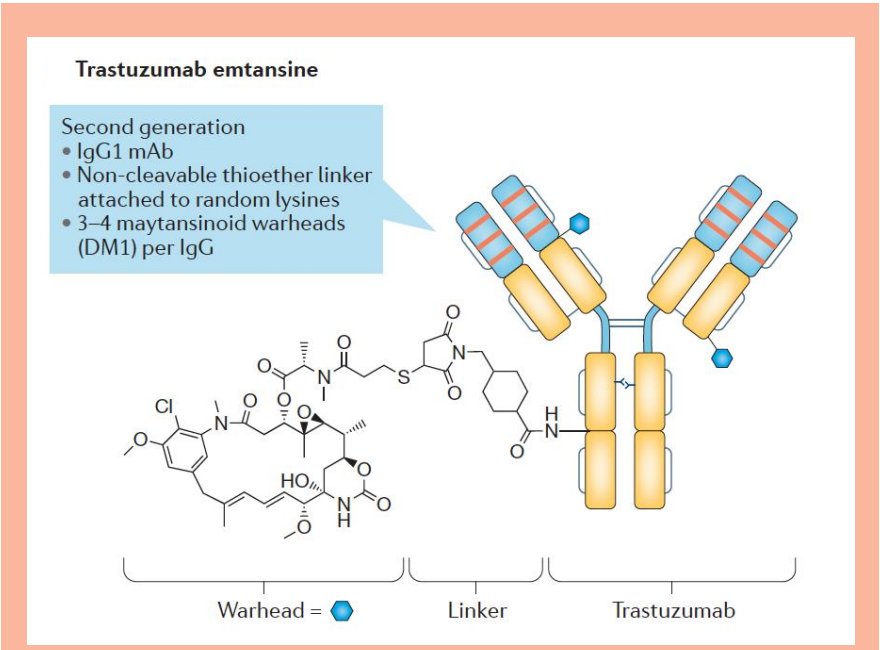
Adcetris is formulated by the conjugation of brentuximab, an anti-CD30 (also known TNFRSF8) monoclonal antibody with payload monomethyl auristatin E (MMAE) via a cleavable peptide linker. Brentuximab is a chimeric IgG1 monoclonal antibody that is developed by grafting the mouse anti-CD30 antibody CDR onto a human Fc framework while the payload, MMAE, an antimitotic agent, is an auristatin derivative that inhibits mitosis by impeding tubulin polymerization. The linker used in Adcetris is a di-peptide Val-Cit (vc) linker with a core structure that is digested by cathepsin B in the lysosome upon internalization and trafficking to release MMAE at its most native form. The payload-linker is conjugated to the antibody via Cys residues.



The Adcetris clinical trial showed clear effect of this ADC against Hodgkin lymphoma and ALCL with increased long-term survive rates. Currently, several clinical trials featuring Adcetris in combination of different chemotherapeutic agents or therapeutic monoclonal antibodies are ongoing for more versatile treatment regimens against Hodgkin lymphoma, CD30+ malignant mesothelioma, recurrent and refractory CD30+ germ cell tumors, ALK-positive anaplastic large cell lymphoma…

Kadcyla

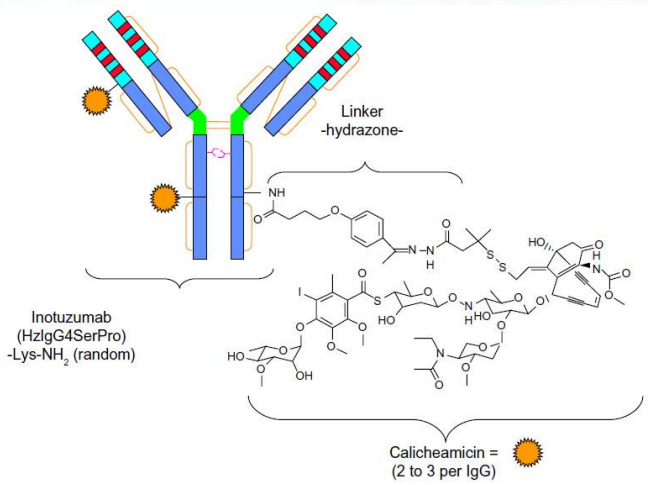
Two years after the FDA approval of Adcetris, in 2013, Kadcyla, an ADC developed by Genentech (now acquired by Roche) and ImmunoGen for the treatment of HER2+ breast cancer, gained fast-track approval by FDA. Kadcyla, also known as T-DM1, with the generic name trastuzumab emtansine or ado-trastuzumab emtansine, is designed by conjugating of trastuzumab with DM1, a maytansinoid derivative via a non-cleavable SMCC linker. Briefly, the antibody portion of Kadcyla, trastuzumab (trade name Herceptin) is a humanized IgG1 monoclonal antibody that specifically target HER2 while its payload, DM1, is also a mitosis inhibitor and functions by disrupting tubulin polymerization. The linker used in Kadcyla is a non-cleavable SMCC linker, which attaches the payload to the Lys residues on the trastuzumab.



Kadcyla underwent a three-phase clinical study with an open-label dose escalation study in phase I that showed a 73% clinical benefit rate whereas the objective response rate (ORR) was 44 % in the first treatment plan. In phase II, patients with HER2-positive MBC were objected to Kadcyla or a combined regimen with Kadcyla plus pertuzumab. The results showed improved PFS and obvious clinical benefit rate with partial or complete responses. Phase III was designed as an EMILIA study: a randomized, open-label, international trial that involved 991 patients from 24 countries with HER2-positive, unresectable, and locally advanced or MBC who had previously been treated with trastuzumab and taxane. Patients showed increased OS, longer symptom progression time, and higher ORR comparing to other methods of therapies. The good efficacy of Kadcyla earned its fast approval in both USA and EU.

Besponsa

Besponsa, with the generic name of inotuzumab ozogamicin, gained FDA approval in Aug 2017, making it the fourth ADC that hits the market in the past 6 years. This ADC is developed by Pfizer for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.



Besponsa is comprised of an anti-CD22 monoclonal antibody (Inotuzumab) conjugated with the payload N-acetyl-gamma-calicheamicin via a bi-functional 4-(4-acetylphenoxy)butanoic acid linker. The payload-linker portion of Besponsa is identical to that of Mylotarg and the payload-linker complex is conjugated via Lys residues of inotuzumab. With improved conjugation method, Besponsa shows better homogeneity and stability comparing to Mylotarg. Non-clinical data have suggested that the anticancer activity of inotuzumab ozogamicin is due to the binding of the ADC to CD22-expressing tumor cells, followed by internalization of the ADC-CD22 complex, and the intracellular release of the payload via hydrolytic cleavage of the linker. Activation of payload induces double-strand DNA breaks and subsequently leads to cell cycle arrest and apoptotic cell death.

Table 1. Summarization of FDA-approved ADCs.

Trade name	Generic name	Main Developer	Target	Cancer	Year of FDA approval	Payload	Linker
Mylotarg	gemtuzumab ozogamicin	Wyeth, Pfizer	CD33	CD33+ AML	2001	calicheamicin	Hydrazone (acid cleavable)
Adcetris	brentuximab vedotin	Seattle Genetics	CD30	Hodgkin lymphoma and ALCL	2011	MMAE	VC (cathepsin B cleavable)
Kadcyla	trastuzumab emtansine	Genentech (Roche)	HER2	HER2+ breast cancer	2013	DM1	SMCC (non-cleavable)
Besponsa	inotuzumab ozogamicin	Pfizer	CD22	relapsed or refractory B-cell precursor acute lymphoblastic leukemia	2017	calicheamicin	Hydrazone (acid cleavable)

International Markets for Approved ADCs

Upon launching, both Adcetris and Kadcyla have created significant revenue for their developers. The annual revenues of these two ADCs exert an increasing trend during the recent years. The annual revenue of Adcetris in USA alone has reached 226 million USD in 2016 while the total revenue of Kadcyla has come to an astonishing 831 million USD in 2016.

In terms of international marketing, for Kadcyla, the sales in USA and EU occupies a major share of the revenue but in the past two years, the sales in Japan and other Asia-Pacific countries, EEMEA (Eastern Europe, Middle East and Africa), Latin America, Canada, and Other countries are also on the rise.

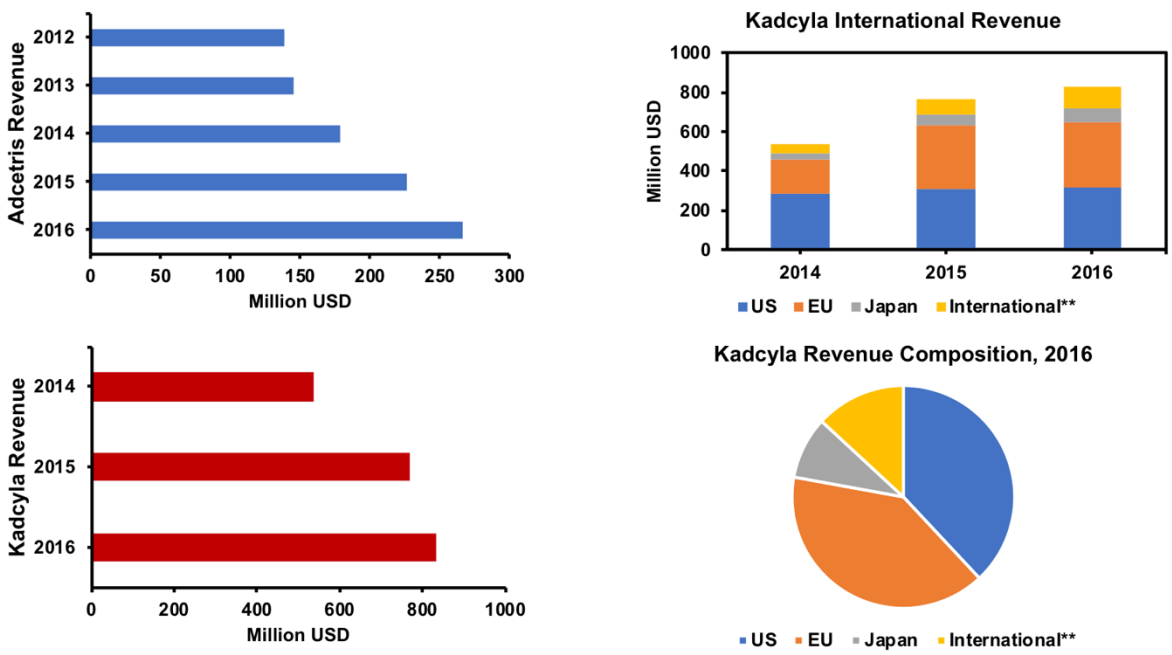


Figure 1. Annual sales revenues of Adcetris and Kadcyla since market approval (left two panels) and the international marketing for Kadcyla (right two panels)

*: The full revenue number of 2017 is lacking but from the first three-quarter sales of Adcetris and the first 6-month sales of Kadcyla in 2017, an increased trend can be expected.

