Antibody drug conjugates (ADC)

Current status and mapping of ADC:s in clinical programs

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Abstract

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A literature study was performed on a new type of cancer medicine: antibody drug conjugates, or ADCs. These consist of a monoclonal antibody, chemically linked to a cytotoxic agent. What makes them unique is their selective toxicity against cancer cells. The first approval of such a pharmaceutical was in the year 2000, with three or four available in different regions of the world today. In the range of 50 registered drugs in clinical development were found, by major and minor corporations. These have been presented in a table in the appendix according to their properties such as type of linker, cytotoxin, development status etc. Furthermore, a detailed study has been done of the chemistry of the linker conjugation as well as an attempt at studying the ADC market. Finally, the mentioned strengths of the drug were compared to its weaknesses, mainly instability and otherwise poor pharmacokinetics. The main conclusion is that these drugs are expected to play a major role in oncology in the future.
Glossary

AcBut  4-(4-acetylphenoxy)butanoic acid
ADC(s)  antibody drug conjugate(s)
AML  acute myeloid leukemia
CAGR  compound annual growth rate
CLL  chronic lymphocytic leukemia
DAR  drug to antibody ratio
DM  drug maytansinoid
FDA  United States Food and Drug Administration
EGFR  epidermal growth factor receptor
EMA  European Medicines Agency
EHR(s)  Electronic Health Record(s)
GGFG  glycine-glycine-phenylalanine-glycine
lys  lysine
mAb  monoclonal antibody
mc  maleimidocaproyl
MMAE  monomethyl auristatin E
MMAF  monomethyl auristatin F
mp  maleimidopropionyl
MPM  malignant pleural mesothelioma
NHL  Non-Hodgkin's lymphoma
(N)SCLC  (non-)small cell lung cancer
PABC  para-amino benzyloxy carbonyl
pAcF  para-acetylphenylalanine
PBD(s)  pyrrolobenzodiazepine(s)
PEG/PEGX  polyethylene glycol/of X repeats
PMDA  Japanese Pharmaceuticals and Medical Devices Agency
R/R  relapsed or refractory
SMCC  succinimidyl 4-(N-maleimidomethyl)cyclohexane-1-carboxylate
SPDB  N-succinimidyl-4-(2-pyridyldithio)butanoate
SPDP  N-succinimidyl 4-(2-pyridyldithio)pentanoate
sulfo-SPDB  N-succinimidyl-4-(2-pyridyldithio)-2-sulfo-butanoate
TNBC  triple negative breast cancer
US$  United States Dollar(s)
VA  valine-alanine
VC  valine-citrulline
1. Introduction

Today cancer is one of the most dangerous diseases in the world and a few of the most common forms are breast cancer, lung cancer, prostate cancer and leukemia (National Cancer Institute, 2017). With so many people directly or indirectly affected by the disease, it is crucial to find new treatments. Antibody drug conjugate is a relatively new class of treatment for cancer. An ADC is composed with a monoclonal antibody, a linker and a cytotoxic agent also referred to as a payload, this is shown in Figure 1. Monoclonal antibodies are identical immune cells that can bind nonspecifically into cancer cells. ADCs are designed with the intention to use an antibody to target cancer cells, while the ADC as a whole is inactive during circulation. Because of the cytotoxin being linked to the antibody, selective toxicity is far greater than conventional cytostatics. ADCs are also designed to allow the use of highly potent payloads which normally are not tolerable due to high levels of toxicity. With improved standards of living throughout the world leading to more cancer diagnoses, ADCs are likely to play a major role in oncology, biologics and perhaps medicine in general in the near future. For this reason, knowledge of this class of drugs is necessary for an aspiring company in the field of biopharmaceuticals. This report is a literature study intended to explore the significance of ADCs and address this issue.

![Figure 1. Illustration of the components of an ADC (ADC Review, 2016).](image)

1.1 Aim

The aim of the project was to map the antibody drug conjugates on the market and some of the ADCs in clinical development, with respect to aspects such as target antigen, cytotoxic, linker and developer. In addition, the report is to cover relevant aspects of applied chemistry, i.e. how the components are linked together and modified to create the drug. Finally, the report is to include an analysis of the antibody drug conjugate market.
2. Background

In this section, information about ADCs themselves is presented with respect to their linkers and payloads. They are further analyzed in the aspects of drug to antibody ratio (DAR) and pharmacokinetics. Finally a review is presented about the concept of clinical trials and a brief study of the ADC market.

2.1 ADC linkers

The ADC linker is located between the cytotoxic payload and the monoclonal antibody. The linker is perhaps the most intriguing part of an antibody drug conjugate, as it is relatively unique to the class of pharmaceuticals. The stability of the linker is important in systemic circulation, as the ADC provides a method for limiting the cytosstatic concentration in the blood and avoiding off-target effects. Nevertheless, the linker has to be stable to deliver the cytotoxic agent expeditiously once the ADC is embodied to the tumor cell (Sau et al. 2017).

There are two major categories of linkers, generally termed cleavable and non-cleavable (Klute et al. 2014). Cleavable linkers have a built-in weakness in the form of a chemical structure for enzymatic and hydrolytic cleavage, releasing the drug. The drug will then simply diffuse to the target. Additionally, the drug from a cleavable linker can occasionally diffuse back outside the cell afterwards which leads to so-called bystander killing of non-targeted adjacent cells. Specifically, there are three types of cleavable linkers: hydrazone, disulfide and peptide linkers. Each correlates to a specific intracellular condition either low pH, high glutathione concentrations or protease activity. Hydrazone linkers undergo acid hydrolysis to release the cytotoxic agent. Disulfide linkers, which are more stable in circulation, are cleaved through interactions with glutathione, a molecule which is part of the immune system and accumulates in cancer cells. The last form of cleavable linker is the peptide linker which is the most stable form compared to the other forms. This form allows better control of the drug release by joining to the payload and monoclonal antibodies. These peptide linkers are optimized to release the payload upon cleavage by the intracellular enzymes such as proteases (Sau et al. 2017).