**: international countries include Asia-Pacific countries (besides Japan), EEMEA (Eastern Europe, Middle East and Africa), Latin America, Canada, and Other countries.

Part 2: Overview of ADCs in Clinical Trials

Major pharmaceutical companies worldwide contribute to the current flourishing number of antibody-drug conjugates (ADCs) in clinical trial pipeline. A total of 38 companies, most of which reside in USA and Europe, provide the world with more than 70 active ADCs under evaluation, which raises a new hope in the battle against more than 35 different types of cancers in ~18 organs and tissues. The ADC targets, indications, and companies contribute to the current ADC landscape will be reviewed in subsequent sections of this document, while this section focuses on each component in the ADCs under clinical evaluations.

Antibody

As mentioned earlier, a typical ADC comprises of an antibody and a cytotoxic payload coupled by a small molecule linker. Monoclonal antibodies against various tumor surface targets (reviewed in next section) are used exclusively in ADC formulation. To reduce potential immunogenicity accompanied by the antibodies, full human antibodies or humanized antibodies are commonly used. In terms of antibody isotype, IgG is the only format used in ADCs under clinical evaluations while IgG1 subclass occupies a dominant portion.

So far, a total of 95 ADCs (include the projects in the “suspended” status) are under clinical evaluation or adjustments, among which 4 are developed based on IgG2 and 5 are based on IgG4 or engineered IgG4. Agensys/Astellas is the main developer with IgG2 format-ADCs with AGS-16C3F (Phase II), AGS-15ME (Phase II), and AGS-67E (Phase I) at different clinical Phases. Glembatumumab vedotin, developed by Celldex for the treatment of melanoma, osteosarcoma, and TNBC, is another IgG2-ADC that is currently under pivotal Phase II. Pfizer is the major developer in IgG4/engineered IgG4 ADCs with Mylotarg (approved in Japan), Inotuzumab ozogamicin (approved in Aug-2017), CMD-193, and CMB-401. CMD-193 and CMB-401 are in Phase I but currently under suspension. Indatuximab ravtansine, developed by Biotest against multiple myeloma, is the last IgG4-ADC that is currently under active Phase II evaluations.

IgG1, being one of the most well characterized IgG subclasses, is the major force in ADC developments and contributes to 88% of the ADCs in clinical evaluation. Regular IgG1 antibodies are susceptible for chemical conjugation at either Lys residues (e.g. Kadcyla) or inter-chain Cys residues (e.g. Adcetris) to form ADCs that usually show a heterogeneous nature in the final conjugate. To improve the homogeneity of an ADC, various engineering approaches have been deployed to introduce specific orthogonal conjugation sites into the antibody sequence constant region. THIOMAB, a unique technical platform developed by Seattle Genetics, introduces engineered Cys residues into the Ab sequence to achieve site-specific conjugations. Five ADCs developed using THIOMAB technique are under clinical evaluation with Vadastuximab talirine at Phase III and SGN CD70A, SGN CD19B, SGN CD123A, and SGN CD352A at Phase I. The payloads use for all the above ADCs are PBD derivatives and the ADCs mainly target hematologic malignancies. A second method to introduce site-directed chemical conjugations is by the incorporation of unnatural amino acids (UAA) into the IgG1 framework. Ambrx and Agensys/Astellas are in the lead of using this technique with ARX788 and AGS-62P1 both in Phase I clinical trial.

Other features of an IgG1 antibody can also be modified to enhance the performance of the ADC. For instance, GSK-2857916, an anti-BCMA ADC developed by GSK against multiple myeloma and haematological malignancies, contains an afucosylated IgG1 with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) at the antibody portion. In another case, MEDI4276, developed by MedImmune, is by far the only ADC that contains a bi-specific IgG1 as the targeting antibody. The two arms of the antibody bind to domain II and domain IV of HER2, respectively, for increased specificity and affinity.

Payload

The payloads used in ADC developments often exert extreme potency in the range of nM or pM and disrupts crucial subcellular pathways to induce apoptosis of cancer cells. With the success of Adcetris and Kadcyla, tubulin inhibitors such as auristatins (MMAE, MMAF) and maytansinoids (DM1, DM4) are the two major classes of payloads used in ADCs in clinical studies. Other tubulin inhibitors, such as tubulysin and new forms of auristatins, have also been incorporated into ADCs. Together with auristatin and maytansinoid derivatives, tubulin inhibitors contribute to more than 73% of the payloads in clinical ADCs.

Another target for ADC payloads is DNA and agents that cause DNA chemical cleavage or cross-linking are also excellent payloads for ADC developments. Compounds such as pyrrolobenzodiazepine (PBD) dimer, indolinobenzodiazepines, calicheamicin, duocarmycin, and doxorubicin belong to this category and about 19 ADCs based on these payloads are under various stages of clinical evaluations. Lastly, agents that disrupts DNA transcription, e.g. DXd (exatecan derivative) and SN38, both topoisomerase I inhibitors, are also developed into ADCs via uniquely designed linkers to compensate for the hydrophobicity of those molecules to reach high ADC drug-to-antibody ratios (DAR).

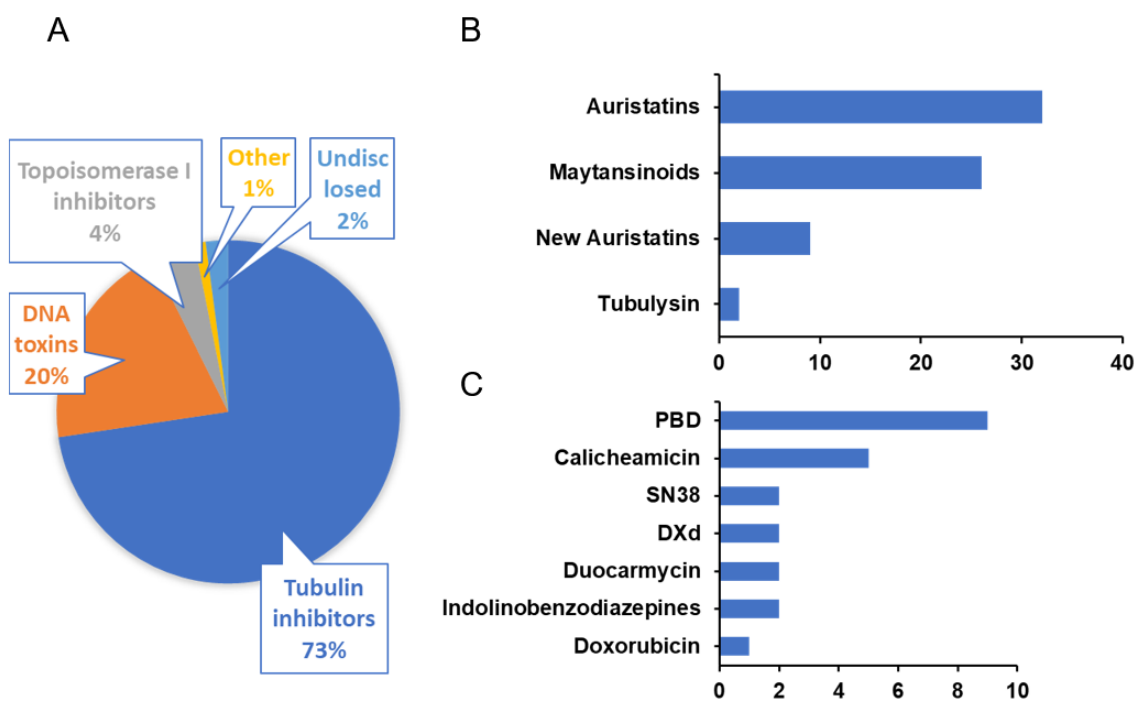
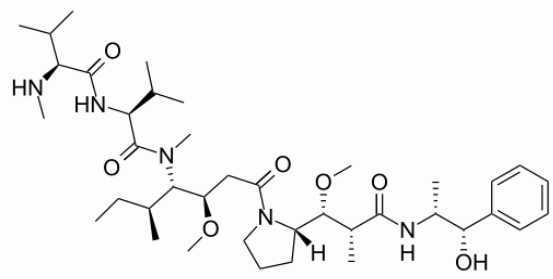


Figure x. Survey of payloads used in ADCs under clinical evaluations. (A) Payloads categorized by their subcellular function; Numbers of ADCs with various tubulin inhibitor payloads (B) and payloads targeting DNA or DNA transcription (C).