Non-cleavable linkers consist of either thioether or maleimidocaproyl - both of them depend on lysosomal enzymatic degradation of the ADC in order to release the payload onto the target. When the drug is released from the antibody, it will obtain a charged lysine or cysteine amino acid. The charged amino acid will prevent diffusion of the drug through the cell membrane. This leads to drug accumulation in the tumor cell and inhibition of bystander effect. A major advantage of non-cleavable linker is that they minimize drug release in the circulation, since they are more stable (Sau et al. 2017).

2.2 ADC payloads

The payload or cytotoxic agent is the most important unit in the ADC. The ADC is dependent on the potency of the payload, as the ADC has to be capable of killing cancer cells. The payload has to be stable in circulation due to intravenous administration of the ADC (Trail et al. 2018). For the aspect of the conjugation, the chemical structure of the payload may need to be modified if no relevant attachment point for the linker is available.

There are different kinds of payloads which are currently being used such as auristatin derivatives, maytansinoids, calicheamicin, duocarmycin, pyrrolobenzodiazepines (PBDs), amatoxin and doxorubicin. Auristatin is not actively used today due to its nonspecific toxicity, but its derivatives MMAE and MMAF are approved payloads. The maytansinoids are thiol derivatives of maytansines, and there are two
such derivatives which are currently in clinical trials, DM-1 and DM-4 (Sau et al. 2017). A table with the different payloads are presented in Table 1.

Table 1. The different payloads and their modes of action.

<table>
<thead>
<tr>
<th>Payloads</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maytansinoids</td>
<td>Inhibit the development of microtubules when attaching itself to the positive end of microtubule.</td>
</tr>
<tr>
<td>Calicheamicin</td>
<td>Inhibits the DNA replication.</td>
</tr>
<tr>
<td>Duocarmycin</td>
<td>Targets the DNA by alkylating the adenine base.</td>
</tr>
<tr>
<td>PBD</td>
<td>Inhibits the DNA replication by alkylation</td>
</tr>
<tr>
<td>Amatoxin</td>
<td>A cyclic peptide that prevents DNA transcription by binding to the RNA-Polymerase II.</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Intercalates and then inhibits DNA synthesis.</td>
</tr>
</tbody>
</table>

2.3 Drug to antibody ratio

Drug to antibody ratio, shortened DAR, defines the amount of drug molecules conjugated to the antibody. DAR appears to range between 0-8 drugs when the antibody is being conjugated either to a lysine side chain or a cysteine interchain. The higher the DAR, the higher the efficacy of the drug due to the higher potency, however with an increased DAR, pharmacokinetics might be affected with further implications on toxicity (Chen et al. 2015).

2.4 ADC pharmacokinetics

While pharmacodynamics is the study of what a pharmaceutical does to the body, perhaps equally important is pharmacokinetics - the study of what the body does to a pharmaceutical. It is vital that the ADC reaches the target cell and then is disposed of. Pharmacokinetics is often summed up in the abbreviation ADME - absorption, distribution, metabolism and excretion. Knowledge of how ADCs behave in these aspects is equally important to knowledge of their potency.

The way a pharmaceutical is absorbed depends mainly on its route of administration. Such routes are first separated into enteral routes, where it is administered through the gastrointestinal tract and parenteral routes, where it is somehow injected into the body. As ADCs are biologics, they are not suitable for the most common route; the peroral administration, through the ingestion of a pill. With the antibodies being protein-based, it is futile to send them through a system that least partially designed to metabolize protein for energy. Apart from that, other enteral routes or specialized routes such as transdermal require the pharmaceutical to be simple and fat soluble, something that does not apply. Thus, ADCs have to be administered parenterally, as it is chemically and physically unstable. Most common are the specialized intravenous injections or infusions, administered by medical professionals. Aside of this, there are also the relatively simple subcutaneous or intramuscular injections. In these cases, we are looking at a delayed or instant, though in either case near-complete, absorption into the bloodstream.
The distribution of a pharmaceutical, especially between the bloodstream and the target tissue, will depend on several factors. It is important that the pharmaceutical neither is locked to the bloodstream nor accumulates in untargeted fatty tissue. A measurement known as volume of distribution, $V_d$, is defined as “[the] fluid volume that would be required to contain the amount of drug present in the body at the same concentration as in the plasma” (University of Lausanne: Faculty of Biology and Medicine, n.d.). While perhaps initially complicated to grasp, the measurement provides information on whether the pharmaceutical can be viewed as distributing over a large volume or being concentrated to the bloodstream. Smaller $V_d$ values are found for pharmaceuticals to be active in the blood, such as anticoagulants, while higher $V_d$ values manifest for highly lipophilic pharmaceuticals, such as antidepressants which need to be lipophilic in order to penetrate the blood-brain barrier. Aside from lipophilicity, $V_d$ is impacted by the extent of plasma protein binding, where especially albumin has a tendency to lock pharmaceuticals inside the bloodstream. This does not readily affect biologics such as antibodies, but the most important factor impacting $V_d$ is likely their hydrophilicity and size leading to a small volume of distribution (Dirks and Meibohm 2010). A low $V_d$ indicates the ADC circulating like an antibody, eventually reaching the cancer cells and releasing the payload (Malik et al. 2017).