Auristatins

Auristatins are a family of complex analogues to the native antineoplastic product dolastatin 10. They are 100 to 1000 times more toxic than Doxorubicin, a conventional cancer chemotherapy medication. The potent agent, dolastatin 10 is a five-subunit penta-peptide discroverde by Pettit et al. from the sea hare Dolabella auricularia in 1987 and chemical modification to dolastatin 10 were applied to generate auristatins. It was later realized that the remarkable cytotoxicity of auristatins owes to their powerful capability to inhibit microtubule formation through the interaction with tubulin at the "peptide sub-site" of tubulin's "Vinca domain" and disrupt tubulin-dependent GTP hydrolysis. Auristatins lead to the arrest of cancer cells in the mitosis stage and eventually, apoptosis. Unfortunately, due to their high cytotoxicity, harmful side-effects and a narrow therapeutic window auristatins are unsuitable as anticancer medications along but are excellent candidates as ADC payloads.

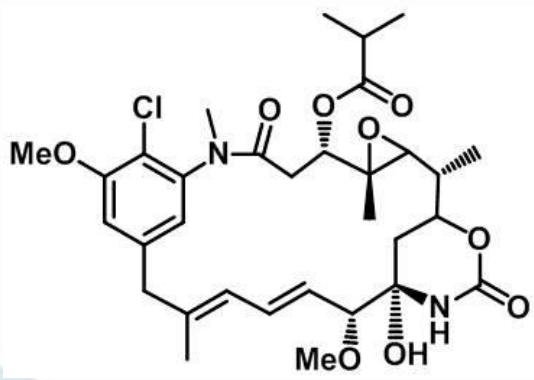
In terms of international marketing, for Kadcyla, the sales in USA and EU occupies a major share of the revenue but in the past two years, the sales in Japan and other Asia-Pacific countries, EEMEA (Eastern Europe, Middle East and Africa), Latin America, Canada, and Other countries are also on the rise.



(MMAE)

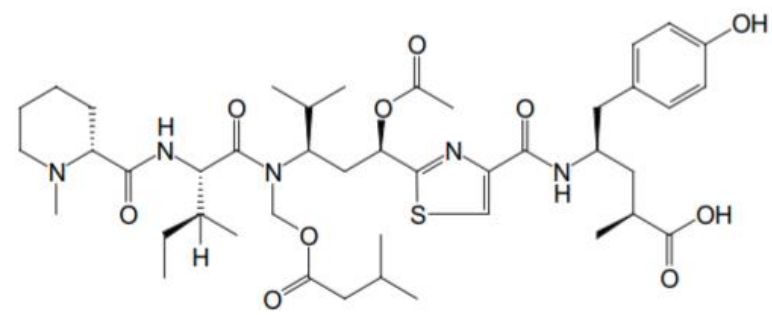
Maytansinoids

Maytansine and its derivatives (named as maytansinoids in general) are members of the ansamycins superfamily and contains a 19-member macrocyclic lactam attached to a chlorinated benzene. Maytansine is originally isolated from an Ethiopian shrub Maytenus ovatus and exerts extremely high anti-mitotic potency. Maytansinoids are microtubule-targeting agents that share same binding site with vinca and function by depolymerizing microtubules and arresting cells in the mitosis stage. Maytansinoids reveal over 100-fold elevated cytotoxicity in cells than vinca alkaloids, making them suitable candidates in anti-cancer therapies utilizing tissue-specific drug delivery strategies, particularly as ADCs. The form of ADC significantly increases the therapeutic window of maytansinoids comparing to the free drugs, enabling the usage of an otherwise highly toxic drug in cancer treatments.



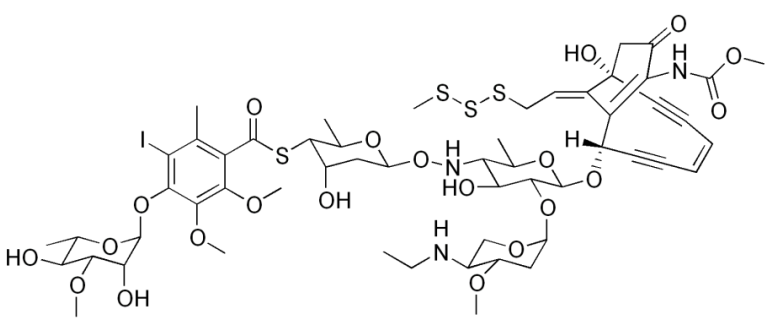
Tubulysins

Tubulysins, originally isolated from myxobacteria, are a series of antimitotic tetrapeptides discovered by Hofle and co-workers in 2000. Functionally similar to dolastatins, tubulysins are among the most powerful cell division inhibitors reported until now. Due to their ability to inhibit tubulin polymerization, tubulysins exert a potent anti-proliferative activity against human cancer cells, even the drug-resistant cancer cells. So far, 14 different tubulysin isoforms have been reported and their conserved core structure, containing a secondary alcohol or acetate at C-11, is comprised of a L-isoleucine (Ile), a tubuvaline (Tuv) and a N-methylD-pipecolic acid (Mep) unit. All natural tubulysins have a special N,O-acetal and either a tubutyrosine (Tut) or a tubuphenylalanine (Tup) at the C-termini for their biological function. Meanwhile, it has been demonstrated that the N,O-acetal can be replaced by a plain alkyl group to offer N-14-desacetoxytubulysin H without any loss in potency.



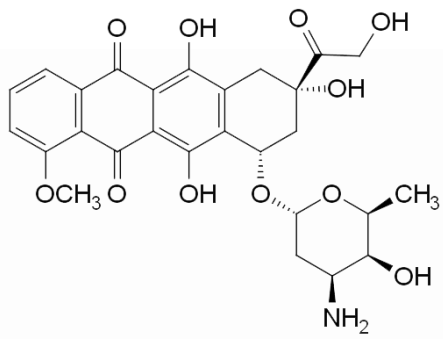
Calicheamicins

Calicheamicins are highly toxic agents against DNA and they induce double-stranded DNA (dsDNA) breakages at sub-picomolar concentrations. For their mode of action, Calicheamicins bind to dsDNA minor groove, within which they undergo a cyclization reaction similar to Bergman cyclization and release a diradical species, namely 1,4-didehydrobenzene. 1,4-didehydrobenzene subsequently extracts hydrogen atoms from DNA deoxyribose (sugar) backbone, resulting in strand scission. The strong potency of the calicheamicins fits the concept of ADC payloads and they have been proven to be outstanding drug candidates for targeted cancer therapies. A hydrazide derived from Calicheamicin γ1 has been conjugated to the proteoglycan portion of the CT-M-01 (anti-polyepithelial mucin) antibody and the resulted ADC has shown promising effects to human breast carcinoma cells.



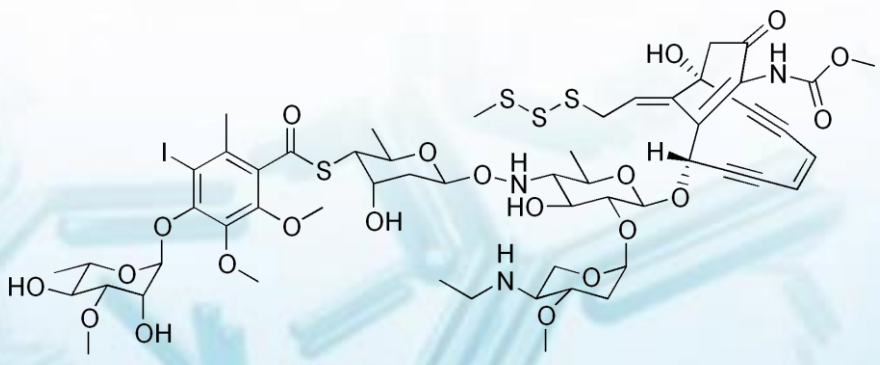
Doxorubicins

Doxorubicin, often regarded by the trade name “adriamycin”, is a member of the anthracycline compounds derived from Streptomyces peucetius var. caesius in the 1960s. These compounds were given the name doxorubicin or daunorubicin. Doxorubicin and its derivatives, function by DNA helix intercalation, topoisomerase poisoning, free radical generation..., are still regarded as some of the most impactful chemotherapeutic antitumor agents. Doxorubicin is a 14-hydroxylated version of daunorubicin and is has been applied to the treatment of a broad range of both solid and liquid tumors. However, the appearance of drug resistance and possible side effects, for example, heart muscle injure after doxorubicin treatment, result in a narrow therapeutic window for doxorubicin-based cancer treatments. For this regard, ADCs are becoming an appearing alternative for targeted doxorubicin delivery to expand its therapeutic window.