In terms of metabolism, the lysosome of the target cell can be expected to be the main source of ADC metabolism, due to the pharmaceutical being stable in circulation, except for a negligible contribution from non-specific proteases (Malik et al. 2017). As stated earlier, when internalized, the ADC will release its payload either through specific cleavage or through general lysosomal degradation. After this, there are three objects rather than one that will be subject to further degradation: the antibody, the payload and the linker. The last, however, is of low clinical significance or even completely irrelevant if attached to either of the other two. As antibodies are naturally occurring proteins, the body is able to simply metabolize them again in the lysosome. This can occur either after internalization or through pinocytosis, the general cellular consumption of proteins. However, a certain limitation to the latter is the so-called FeRn salvage pathway, intended to conserve therapeutic concentrations of antibodies in the plasma. After pinocytosis occurs, the endosome is somewhat acidified, allowing antibodies to bind to the FeRn receptor, protecting them from proteolytic degradation. They are later released through exocytosis once physiological pH is re-established (Ryman and Meibohm 2017). Hence, there is no specific excretion of the antibody, as its amino acids are indistinguishable from other amino acids in the body.

The metabolism of the payload is of great importance due to it being a highly potent cytotoxin. Erickson and Lambert (2012) describe how three ADCs are metabolized and where, notably stating that “all three ADCs were effectively detoxified during hepatobiliary elimination in rodents” (p. 799). Two out of three ADCs used in the study were sulfur-containing and underwent S-oxidation, while the last contained a peptide segment that might have made it hydrophilic enough to excrete directly. It is thus likely that payloads, after having attacked the tumour cell, will systematically circulate to the liver where they are excreted through the bile and faeces. Such circulation similar to the bystander effect is likely in subtoxic concentrations (Malik et al. 2017).

### 2.5 Clinical trials

The ADCs require an extensive documentation for a medicine in order to be approved before commercialization. The outline of clinical testing is worth knowing about for anyone studying pharmaceutical development. The pathway to the market for the ADCs consist of phases I, II and III in clinical trials.
Before Phase I, preclinical studies are performed. The treatment is first tested on animals and on cells in test tubes before the same testing is performed on humans (Läkemedelsverket, 2015).

Phase I is the first step in clinical drug development. In this phase studies are conducted to check the safety of the product. These studies usually include around 20-60 people, mostly men being the subjects of these experiments. It is important to look for side effects, which pharmacological properties the substance has and how the substance breaks down in the body in order to see how it gets disposed. A very low dose of the substance is first tested and then the dose gradually increases. After every gradual increase a safety assessment is done (Kliniska Studier Sverige, 2017).

The second step in clinical drug development is Phase II. The new treatment is compared to treatments that are already available or placebo and further information of the substance can be acquired. Depending on the disease the subsequent potency of the treatment and the optimal dosage can be evaluated to a certain degree (Kliniska Studier Sverige, 2017).

The last step in clinical drug development is Phase III. In this phase, there are between 200 and 3000 people, or sometimes even more with the purpose of confirming the potency and safety of the treatment, compared to placebo for a longer time period. The optimal amount of administered dosage has already been determined in Phase II. If Phase III studies are successful, companies will apply to get the product or treatment approved before the substance enters the market (Kliniska Studier Sverige, 2017).

The ADC development is getting better as researchers are improving the antibody bioengineering as well as linker chemistry and producing more potent drugs. With different regulatory requirements around the world, three ADCs can be found on the European market today, **ADCETRIS®** (brentuximab vedotin), **Kadcyla®** (trastuzumab emtansine) and **Besponsa®** (inotuzumab ozogamicin). Furthermore, there are over 50 ADCs in clinical trials for solid tumors and over 20 for hematological cancers. Some of the ADCs in Phase I which use maytansinoid or auristatin show remarkable results for different types of cancer forms (Sau et al, 2017). It is also worth noting that there are some ADCs that are approved for treatment of a certain kind of cancer. But these are in clinical trial for another cancer form, an example of this being inotuzumab ozogamicin (**Besponsa®**), approved for the treatment of precursor B-cell lymphoblastic leukemia-lymphoma and in trial for the treatment of R/R CD22-positive acute lymphocytic leukemia (clinicaltrials.gov, 2018).

### 2.6 ADC market

Today, ADCs are one of the fastest growing classes of oncology drugs worldwide. The popularity and growth of ADCs has increased, and both large and small companies have invested in the development of ADCs. auran (2015) lists five companies - Seattle Genetics, F. Hoffmann-La Roche, ImmunoGen, ADC Therapeutics SA and Pfizer ,have been successful with ADCs. A number of ADCs in clinical development play a major role in biopharmaceutical growth, where the future of the market depends on their clinical success. More than half all ADCs are in discovery or pre-clinical stages (Wood, 2017) and approximately 10% of these therapies are in advanced step II or higher phases.
2.6.1 The global Antibody drug conjugate market by region
The ADC market is the greatest in North America and Europe as shown in Figure 2, owing to a high portion of the population diagnosed with cancer (Medgadget, 2018). Asia Pacific, has also a rapidly growing region with countries like India and China followed by Latin America, Middle East and Africa. These regions have comparably smaller ADC market but still have a large growth (Tauran, 2015).

2.6.2 Antibody drug conjugates market segments
Since monoclonal antibody drugs can be used to treat other diseases than just cancer. There are other companies that have been working with treatments of diseases such as orthopaedic diseases, immune diseases, cardiovascular diseases and infectious diseases as shown in Figure 3 (Creative Biolabs, 2018). Sanofi and Regeneron Pharmaceuticals collaborated and developed sarilumab (Kevzara) that can be used to treat rheumatoid arthritis (Creative Biolabs, 2018). Companies are continuously investing new products to capture the market globally.
Figure 3. Description of the different indications of approved monoclonal antibody drugs.
3. Method

Scientific databases were used to obtain credible information. Throughout the project, seven different databases were used at some point, SciFinder, ScienceDirect, PubMed, Web of Science, Google Scholar, AdisInsight, clinicaltrials.gov and EuroMonitor International, as well as general library searches through the Uppsala university library showing only peer reviewed results. In general, these databases were chosen mainly because the authors were confident in how to use them - although they do cover many relevant aspects of the natural sciences. These include chemistry (SciFinder) and medicine (PubMed) as well as detailed aspects such as clinical trials (clinicaltrials.gov) or market reports (EuroMonitor International). The search term “antibody drug conjugate” or even “ADC”, plus terms such as “market”, “linker”, “linker chemistry”, or “target” were used to obtain general information, particularly in the early stages. Furthermore, studying the individual substances, searches were conducted using the names of the registered substances, as well as with the term “structure”. Such specific name searches were often conducted first in found list-including review articles, followed by scientific databases and finally search engines such as Google. The databases were generally available through the university library. The pharmacokinetics of the ADCs were studied through the search term “pharmacokinetics of antibody drug conjugates” and “pharmacokinetics of antibodies”. Another important aspect was so-called snowballing, or the following of the references of found articles. All the researches done throughout the project are too numerous to list in this report. When searching through the results, sources were typically chosen with information about the relevant topic - be it linkers, payloads or just a comprehensive list of ADCs in clinical development.

One of the initial searches was done in PubMed, using the term “all types of antibody drug conjugates” which led to 185 results. Abstracts were studied until one appeared including the sentence “[w]e identified 87 ADCs” (Moek et al. 2017) which was investigated further. This article contained a comprehensive list of ADCs that eventually formed the basis of the continued searching. Another comprehensive list (de Goeij and Lambert 2016) was found using the search term “glematatumumab vedotin” on ScienceDirect, the article being chosen from among seven results on the basis of publication type and date.

3.1 Delimitations

An important delimitation of the report decided upon is not to cover the regulatory requirements or mapping the excipients used. Another delimitation regarding the aspects of applied chemistry is not to cover specific linker systems and enzymatic conjugations that are not used in ADCs on the market or in clinical development today. Finally, the report is not to cover ADCs whose linkers or payloads are not disclosed, as these are relatively few.
4. Results

In this section, general information on some of the ADCs found to be particularly important, due to having achieved or being close to market approval or having other intriguing properties, is listed. A full list of ADCs with chemical structures are found in the Appendix. The results about linker chemistry and conjugation are also presented, as well as a brief section about the market.

4.1 Approved

The first approved antibody drug conjugate in the year 2000 was gemtuzumab ozogamicin, sold under the brand name Mylotarg® by Pfizer Inc. It targets the CD-33 receptors of myeloid leukemias and B-cell lymphomas and is currently indicated for the treatment of acute myeloid leukemia. The drug uses a hydrazone acetyl butyrate acid-labile cleavable linker, attached to a lysine sidechain of the antibody via an amide bond. The payload is a calicheamicin cytotoxin and because of the cleavable linker it is known to utilize bystander effect (Ricart, 2011). Its process toward approval has been very complicated - it was approved in the USA between 2000 and 2011, however retracted in 2011 in the wake of a series of fatal adverse effects (Tanimoto et al. 2013). In Japan, it was approved in 2005 and has been since then, while in the EU it was refused in 2008. In 2017, it was once again approved by the FDA (2017b), a short while after the approval of its sibling compound, inotuzumab ozogamicin, also known as Besponsa® (FDA, 2017a). The two compounds share the same developer, linker, linker-antibody bond, cytotoxin and bystander effect. The latter, however, was also approved in the EU around the same time and is indicated for the treatment of acute lymphoblastic leukemia, for which it has had orphan drug status as well as breakthrough therapy designation in the USA (EMA, 2017; Lamb, 2017).

The second approved ADC, which unlike inotuzumab ozogamicin remains approved in the US, EU and Japan, was brentuximab vedotin, developed by Seattle Genetics, Inc. in cooperation with Takeda Pharmaceutical Company Ltd. It is sold under the trade name ADCETRIS® (Seattle Genetics Inc., n.d.) and is indicated for the treatment of Hodgkin’s lymphoma and targets the CD-30 antigen expressed on most cells of said disease, as well as on several other types of lymphoma. The company states that it is being tested clinically in Phase III for other indications and new FDA approvals arrive as this report is being written (FDA, 2018a). Other facts about it are its protease-cleavable mc-VC-PABC linker and MMAE cytotoxin - a combination which, as will be seen later, appears to be the most common among ADCs in development today (Moek et al. 2017). The linker used implies a bystander effect and a disulfide bridge to a cysteine residue of the antibody. Having been approved since 2011, 2012 and 2014 in the above-mentioned areas (EMA, 2018a; FDA, 2018b; PMDA, 2013a), it is estimated to be the best-selling ADC by 2021 (iHealthcareAnalyst, 2017).

The final approved ADC as of this date is trastuzumab emtansine, developed by Roche Registration GmbH and sold under the brand name Kadcyla®. One might recognize trastuzumab as a standalone medication - the antibody targets the antigen HER-2, human epidermal growth factor, frequently overexpressed in cancer cells. This triggers an immune response while also limiting the activity of growth signals and limiting tumor growth (EMA, 2018b), although this is less potent than targeting HER-2 with an ADC. Trastuzumab emtansine uses a DM-1 maytansinoid payload and a non-cleavable SMCC linker with limited bystander effect and amide antibody-linker bond (Moek et al. 2017). It is indicated for the treatment of proven HER-2-positive breast cancer under certain conditions depending on the area and has been approved in the US, EU and Japan since 2013 (EMA, 2018c; FDA, 2013; PMDA, 2013b).
4.2 Phase III
A few ADCs have been found in the third phase of clinical development and are expected to reach the market relatively soon. As previously mentioned the approved ADCs differ somewhat in their properties.