Duocarmycins

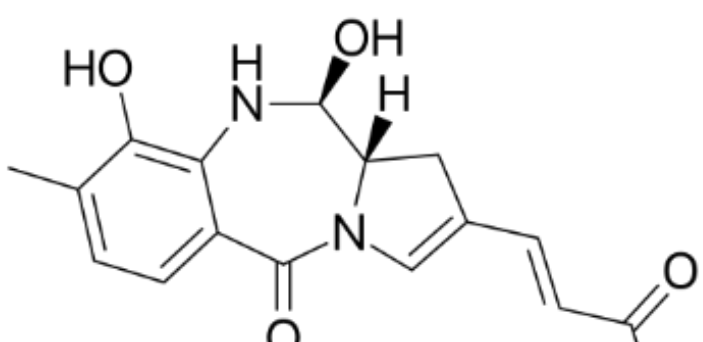
Duocarmycins are a series of natural products originally isolated from Streptomyces bacteria in 1988. They exhibit an impressively high cytotoxicity and are subsequently developed into anti-tumor agents. Duocarmycin analogues, among which CC-1065 and duocarmycin SA are the most widely used, represent a series of extremely powerful antineoplastic compounds that display high cytotoxicity against the growing cancer cells in culture. Duocarmycin analogues are DNA minor groove binding agents that also exert adenine-N3 alkylation activity and an AT-sequence selectivity. In terms of mode of action, duocarmycin analogues bind the minor groove of DNA and then induce irreversible DNA alkylation that hinders DNA architecture and structural integrity. The alkylation of DNA eventually leads to DNA cleavage and subsequently, tumor cell death via apoptosis. Duocarmycins are capable of applying this MOA at any phase in the cellular cycle and they are believed to have better anti-tumor activities comparing to tubulin binders, which only attack tumor cells during the mitotic state. What’s more, duocarmycin analogues have also been demonstrated to be effective on solid tumors.



(CC1065)

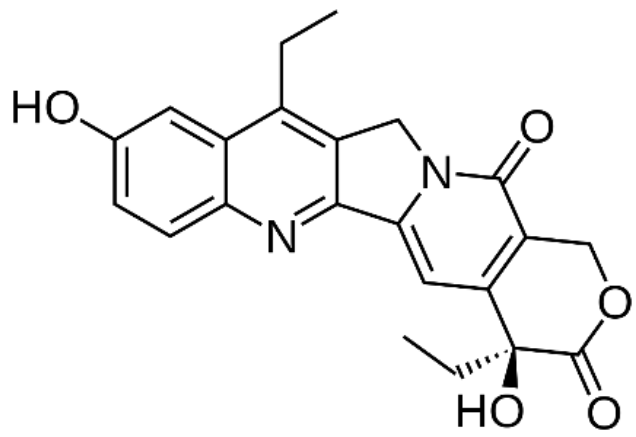
Pyrrolobenzodiazepines (PBDs)

Pyrrolobenzodiazepines (PBDs) is a series of natural products derived from various actinomycetes that show strong anti-tumor or antibiotic activities. They are sequence-dependent DNA alkylating compounds and are proven to be more powerful than systemic chemotherapeutic drugs. As DNA minor groove binding agents, PBDs selectively cross-link specific DNA segments, hindering cell division and eventually lead to cell death. The non-discriminative working mechanism of PBD and PBD derivatives averts the usual phenomenon of emergent drug resistance, making them excellent candidates for anti-tumor therapies. Several dimeric PBDs (PBDs-dimers) have been used as cytotoxic drug payloads in ADCs, such as vadastuximab talirine, for acute myeloid leukemia (AML) treatment.



SN-38

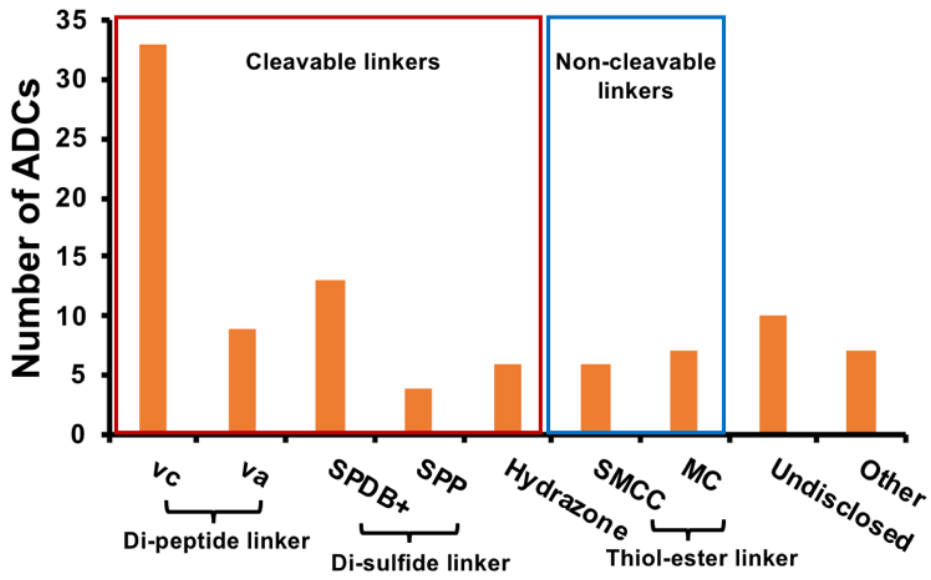
SN-38 is the active metabolite of irinotecan, an alkaloid camptothecin derivative that acts as a potent inhibitor of DNA topoisomerase I. It is formed by the hydrolysis of irinotecan by carboxylesterases and metabolized through glucuronidation by UDP glucuronosyl transferase 1A1. SN-38 is a very potent topopisomerase I inhibitor and it is proven to be more cytotoxic towards HT-29 colon cancer cells (IC50= 8.8 nM) compared to irinotecan (IC50 > 100 nM).



Linkers

A linker is a crucial component in an ADC that bridges the payload with the antibody and dictates the release mechanism of the payload. Linkers play an important role in ADC stability to ensure minimum off-target drug release within circulation. Based on the drug release mechanism, linkers can be divided into cleavable and non-cleavable linkers. Among all ADCs in clinical trials (active and suspended), cleavable linkers, especially the di-peptide Val-Cit linker, are more commonly used comparing to non-cleavable linkers (figure xxx).

Cleavable linkers are a series of small chemical linkages that are cleaved upon the exposure of a change in the chemical or biochemical environment. Peptide linkers, which dominate in the ADCs in clinical studies as indicated in figure xxx, are susceptible to lysosomal enzyme (e.g. Cathepsin B, CatB) degradation upon the internalization of the ADC. Due to the absence of lysosomal enzymes in blood circulation, peptide linkers show excellent serum stability. In the meantime, the build-in PABC module in many peptide linkers (vc, CL2A…) result in the release of the payload in its most native form, ensuring the delivery of the full potency into tumor cells. With these advantages and the success of Adcetris, which bears a vc linker, peptide linkers are the first-line choice in many ADC development projects.



Di-sulfide linker is another subcategory of cleavable linkers that release the payload upon the change in the oxidation-reduction potential once internalized. They are the linker of choice for maytansinoids (DM1 and DM4) payloads and release the payload in a format closer to native maytansinoids comparing to Kadcyla, which uses a thiol-ester linker. This is the one of the major reasons for the application of di-sulfide linkers in maytansinoid-based ADCs in clinical trials. Problems associated with disulfide linker is that thiol-exchange is sometimes observed in circulation, which might lead to off-target drug release. Solutions to this problem have been actively exploited by adding steric hindrance into the linkers to reach a balance to minimize off-target drug release and in the meantime, ensure proper release kinetics after internalization.

Lastly, hydrazone linkers are also used in ADC developments and the approved Mylotarg (now approved in Japan) and Besponsa. These linkers contain an acid-labile (or sometimes referred to as “pH-sensitive”) module that releases the payload in the acidic lysosomal environment (pH 7.0 in circulation vs pH 5.5 in lysosome). Comparing to peptide linkers and di-sulfide linkers, hydrazones are more prone to payload off-target release upon the fluctuation of blood pH. Even with successful ADCs, half of the clinical trials with ADCs bearing hydrazone linkers have come to a suspension, indicating the somehow “labile” nature of those linkers.

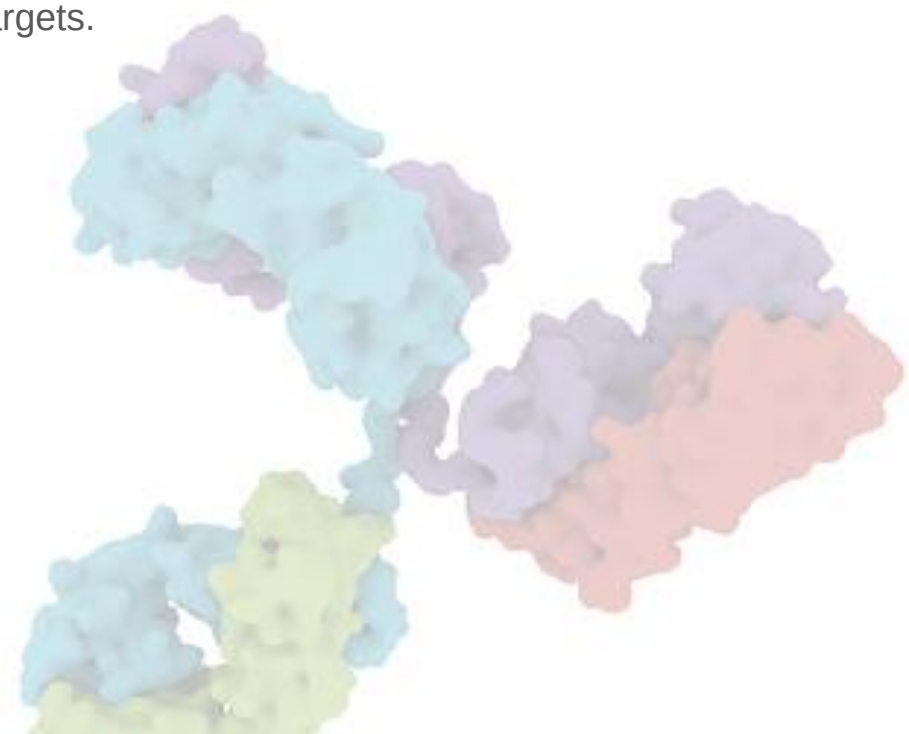
Non-cleavable liners are regarded as the most stable linker in circulation. Short ester of thiol-ester linkers of this category are also suitable for ADCs with maytansinoid payloads. With the success of kadcyla, the total number of ADCs in clinical pipeline bearing non-cleavable linkers are similar to that with di-sulfide linkers. Due to the chemical structure of non-cleavable linkers, the payload is released only after the complete degradation of the antibody inside lysosome and the payload is modified with the linker and the amino acid residue that serves as conjugation site. A series of payload modification and evaluation is required prior to ADC development to ensure the comparable potency of the modified payload.