*Rovalpituzumab tesirine*, with the brand name Rova-T®, is a pyrrolobenzodiazepine-based ADC. This payload is even more potent than the ones mentioned above, its DNA alkylating ability makes it in the range of a million times more cytotoxic than generic cytostatics (Spirogen Ltd., n.d.). It is developed by AbbVie Inc. and targets the DLL-3 antigen of small cell lung cancer and large-cell neuroendocrine carcinoma cancer cells. The PBD dimer is linked to the antibody via a disulfide bond to a mc-PEG8-Val-Ala-PABC dipeptide linker; the PEG oligomer added for enhanced water solubility. With the linker being protease cleavable, it utilizes bystander effect (Rudin et al. 2017; Moek et al. 2017). Finally, a significant trial in expected to finish in 2020 (clinicaltrials.gov, 2017), and the ADC is also expected to have among the three largest market shares in 2021 (iHealthcareAnalyst, 2017). However, a series of phototoxic reactions were reported during clinical trials of the drug in early 2018 (Lou and Bridges) - adverse reactions when a patient was exposed to sunlight.

*Mirvetuximab soravtansine*, also known as IMGN853, is being developed by ImmunoGen, Inc. It targets the folate receptor α, an antigen with several different abbreviations overexpressed in several epithelial tumours. In early 2018, a Phase III study was presented with the drug being tested against platinum-resistant ovarian cancer. The linker is of the sulfo-SPDB type, a more polar version of the relatively common SPDB linker. It is cleavable via an internal disulfide bond, providing ground for a bystander effect and binds into both the payload and the antibody through a carboxylic acid group, indicating amide bond in the latter case (Moek et al. 2017). In this particular drug, the payload used is DM-4 (Moore et al. 2017). The drug is expected to have a decent share of the ADC market in 2021 (iHealthcareAnalyst, 2017).

Finally, *sacituzumab govitecan* or *IMMU-132* is developed by Immunomedics, Inc. and targets TROP-2, also an antigen overexpressed in several epithelial tumours (Starodub et al. 2015). While mostly studied as a treatment for metastatic triple negative breast cancer, it has received several designations for other indications as well. It uses the slightly less potent SN-38 topoisomerase inhibitor payload Immunomedics, Inc. (n.d.) points out that the lower potency of the payload allows for higher drug to antibody ratios - and a complicated PEG8- and triazole-containing PABC-peptide-mc linker called CL2A (McCoy et al. 2017). This linker is cleavable through pH sensitivity, giving rise to bystander effect, and binds the antibody at a cysteine residue via a disulfide bond (Starodub et al. 2015).

4.3 Phase II
Furthermore, the earlier stages of clinical development the ADCs become too numerous to handle with the above detail. In this phase the drug is tested for dose-ranging, which means if the drug has any biological activity or effect on the cancer cells. Speaking in more general terms, the most common indications of ADCs in Phase II are mostly breast cancer and b-cell lymphoma, for example *glembatumumab vedotin* that contains the payload MMAE. Another example is *coltuximab ravtansine* which contains the payload DM-4 where the indication is B-cell lymphoma. Unique linkers and payloads include those of *labetuzumab govitecan*, comparable to the earlier-mentioned *sacituzumab govitecan*, MedImmune’s tubulysin-equipped MEDI-4276 and Immunomedics’ *milatuzumab doxorubicin*. 
4.4 Phase I
There are several similarities observed in Phase I such as linkers used and indications. An example of this is ADCT-402 and ADCT-301, where their chemical structure is exactly the same. Both of them contain the same linker and payload which is PEG-Val-Ala linked to a PBD payload. They also have the same indication, renal cell cancer, but the difference between them is their different targets and that ADCT-402 also has leukemia as indication. However, a special ADC was observed called ARX-788 which contains an unnatural amino acid as a linkage, indicated for the treatment of breast and gastric cancer and equipped with the MMAF payload. Another special ADC is XMT-1522, developed by Mersana Therapeutics, Inc., due to its massive and complicated polymer ester linker unlike any other ADC. This ADC is indicated for the treatment of breast cancer and also contains MMAF as payload.

4.5 Discontinued ADCs
Some of the 87 originally found ADCs were either terminated or discontinued. It is usually different ADCs in Phase I that get discontinued, as shown in Appendix, section 7.3. It appears that the main reasons for this are either adverse effects or focus on other product candidates (Moek et al. 2017).

4.6 Linker chemistry and conjugation
There are two nucleophilic groups which are accessible for the linker to attach to in the antibody, which are the amine of lysine and the sulfhydryl group of cysteine. These two conjugation sites don’t need to be modified to be able to link to the payload. However, the negative aspect of these conjugation methods is the imbalance and heterogeneity of the products (McComb et al. 2015).

4.6.1 Amide conjugation
Amide conjugation is when the amine from lysine links the cytotoxic agent to the antibody by utilizing linkers with activated carboxylic acids and esters as shown in Figure 4. There are almost 80 lysine residues on an antibody, but only ten of these residues are available for chemical conjugation (McComb et al. 2015). Therefore, lysine conjugation results in several ADC species with a wide range of DARs, for an example of this is the Maytansinoids - DM1 gave an average of 3.5-4 drugs that were linked per antibody and a distribution of 0-7 (Lazar et al. 2005). When constructing ADCs with this method, a heterogeneous mixture is manufactured which has a lot of species that are complicated to purify and characterize (McComb et al. 2015).

![Figure 4. Mechanism of amide conjugation (Tsuchikama and An 2018).](image)

4.6.2 Cysteine conjugation
Cysteine conjugation is more common than its lysine counterpart. This conjugation is located in the interchain disulfide bridges of the antibody and the thiol group of the payload. There are four plus twelve
interchain disulfide bonds in an IgG1 antibody which is the most common used antibody. Of these, four interchains can undergo a reduction by tris(2-carboxyethyl)phosphine, TCEP, or dithiothreitol, DTT, this result in eight free thiols and consequently only eight possible conjugation sites. The other twelve disulfide bonds stay intact (Yao et al. 2017). This method has a DAR lower than eight because of the fewer available sites, but unlike the lysine coupling it is easier to characterize the species when producing ADCs. For these types of linkers, maleimides are used as the reactive element of the drug to bind the antibody via cysteine residues, which can be seen in Figure 5A (McComb et al. 2015). An example of ADC which utilizes this kind of attachment is the approved ADC; ADCETRIS®.