Part 3: Selected Targets for ADCs in Clinical Trials

Based on its principle design, an antibody-drug conjugate (ADC) delivers a highly cytotoxic payload into a cancer cell to bring lethal damage to certain subcellular metabolic pathways and as a result, induce apoptosis. Due to the nM or even pM toxicity of the payload, the target of an ADC shall be carefully selected to avoid collateral damage to the healthy tissues. A valid ADC target usually meets these stringent criteria:

1. Cell surface localization: to allow efficient antibody/ADC binding.
2. Tumor specific with decent protein expression: to ensure ADC specificity and efficacy.
3. Higher tumor surface expression: when the identification of a tumor specific antigen is proven to be difficult, a shared cell surface antigen can also be considered under the condition that it shows a much higher expression at cancer cell surfaces comparing to that on normal cells.
4. Internalization: to ensure the ADC incorporation via receptor mediated endocytosis upon ADC binding.
5. Desired turnover time: to facilitate maximizing ADC efficiency and efficacy.

More than 60 cancer cell surface targets have been exploited in ADCs in clinical trials, targeting major cancers including prostate cancer, non-Hodgkin lymphoma, non-small cell lung cancer, ovarian cancer, myeloma, gastrointestinal cancer… Popular targets include PSMA, CD19, mesothelin, CD70, HER2, CD33… with more than 2 ADCs developed targeting corresponding cancers bearing these targets.



Target	Cancer	# of ADCs
CD30	ALCL and Hodgkin lymphoma	1
GPNMB	Melanoma, osteosarcoma and TNBC	1
EGFRvIII	Glioblastoma and solid tumors, Recurrent gliomas	2
GPNMB	Melanoma, osteosarcoma and TNBC	1
EGFRvIII	Glioblastoma and solid tumors, Recurrent gliomas	2
PSMA	Prostate cancer	3
CD79b	NHL	1
CD19	B-NHL, DLBCL, Relapsed NHL, B ALL	4
ENPP3	RCC	1
TIM1	RCC	1
LY6E	HER2– breast cancer and NSCLC	1
LIV1	Breast cancer	1
Nectin 4	Solid and urothelial tumors	1
SLITRK6	Metastatic urothelial cancer	1
CD37	HER2– breast cancer and NSCLC	1
LIV1	NHL	2
HGFR	Advanced solid tumors	1
SLAMF7	Multiple myeloma	1
EGFR	Solid tumors, NSCLC and SCCHN	2
BCMA	Multiple myeloma and hematological malignancies	1
Tissue factor (CD142)	Multiple solid tumors	1
AXL	Multiple solid tumors	1
CD22	NHL, ALL and CLL	2
NaPi2B	NSCLC and ovarian cancer	1
GCC	Gastrointestinal malignancies	1
STEAP1	Prostate cancer	1
MUC16	Ovarian cancer	1
Mesothelin	Ovarian and pancreatic cancers, solid tumors	3
ETBR	Melanoma	1

Target	Cancer	# of ADCs
CD70	NHL, RCC, renal cancer	4
EphA2	Solid tumors	1
5T4	Solid tumors	1
HER2	HER2+ metastatic breast cancer, gastric cancers, NSCLC…	7
FOLR1	Advanced epithelial ovarian cancer	1
CD138	Multiple myeloma	1
CEACAM5	Solid tumors	2
LAMP1	Solid tumors	1
Cadherin 3 (P-cadherin)	Head and neck cancer, esophageal cancer and TNBC	1
Cadherin 6	EOC and RCC	1
FGFR3	Advanced metastatic cancers	1
CA6	Breast, cervical, lung and ovarian cancers	1
CD56	MCC, multiple myeloma and ovarian cancer	1
CanAg	Solid tumors	2
Integrin αV	Solid tumors	1
CD44v6	SCCHN	2
CD33	AML	4
Cripto 1 growth factor (TDGF1)	Solid tumors	1
KIT (CD117)	AML and solid tumors	1
CD123	AML	2
CD352	Multiple myeloma	1
DLL3	SCLC	1
CD25	Hodgkin lymphoma and NHL	1
Ephrin A4	TNBC and ovarian cancer	1
Lewis Y antigen (CD174)	Neoplasms	1
MUC1	Ovarian carcinoma	1
TROP2	TNBC	2
HER3	Solid tumors	1
CD74	NHL, CLL	1
PTK7	NSCLC, TNBC and ovarian cancers	1
NOTCH3	Breast cancer	1
C4.4A	Lung squamous cell carcinoma	1
FGFR2	Solid tumors	1
FLT3	AML	1
Transferrin receptor protein 1 glycotope	Colorectal, pancreatic and stomach cancers	1
S. aureus	S. aureus infection	1
Targets undisclosed		6

CD19

CD19, also known as B4 or CVID3, is a membrane immunoglobulin that is expressed on follicular dendritic cells and B cells. It contains two Ig-like C2-type domains in the extracellular portion while the cytoplasmic portion undergoes phosphorylation upon the recipient of different cellular signals. CD19 is involved in the B cell response to antigens. It is a low-affinity antigen receptor that is crucial for the decreasing of the threshold for antigen receptor-dependent stimulation. CD19 is often associated with CD21, CD81, CD82, VAVA2, and Complement receptor 2 for its biological function. Defects in CD19 are the main cause of immunodeficiency common variable type 3 (CVID3), or antibody deficiency, a disorder that is characterized by poor B-cell differentiation and impaired antibody production. CD19 is a biomarker for B-cell lymphomas. It is now under evaluation as a target for antibody-based immunotherapies against B-cell lymphomas as well as some autoimmune diseases.

PSMA

Folate hydrolase 1 (FOLH1), often referred to as PSMA, is a cell membrane peptidase that belongs to the M28B subfamily of the peptidase M28 family. It is also known as FGCP, FOLH, GCP2, PSM, mGCP, GCPII, NAALAD1, or NAALAdase. PSMA has both folate hydrolase (in the C-terminal region) and N-acetylated-alpha-linked-acidic dipeptidase (NAALADase) activity, with the later resides in the central region of the protein. PSMA exerts preference for tri-alpha-glutamate peptides regarding its peptidase activity and it plays a crucial role in folate uptake in the intestine and modulating excitatory neurotransmission in brain via the hydrolysis of N-aceylaspartylglutamate (NAAG) to release glutamate. PSMA is expressed in a wide distribution of tissues with a highest leave in the prostate. It is also demonstrated as a major up-regulated gene in prostate cancer with an 8- to 12- fold increase in gene expression comparing to that in noncancerous prostate cells. Currently, PSMA is used as a biomarker for prostate cancer and it is also exploited as a target for antibody-based immunotherapies.

Mesothelin

Mesothelin (MSLN), also known as MPF, SMRP, CAK1 antigen or Pre-pro-megakaryocyte-potentiating factor, is a 40 kDa glycosylphosphatidylinositol-anchored glycoprotein. The MSLN gene encodes a preproprotein that is proteolytically processed to generate two protein products, megakaryocyte potentiating factor and mesothelin. As a glycosylphosphatidylinositol-anchored cell-surface protein, mesothelin may function as a cell adhesion protein, while megakaryocyte potentiating factor functions as a cytokine stimulating colony formation of bone marrow megakaryocytes. It is reported that mature human mesothelin shares 60% amino acid identity with mouse and rat mesothelin. This mesothelin protein is found to be expressed on mesothelial cells in the pleura, pericardium and peritoneum, and it is overexpressed in multiple cancers including epithelial mesotheliomas, ovarian cancers as well as specific squamous cell carcinomas. This protein can serve as a potential target for various cancer immunotherapy strategies, including monoclonal antibody, immunotoxin and antibody-drug conjugate (ADC).

CD70

CD70, also known as CD27L, CD27-L, CD27LG, TNFSF7, or TNLG8A, is a cytokine that belongs to the tumor necrosis factor (TNF) superfamily. It is a type II transmembrane protein containing 193 amino acids with a molecular weight of ~50 kDa. CD70 is a ligand for TNFRSF27 (CD27) and the interaction between CD70 and CD27 is crucial for T-cell activation, costimulated T-cells proliferation, and cytolytic T-cell generation. CD70 is also reported to participate in B-cell activation. CD70 is essentially absent in normal non-lymphoid tissues while its constitutive expression is observed in many hematological malignancies and solid tumors. High level CD70 expression has been documented in lymphomas, renal cell carcinoma (RCC), nasopharyngeal carcinoma, and Epstein-Barr virus-induced carcinomas while the expression level of CD27, its receptor, also showed positive correlation to that of CD70 in some cases. CD70 has become an active target for immunotherapy development. Current therapies against CD70-bearing cancer cells include antibody-induced ADCC, ADC, and antibody-mediated CD70 blockage.