A new method called cysteine re-bridging was developed to improve heterogeneity and to better control the DAR of ADCs. There are two types of molecules that are able to conjugate with such proximal cysteine residues to later rebridge the antibody. These are dibromopyidazinediones and 1,3-bis(p-toluenesulfonyl)propanes. This method, shown below in Figure 5B, leads to a better stability, heterogeneity and a more controlled DAR (Bryant et al. 2015).

Figure 5. Mechanism of cysteine conjugation. (A) shows the maleimide alkylation. (B) shows re-bridging of two cysteine (Tsuchikama and An 2018).

4.6.3 Non-natural amino acids conjugation
Another method used is with unnatural amino acid residues in proteins as a handle for conjugation (Axup et al. 2012). This was made by placing a pAcF amino acid in the so-called Fab region of the heavy chain of an anti-HER2 antibody. This was done because they wanted a more strict control of DARs. The carbonyl groups will then react with alkoxyamine-functionalized linkers to provide oxime conjugated ADCs as shown in Figure 6. ADCs containing alkoxy-amine with functional ariastatin linked to pAcF show a homogeneous DAR of 2. As mentioned previously, for an example of this is the ADC ARX-788 which is in Phase I. The disadvantage of this conjugation method is that it requires a long reaction times, usually 1-4 days (McComb et al. 2015).
4.6.4 Linkers
The hydrazone linkers are very stable in the bloodstream, but once they reach the acidic endosomes (pH 5.0-6.0) and lysosomes (pH 4.5-5.0), they rapidly undergo hydrolysis as shown in Figure 7A. In the early 90s, scientists developed BR96-DOX which is a BR96 humanized monoclonal antibody linked to doxorubicin by hydrazone conjugation to the cysteine residues. However, BR96-DOX ADC, like Mylotarg®, got withdrawn due to its toxicity profile, because of the slow hydrolysis of the hydrazone linker which releases the payload in circulation (Tsuchikama and An 2018).

Another cleavable linker is called cathepsin B and is analogous to the substrate of a lysosomal protease found in multiple cancer cells. This protease can identify phenylalanine-lysine (Phe-Lys) and VC dipeptides, cleaving the peptide bond on the C terminus of the sequence. The linkers VC and VA are stable, always coupled with a PABC spacer and are the most common linkers today. The spacer role is to separate the payload from the site of the enzymatic cleavage which can be seen in Figure 7B (Tsuchikama and An 2018).

Disulfide linkers is dependent on the intracellular glutathione concentration. The bonds are more stable and further strengthened by the two methyl groups inserted next to the disulfide bond which is necessary for the stability in circulation. A special example of cleavable disulfide base linker is when it is actively paired with an amide conjugation. The disulfide bond is located within the linker, making it inaccessible to cleave in circulation but still allowing the glutathione to cleave the disulfide bond after internalization as shown in Figure 7C (Tsuchikama and An 2018).
4.7 Global antibody drug conjugate market

According to The World Cancer Research (Medgadget, 2018), cancer was the second leading cause of death worldwide. The IMS Institute for Health states that the global cost for oncology medicines was 100 billion US$ in 2014. It is expected to rise to nearly 150 billion US$ by 2023 and a CAGR of 30.2% (Medgadget, 2018). According to the global Internet pharmacies market is expected to reach 76.9 billion US$ by 2021 and a CAGR of 17.4% between 2017 and 2021 (iHealthcareAnalyst, 2017).

The online pharmacies are a new kind of platform for customers to be able to order by mail and will therefore save time and money (iHealthcareAnalyst, 2017). The global electronic health records (EHR) market is expected to reach 23.5 billion US$ by 2021 and a CAGR of 6.0% between 2017-2021. The EHR system across healthcare facilities has had an impact on large and small medical practices. Implementation of electronic health records has also proven to decrease medical costs and improve patient care. Recent technological EHR advancements include cloud based EHRs, improved patient portals, growth of the telehealth industry and mobile accessibility. These are factors worth considering that might impact healthcare and pharmaceutical industries alike - mainly positively, leading to increased demands for these products and services.
5. Discussion

The results show us that almost all of the studied ADCs use similar types of linkers and payloads despite their different indications. While all ADCs use similar modes of action, their uniqueness in being able to achieve selective toxicity against cancer cells cannot be overstated.

5.1 Different phases
The regulatory approval of both ADCETRIS® and Kadcyla indicates a high capacity for antibody delivery for both hemotoxic malignancies and solid tumors. In additional, there are a variety of opportunities for optimizing antibodies and designing innovative linkers and conjugation methods. The clinical data emerging from these next generations of ADCs will contribute to an opportunity to better understand the impact of changes in the ADC properties on therapeutic activity and safety, and new practices of clinical use of ADC in combination with other treatment modalities, including conventional cytotoxic drugs. The most important factor, however, is the huge amount of pipeline drugs, indicating the potential of these products.

5.2 Linker chemistry
The most common and recurring bond between the linker and antibody is either the amide or cysteine linked with a maleimide derivative. This can be seen in the structures of all the ADCs studied - they almost all have this type of conjugations and same type of linker. This could indicate that ADCs with these systems are better, ADCETRIS® being the most obvious example. As previously mentioned, the ADC that most clearly differs from the rest is ARX-788, which is conjugated with an unnatural amino acid. The conjugation with the unnatural amino acid provides a homogenous ADC, perhaps making it more stable than cysteine and amide conjugation. However, as mentioned in the results the unnatural conjugation reactions takes time. Another method mentioned in the results is the cysteine re-bridging conjugation, however this method does not occur in the ADCs studied because it is relatively new. It is possible that this method is going to be more favorable than the regular cysteine conjugation in the future due to its controlled DAR and stability.

5.3 ADC market
The benefits with ADC treatment is that it has a design with a highly potent payload and is therefore more tolerable for high level of toxicity compare to cytostatics. Some weaknesses of ADC treatment is that there is a high risk of the drug to be hydrolyse or oxidize, as well a tendency to aggregate. However, this can be avoided by formulating the drug as amorphous, also known as freeze-drying it. The ADC has a low membrane permeability which also makes it hard for it to pass biological membranes. It has a short half-life and fast elimination and the drug cannot be administered orally. There are some threats to the development of these drugs, such as new advances in genomics and patent issues that can in some cases be very expensive. On the other hand, if it is possible to get a multifunctional peptide and conjugate it can be very useful for getting a successful business. Newer drugs in development, however, can be very expensive compared to those already on the market. A trend that was observed in the ADC market is that there seems to have been an increased cooperation between the different companies and its technology. One of the reasons for the enormous growth is that companies can make the original antibody more profitable. Therefore they can build their strengths and improve their weaknesses. The new technologies also include alternative administration routes beyond the dominant parenteral injection route and
conjugates of peptides to antibodies. However, the medicinal antibody drug conjugates chemistry could be compared to a microelectronics or LEGO bricks which makes it possible to combine amino acids. The intelligent assembly of known modules with unique properties could lead to the construction of multifunctional molecular medicines with improved efficacy, pharmacokinetic properties and targeted delivery.

5.4 Conclusion and future perspectives

The different ADCs have been mapped according to different aspects and presented in the appendix as well as briefly in the results. As new pharmaceuticals enter development continuously such a list will never be complete, however, ours is both thorough and well-referred, for the time being.

As for studying relevant aspects of applied chemistry, it is obvious that not only the payload that is crucial to the ADC, but also the conjugation method and linker chemistry. Thus, we can conclude that every unit is important to make a profitable and clinically successful ADC.

Hydrazone linkers, if any, seem to be going out of favour. These are the most labile of the cleavable linkers and eventual efficacy advantages due to bystander effect are outweighed by off-target effects. This notion is further strengthened by the market withdrawal of Mylotarg® and the low amount of such linkers in clinical development - particularly in the earlier stages. On the other hand, for further studies in designing and developing linker-payload systems, we would recommend either of two choices that stand out. The first is to use the common, first-generation mc-VC-PABC-MMAE combination. It is a well-regarded, and through ADCETRIS® thoroughly tested, system that is already being used by in the range of fifteen companies. However, it is a first-generation system that lacks the finesse of some of the newer ADCs. Thus, another possible combination would be to combine a very potent payload - a PBD dimer comes to mind - with a sturdy linker such as pAcF. The combination will be incredibly potent, while the risk of off-target killing is reduced by the non-cleavable linker and the product purity guaranteed by the fixed DAR.

We are convinced that the enormous growth of ADCs will continuing to raise in the future. It is impossible to say how many ADCs and from which corporations will exist on the market in fifteen years - the approximate time period for the development of a new pharmaceutical. With little doubt, ADCs will play a significant role in the future of cancer treatment, the main reason being that this is the closest to a “golden bullet” against cancer that has been achieved so far.
6. References


## 7. Appendix

### 7.1 Comprehensive list of ADCs on the market and in clinical development
Below is a list of all found non-terminated ADCs.

Table 2. A list of all non-terminated ADCs.