HER2

Erb-b2 receptor tyrosine kinase 2(ERBB2), commonly referred to as HER2, is an epidermal growth factor (EGF) receptor family tyrosine kinase. It is also referred to as ERBB2, NEU, NGL, TKR1, CD340, MLN 19, or HER-2/neu under different circumstances and it is a unique EGF receptor. There is no reported ligand that interacts with HER2. It is not susceptible to any epidermal growth factor binding. However, HER2 forms heterodimers with other EGF receptors, especially HER1 and HER3, upon EGF binding to these receptors, and triggers downstream signaling cascades that promotes cell proliferation. The overexpression of HER2 is associated with a variety of cancers, including gastric cancer, glioma, hereditary diffuse gastric cancer, lung cancer, ovarian cancer.... HER2 level has been used as a cancer diagnosis and due to its abundant expression in cancer tissues verses normal tissues, HER2 is an important target for antibody-based cancer immunotherapies. Herceptin, an anti-HER2 monoclonal antibody and Kadcyla, the ADC version of Herceptin, has been approved for breast cancer treatment.

CD33

CD33 is a lectin (sialic acid binding Ig-like lectin 3) expressed mainly on cells of myeloid lineage and on some lymphoid cells. It is also known by acronyms such as p67, SIGLEC3, or SIGLEC-3. CD33 contains two immunoglobulin domains within its extracellular portion, one Ig-like C2 type domain and one Ig-like V type domain, respectively, and two immunoreceptor tyrosine-based inhibitor motifs (ITIM) in its cytoplasmic portion. CD33 is speculated as an adhesion molecule of the myelomonocytic-derived cells and it has been proposed to participate in mediating sialic-acid dependent interactions, during which it shows high preference towards alpha-2,6-linked sialic acid. Upon ligand binding, CD33 exerts an action mode as an inhibitory receptor that blocks signal transduction and inhibits downstream cellular activities during immune responses. By far, CD33 is a classic target used in the treatment of acute myeloid leukemia by ADC-based immunotherapy by gemtuzumab ozogamicin (Mylotarg).

Part4: Indications

As an extension of monoclonal antibody-based therapeutics, ADCs have been developed to target a variety of major cancers. Being major targets for ADC development, CD19, CD33, CD70, and HER2 related tumors take up a good portion of ADCs in clinical trials but since many tumors share surface targets, one ADC can be used to treat different tumors. Based on the structure of the tumor and the surface target antigen expression level, the efficacy can vary from case to case but generally, ADC in the clinical trials show a pattern of dispersed indications against various tumor types.

A significant amount of effort has been deployed to develop ADCs for the treatment of hematologic malignance, for instance various types of lymphomas and myelomas. Due to the easy access of target and low barriers with tumor penetration, ADCs show promising results in different treatment regimes in clinical trials. Popular antigens such as CD19, CD33, CD70 are heavily targeted, and more than 40 indications have been reported with ADCs in clinical trials (both on-going and stopped). Solid tumor is another major frontier for ADCs but due to limited tumor penetration, different ADC regimens and treatment schemes with ADC in combination of chemotherapeutics or other immunotherapeutics have been exploited.

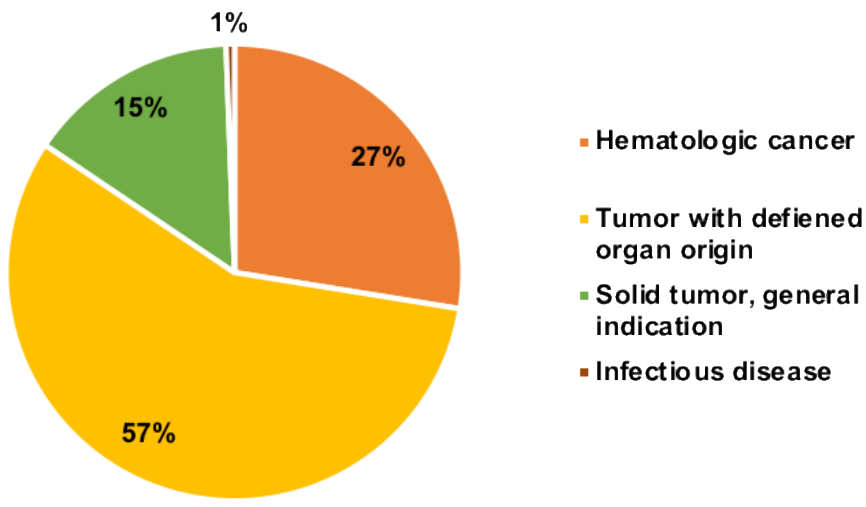


Figure x. Indication of ADCs in clinical trials: ADCs in the treatment of various tumor types.

Non-Hodgkin lymphoma (NHL) is by far the most extensively targeted hematologic malignance by ADC therapies with ~16 ADCs in clinical trial, followed by that of ovarian cancer and Non-small-cell lung carcinoma (NSCLC). Breast cancer, another form of solid tumor, is also a major focus in ADC developments, with HER2 being one of the predominant targets. A total of 35 different cancer types have been targeted by ADCs in clinical trials that covers 17 different organs (figure y). Lymph nodes are a hot spot for ADC applications followed by breast, lung, bone marrow, and ovary (figure z). In one special occasion, an antibody against Staphylococcus aureus (S. aureus) has been developed into an ADC (designated as DSTA4637S by the developer Genentech and Symphogen). DSTA4637S has entered phase 1 clinical trial and it is by far the only ADC in clinical trial that is designed against an infectious disease instead of cancer, proving the pharmaceutics community with a new application of ADCs.

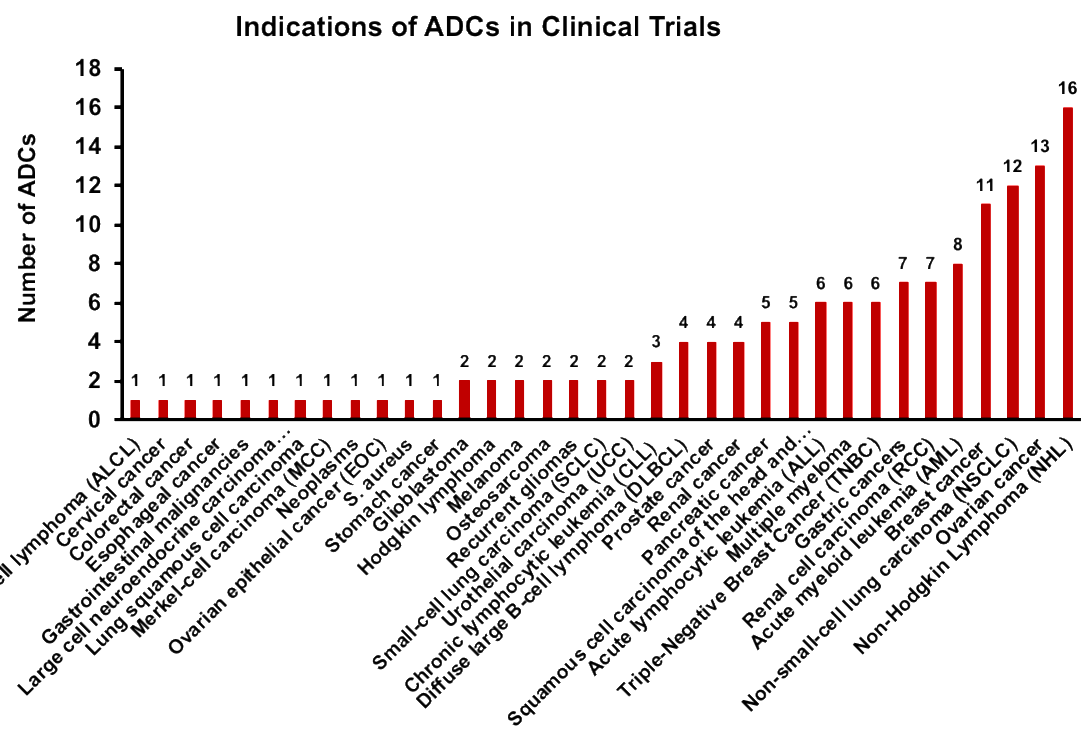


Figure y. Indication of ADCs in clinical trials: tumors targeted by ADC treatments.

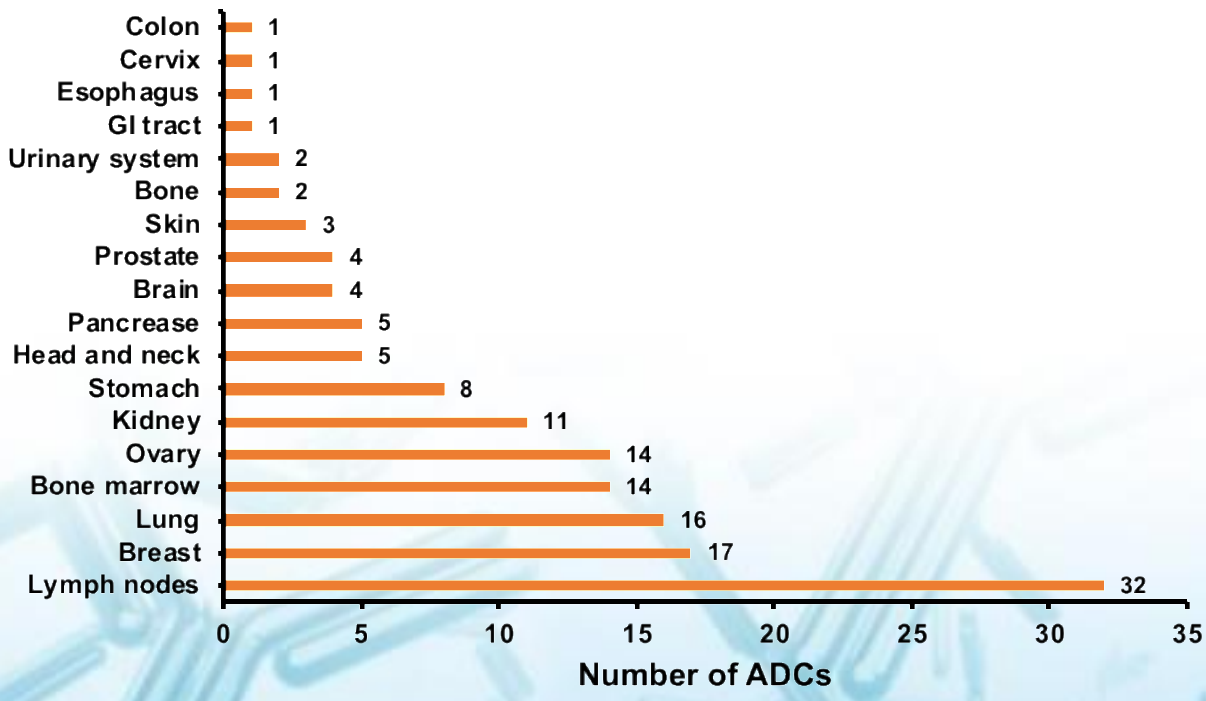


Figure z. Indication of ADCs in clinical trials: organs of tumor origins targeted by ADC treatments.

Part 5: Status of ADCs Clinical Trials

Besides of the common definition of Phase I, Phase II, and Phase III of clinical trials, ClinicalTrials.gov, a database of privately and publicly funded clinical studies conducted around the world, adds new insights into the status of each trial by categorizing them as recruiting, active, completed, suspended, withdrawn and unknown status. Statistics of the current ADCs in clinical trials show that active trials occupy over half of the total ADCs while a significant portion ADC trials (~30% of the total number of trials), have been suspended for various reasons. Only a small number of trials are actively recurring while one candidate, anetumab ravtansine, developed by Bayer, has been determined to fail without showing improvement in the progression-free survival (PFS) of patients suffering from mesothelioma.

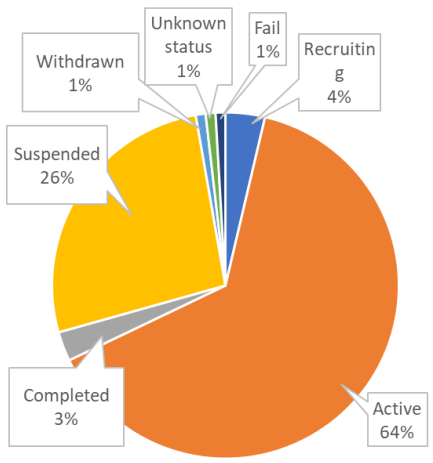


Figure x. Status of ADCs in clinical trials

Table 3. ADC clinical trials in recruiting status

Name	Developer	Target	Payload	Indication	Phase
SC16LD6.5	StemCentrx	DLL3	PEG8 va–SG3199	SCLC	II
PSMA ADC	Progenics	PMSA	MMAE	Prostate cancer	II
MLN-0264	Millennium/Takeda	GCC	MMAE	Gastrointestinal malignancies	II
DS-8201	Daiichi Sankyo	HER2	DX-8951 derivative	Advanced breast cancer and gastroesophageal cancer	I

A majority of the active ADC clinical trials resides in Phase I, with only 4 trials that have progressed to Phase III: Mirvetuximab soravtansine by ImmunoGen, Vadastuximab talirine by Seattle Genetics, Rovalpituzumab tesirine by AbbVie/StemCentrx, and Sacituzumab govitecan by Immunomedics (licensed to Seattle Genetics), respectively. The coming years will witness the rise or fall of those ADCs but based on the good results from the previous two phases of clinical studies, the chances are in favor of them getting FDA approval.

Interestingly, for the trials that currently in suspension, 86% of those trials are suspended in Phase I, suggesting that Phase I is a crucial stage that foresees the fate of the ADC. Now, with the majority of ADC in clinical studies reside in this stage, there will inevitably be failure among those on-going trials. Suspended trials might re-open when proper changes are made to the ADC or to the administration regimens that are demonstrated to show improved clinical parameters such as objective response rate (ORR)...

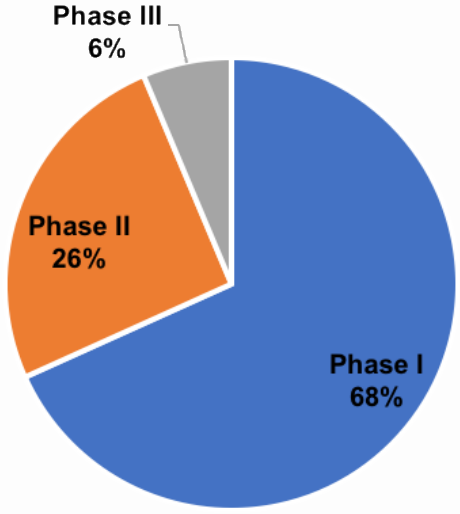
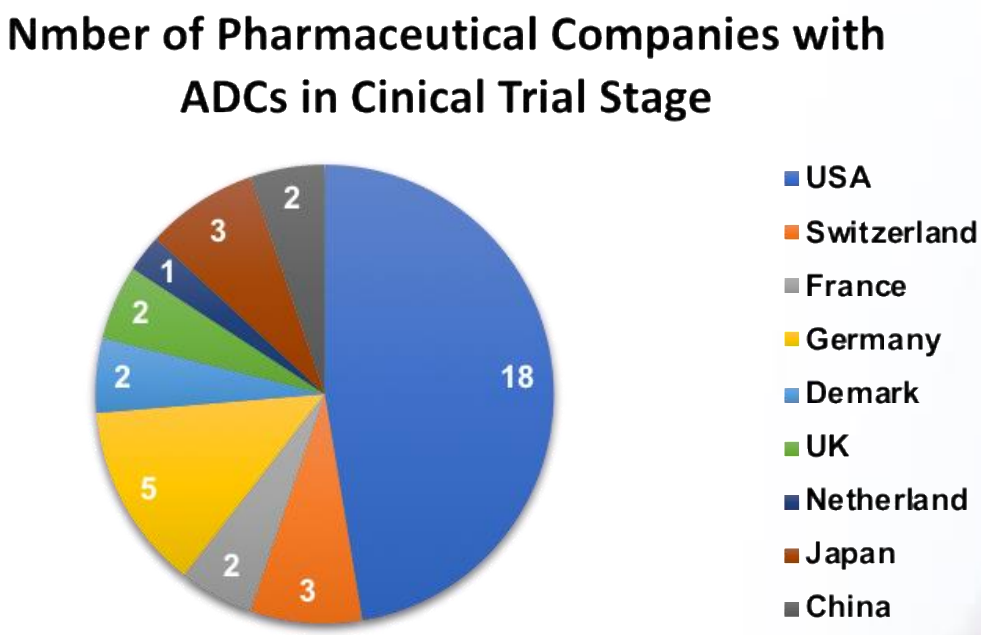


Figure y. Phases distribution of current ADCs in clinical trials.

Part 6: companies and institutes

Due to the extensive cost required for antibody-drug conjugate (ADC) therapeutics developments, world's leading pharmaceutical companies are the major contributors to the ADCs in clinical trials. A total number of 38 companies now have ADC candidates in the clinical pipeline, among which United States is in the lead with 18 companies that are actively exploiting ADC therapeutics, followed by the EU with 15 companies from 6 countries. ADC development in the Pacific rim is relatively less active with 3 major Japanese pharmaceutical companies and 2 Chinese companies contributing to the total tally of ADCs in the clinical trial.



Among the 38 major pharmaceutical companies with candidates participating in the ADC clinical trials, including both on-going and stopped trials, Roche, who has acquired Genentech I 2009, is in the lead with 11 candidates in the clinical stage followed by Seattle Genetics and ImmunoGen, with 10 candidates, respectively. In the meantime, until 2017, 6 out of the 38 companies have more than 5 ADC candidates in the clinical pipeline, contributing a major force in the ADC development against cancer. Table x offers a brief summarization of the current participants in ADC clinical trials.

Table 4. ADC clinical trials in recruiting status

Main Developer	Co-developer (country)	# of ADC	Targets
United States			
Seattle Genetics	Takeda (Japan)	1	CD30
Seattle Genetics		9	CD19, LIV1, CD70, CD33, CD123, CD352
Celldex		2	GPNMB, TIM1
AbbVie		4	EGFRvIII, SLAMF7, EGFR
AbbVie	Stemcentrx	3	DLL3, undisclosed
AbbVie	Pierre Fabre (France)	1	HGFR
Progenics	Seattle Genetics	1	SMPA
Agensys	Astellas (Japan)	5	ENPP3, Nectin 4, SLITRK6, CD37, FLT3
MedImmune		3	EphA2, PSMA, HER2
Amgen		3	CD70, EGFRvIII
Eli Lilly		1	FGFR3
Biogen		1	Cripto 1 growth factor
Immunomedics		3	TROP2, CEACAM5, CD74
BMS		2	CD70, Mesothelin
Mersana		1	HER2
AbGenomics		1	CD71 glycotope
Genentech	Roche	11	CD79b, LY6E, CD22, NaPi2B, STEAP1, MUC16, Mesothelin, ETBR, HER2…
Genentech	Symphogen (Germany)	1	S. aureus
ImmunoGen		10	FOLR1, CD19, CD37, CD56, CanAg, EGFR, Integrin aV, CD33, CD123
Pfizer		6	CD33, CD22, CD174, MUC1, NOTCH3, TROP2
Pfizer	AbbVie (Stemcentrx)	2	Ephrin44, PTK7

Table 4. ADC clinical trials in recruiting status

Main Developer	Co-developer (country)	# of AD	Targets
Europe			
GSK		1	BCMA
Oxford Biotech	Pfizer (USA)	1	5T4
Bayer		3	Mesothelin, C4.4A, FGFR2
Sanofi		4	CEACAM5, LAMP1, CA6, CD33
Novartis		3	Cadherin3, Cadherin6, KIT
ADC Therapeutics	Genmab	1	CD25
ADC Therapeutics		1	CD19
Genmab		2	CD142, AXL
Biotest		1	CD138
Boehringer Ingelheim		1	CD44v6
Synthon		1	HER2
Asia			
Takeda	Millennium	2	PSMA, GCC
Daiichi Sankyo		2	HER2, HER3
Zhejiang Medicine Co.	Ambrx (USA)	1	HER2
Remegen		1	HER2

Part 7: Summary and Outlooks

As a new frontier in the battle against cancer, an increased number of antibody-drug conjugations in clinical trials is bring us a new wave of potent immunotherapeutics against over 30 different type of cancers in almost all major organs and tissues. The current status put over 70 ADCs in active clinical trials among which 4 candidates have gained FDA approval. Approved ADCs show promising market share among other immunotherapeutics with increased annual sales, a driving force for the investment in other ADCs. As a brief summary, we are in an age of an “ADC boom” and with the hope that more ADCs to survive and thrive in clinical evaluations, they could add powerful weapons into the arsenal of immunotherapies.

Challenges, however, still remain: the full-size antibody, based on which all current ADCs are constructed, is a limitation for tumor penetration against solid tumors and as a result, might have significant impact on the efficacy of those ADCs. Secondly, there is a limited number of available payloads and a lack of ingenuity and creativity in the linking mechanisms. With majority of the ADCs in clinical trials formulated around vc-auristatin and maytansinoids-ester linkages, complications might soon surface when the efficacy of those payloads fail to efficiently eliminate corresponding tumors. Thirdly, over 68% of the active ADCs are in Phase I, a stage where most of the ADC trial suspensions take place. Thus, it is still too early to draw any conclusions regarding the fate of the majority of ADCs.

Embracing Besponsa and with the emerging of new targets, antibodies, as well as payload-linkers, we anticipate an expanding number of ADCs to reach the clinical trials and FDA approval to benefit us all.

Appendix: ADCs under Active Clinical Trials

Name	Target	IgG	Payload-linker	Developer	Indication
ADCs in Phase I Clinical Trials					
ABBV-838	SLAMF7	IgG1	vc–MMAE	AbbVie	Multiple myeloma
ABBV-221	EGFR	IgG1	vc–MMAE	AbbVie	Solid tumors
ABBV-085	Undisclosed	IgG1	vc–MMAE	AbbVie	Solid tumors
SC-002	Undisclosed	Undisclosed	Undisclosed	AbbVie (Stemcentrx	SCLC, LCNEC
SC-003	Undisclosed	Undisclosed	PBD	AbbVie (Stemcentrx)	Ovarian cancer
Telisotuzumab vedotin	HGFR	Engineered IgG1	vc–MMAE	AbbVie/Pierre Fabre	Advanced solid tumors
AbGn-107	CD71 glycotope	IgG1	Cleavable linker-tubulin inhibitor	AbGenomics	Colorectal, pancreatic and stomach cancers
ADCT-402	CD19	IgG1	PEG8 va–SG3199	ADC Therapeutics	B-ALL
ADCT-301	CD25	IgG1	PEG8 va–SG3199	ADC Therapeutics/Genmab	Hodgkin lymphoma, NHL
Enfortumab vedotin	Nectin 4	IgG1	vc–MMAE	Agensys/Astellas	Solid tumors, urothelial tumors
ASG-15ME	SLITRK6	IgG2	vc–MMAE	Agensys/Astellas	Metastatic urothelial cancer
AGS-67E	CD37	IgG2	vc–MMAE	Agensys/Astellas	NHL
AMG 224	Undisclosed	IgG1	Undisclosed	Amgen	Relapsed or refractory multiple myeloma
Lupartumab amadotin	C4.4A	IgG1	Auristatin W	Bayer	Lung squamous cell carcinoma
U3-1402	HER3	IgG1	Peptide linker with DX-8951 derivative	Daiichi Sankyo	Solid tumors
LY3076226	FGFR3	IgG1	Undisclosed	Eli Lilly	Advanced metastatic cancers
DSTA4637S	S. aureus	Engineered IgG1	vc-rifalogue	Genentech/ Symphogen	S. aureus infection
RG7841	LY6E	IgG1	vc–MMAE	Genentech/Roche	HER2- breast cancer, NSCLC

Appendix: ADCs under Active Clinical Trials

Name	Target	IgG	Payload-linker	Developer	Indication
RG7882	Undisclosed	IgG1	vc–MMAE	Genentech/Roche	Ovarian cancer, pancreatic cancers
RG7986	Undisclosed	IgG1	vc–MMAE	Genentech/Roche	NHL
Tisotumab vedotin	CD142	IgG1	vc–MMAE	Genmab	Multiple solid tumors
HuMax-Axl-ADC	AXL	IgG1	vc–MMAE	Genmab	Multiple solid tumors
GSK-2857916	BCMA	Engineered IgG1	mc–MMAF	GSK	Multiple myeloma, hematological malignancies
IMGN779	CD33	IgG1	sulfo-SPDB-DGN462	ImmunoGen	AML
MEDI3726	PSMA	IgG1	PEG8 va–SG3199	MedImmune	Prostate cancer
MEDI4276	HER2	Engineered IgG1	AZ13599185	MedImmune	Solid tumors
XMT-1522	HER2	IgG1	Fleximer polymer linker with auristatin F	Mersana	NSCLC, breast and gastric cancers
PCA062	Cadherin 3	IgG1	Undisclosed	Novartis	Head and neck cancer, oesophageal cancer, TNBC
HKT288	Cadherin 6	IgG1	SPDB-DM4	Novartis	EOC and RCC
PF-06647263	Ephrin A4	IgG1	Hydrazone-CM1	Pfizer/AbbVie (Stemcentrx)	TNBC, ovarian cancer
PF-06647020	PTK7	IgG1	vc-based linker with Aur0101	Pfizer/AbbVie (Stemcentrx)	NSCLC, TNBC, ovarian cancers
RC48-ADC	HER2	IgG1	vc-MMAE	Remegen	Breast cancer
SAR566658	CA6	IgG1	SPDB-DM4	Sanofi	Breast, cervical, lung and ovarian cancers
SGN-LIV1A	LIV1	IgG1	vc–MMAE	Seattle Genetics	Breast cancer
SGN-CD70A	CD70	Engineered IgG1	va–SGD1882	Seattle Genetics	RCC
SGN-CD19B	CD19	Engineered IgG1	va–SGD1882	Seattle Genetics	Relapsed NHL
SGN-CD123A	CD123	Engineered IgG1	va–SGD1882	Seattle Genetics	AML
SGN-CD352A	CD352	Engineered IgG1	va–SGD1882	Seattle Genetics	Multiple myeloma
Trastuzumab duocarmazine	HER2	IgG1	vc–seco-DUBA	Synthon	Breast and gastric cancers

Appendix: ADCs under Active Clinical Trials

Name	Target	IgG	Payload-linker	Developer	Indication
ARX788	HER2	Engineered IgG1	Auroxime	Zhejiang Medicine Co./Ambrx	Breast and gastric cancers
ADCs in Phase II Clinical Trials					
Depatuxizumab mafodotin	EGFRvIII	IgG1	mc–MMAF	AbbVie	Glioblastoma and solid tumors
AGS 16C3F	ENPP3	IgG2	mc–MMAF	Agensys/Astellas	RCC
AGS62P1	FLT3	Engineered IgG1	Auroxime	Agensys/Astellas	AML
Anetumab ravtansine	Mesothelin	IgG1	SPDB-DM4	Bayer HealthCare	Mesothelin-expressing tumors
Indatuximab ravtansine	CD138	IgG4	SPDB-DM4	Biotest	Multiple myeloma
BMS-986148	Mesothelin	IgG1	Undisclosed	BMS	Solid tumors
Glembatumumab vedotin	GPNMB	IgG2	vc-MMAE	Celldex	Melanoma, osteosarcoma, TNBC
CDX 014	TIM1	IgG1	vc–MMAE	Celldex	RCC
DS-8201a	HER2	IgG1	Peptide linker with DX-8951 derivative	Daiichi Sankyo	Solid tumors
Polatuzumab vedotin	CD79b	IgG1	vc-MMAE	Genentech/Roche	NHL
Coltuximab ravtansine	CD19	IgG1	SPDB-DM4	ImmunoGen	DLBCL
Naratuximab emtansine	CD37	IgG1	SMCC-DM1	ImmunoGen	NHL
Labetuzumab govitecan	CEACAM5	IgG1	CL2A-SN38	Immunomedics	Metastatic CRC
PSMA ADC	PSMA	IgG1	vc–MMAE	Progenics/Seattle Genetics	Prostate cancer
SAR408701	CEACAM5	IgG1	SPDB-DM4	Sanofi	Solid tumors
SAR428926	LAMP1	IgG1	SPDB-DM4	Sanofi	Solid tumors
Denintuzumab mafodotin	CD19	IgG1	mc–MMAF	Seattle Genetics	B-NHL
ADCs in Phase III Clinical Trials					
Rovalpituzumab tesirine	DLL3	IgG1	PEG8 va–SG3199	AbbVie (Stemcentrx)	SCLC
Mirvetuximab soravtansine	FOLR1	IgG1	sulfo-SPDB-DM4	ImmunoGen	Advanced epithelial ovarian cancer
Sacituzumab govitecan	TROP2	IgG1	CL2A-SN38	Immunomedics/Seattle Genetics	TNBC
Vadastuximab talirine	CD33	Engineered IgG1	va–SGD1882	Seattle Genetics	AML