<table>
<thead>
<tr>
<th>ADC</th>
<th>Target</th>
<th>Payload</th>
<th>Linker</th>
<th>Indication</th>
<th>Developer</th>
<th>Status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBV-085 (1)</td>
<td>LRR-C15</td>
<td>MMAE</td>
<td>mc-VC-PABC</td>
<td>Lung, pancreatic and breast cancer</td>
<td>AbbVie Inc.</td>
<td>Phase I</td>
<td>(Purcell et al. 2016)</td>
</tr>
<tr>
<td>ADCT-301 (4)</td>
<td>CD25</td>
<td>PBD dimer</td>
<td>mp-PEG8-VA-PABC</td>
<td>NHL, Precursor B-cell lymphoblastic leukemia-lymphoma</td>
<td>ADC Therapeutics SA</td>
<td>Phase I</td>
<td>(Flynn et al. 2016)</td>
</tr>
<tr>
<td>ADCT-402 (4)</td>
<td>CD19</td>
<td>PBD dimer</td>
<td>mp-PEG8-VA-PABC</td>
<td>Renal cell carcinoma, NHL, Precursor B-cell lymphoblastic leukemia-lymphoma</td>
<td>ADC Therapeutics SA</td>
<td>Phase I</td>
<td>(Zammarchi et al. 2018)</td>
</tr>
<tr>
<td>AGS-16C3F (5)</td>
<td>ENPP3</td>
<td>MAAF</td>
<td>mc (non-cleavable)</td>
<td>Refractory renal cell carcinoma</td>
<td>Astellas Pharma Inc.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
<td>AGS67E (1)</td>
<td>CD37</td>
<td>MMAE</td>
<td>mc-VC-PABC</td>
<td>AML, CLL, hairy cell leukemia, lymphoid leukemia, NHL</td>
<td>Astellas Pharma Inc.</td>
<td>Phase I</td>
<td>Pereira et al. 2015</td>
</tr>
<tr>
<td>AMG-172 (2)</td>
<td>CD27L</td>
<td>DM-1</td>
<td>SMCC (non-cleavable)</td>
<td>Renal cell carcinoma</td>
<td>Amgen Inc.</td>
<td>Phase I</td>
<td>(Pharmaco dia Holding Ltd, 2016)</td>
</tr>
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<td></td>
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<td></td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
<td>AMG-595 (2)</td>
<td>EGFR-vIII</td>
<td>DM-1</td>
<td>SMCC (non-cleavable)</td>
<td>Anaplastic astrocytoma</td>
<td>Amgen Inc.</td>
<td>Phase I</td>
<td>(Hamblett et al. 2015)</td>
</tr>
<tr>
<td>Anetumab ravtansine (BAY 94-9343) (14)</td>
<td>Meso-thelin</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>MPM</td>
<td>Bayer Healthcare Pharmaceuticals</td>
<td>Phase II</td>
<td>(Golfier et al. 2014)</td>
</tr>
<tr>
<td>ASG-15ME (1)</td>
<td>SLIT-RK6</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Metastatic urothelial cancer</td>
<td>Astellas Pharma Inc.</td>
<td>Phase I</td>
<td>(Morrison et al. 2016)</td>
</tr>
<tr>
<td>BIIB015 (14)</td>
<td>Cripto protein</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>R/R solid tumours</td>
<td>Biogen, Inc.</td>
<td>Phase I</td>
<td>(Kelly et al. 2011)</td>
</tr>
<tr>
<td>CDX-014 (1)</td>
<td>TIM-1</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Ovarian carcinomas</td>
<td>Celldex Therapeutics, Inc.</td>
<td>Phase I</td>
<td>(Thomas et al. 2016)</td>
</tr>
<tr>
<td>Compound</td>
<td>Target(s)</td>
<td>Type</td>
<td>Cancer Type</td>
<td>Company</td>
<td>Phase</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Coltuximab ravtansine (SAR3419)</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>Large B-cell lymphoma</td>
<td>ImmunoGen, Inc.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
<td></td>
</tr>
<tr>
<td>Depatuxizumab mafodotin (ABT-414)</td>
<td>EGFR</td>
<td>MMAF mc (non-cleavable)</td>
<td>R/R B-/lineage acute leukemia and other lymphoma</td>
<td>AbbVie, Inc.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
<td></td>
</tr>
<tr>
<td>DS-8201A</td>
<td>HER-2</td>
<td>Irino-tecan GGFG (protease cleavable)</td>
<td>Breast and gastric cancer</td>
<td>Daichi Sankyo Co., Ltd.</td>
<td>Phase I</td>
<td>(Trail et al. 2018)</td>
<td></td>
</tr>
<tr>
<td>Glembatumumab vedotin</td>
<td>Glycoprotein NMB /osteoenactivin</td>
<td>MMAE mc-VC-PABC (protease cleavable)</td>
<td>Breast cancer, melanoma</td>
<td>Cellxide Thapeutics, Inc.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
<td></td>
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<tr>
<td>GSK28579-16</td>
<td>BCMA</td>
<td>MMAF mc (non-cleavable)</td>
<td>Multiple myeloma</td>
<td>GlaxoSmit hKline PLC</td>
<td>Phase I</td>
<td>(ADC Review, 2017)</td>
<td></td>
</tr>
<tr>
<td>IMGN-289</td>
<td>EGFR</td>
<td>DM-1 SMCC (non-cleavable)</td>
<td>Solid tumours</td>
<td>ImmunoGen, Inc.</td>
<td>Phase I</td>
<td>(de Goeij and Lambert 2016)</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Antibody</td>
<td>Target</td>
<td>Linker</td>
<td>Activity</td>
<td>Indication</td>
<td>Phase</td>
<td>Reference(s)</td>
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<td>IMGN-529</td>
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<td>DM-1</td>
<td>SMCC (non-cleavable)</td>
<td>CLL, NHL</td>
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<td>II</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
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<td></td>
<td>(Hicks et al. 2017)</td>
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<td>Indatuximab ravtansine, BT-062</td>
<td>CD138</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>Multiple myeloma</td>
<td>Biotest Pharmaceuticals Corporation</td>
<td>II</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>(Schönfeld et al. 2017)</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin (Besponsa®)</td>
<td>CD-22</td>
<td>Calicheamicin</td>
<td>AcBut (pH cleavable)</td>
<td>Precursor B-cell lymphoblastic leukemia-lymphoma</td>
<td>Pfizer, Inc.</td>
<td>II</td>
<td>Approved: USA, EU 2017</td>
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<td></td>
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<td>(Ricart, 2011)</td>
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<tr>
<td>Labetuzumab govitecan (17)</td>
<td>CEA-CAM5</td>
<td>SN-38</td>
<td>CL2A (pH cleavable)</td>
<td>Colon cancer</td>
<td>Immuno- medics, Inc.</td>
<td>II</td>
<td>(de Goeij and Lambert 2016)</td>
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<td></td>
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<td>(Dotan et al. 2017)</td>
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<tr>
<td>Lifastuzumab vedotin (DNIB0600 A)</td>
<td>NaPi2b</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Platinum resistant ovarian cancer</td>
<td>Genentech /Roche Registratio n GmbH</td>
<td>II</td>
<td>(de Goeij and Lambert 2016)</td>
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<tr>
<td>Lorvotuzumab mertansine (8)</td>
<td>CD56</td>
<td>DM-1</td>
<td>SPDP (glutathione cleavable)</td>
<td>SCLC, solid tumors including Wilms tumor, neuroblastoma and sarcomas</td>
<td>Immuno-Gen, Inc.</td>
<td>II</td>
<td>(Whiteman et al. 2014)</td>
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<tr>
<td>LY-3076226 (6)</td>
<td>FGFR-3</td>
<td>DM-4</td>
<td>Sulfo-SPDB (glutathione cleavable)</td>
<td>Metastatic cancer</td>
<td>Eli Lilly and Company</td>
<td>I</td>
<td>(Pharmaco dia Holding Ltd, 2016)</td>
</tr>
<tr>
<td>MDX-1203 (9)</td>
<td>CD70</td>
<td>Duo- carmycin</td>
<td>Modified mc-VC-PABC (protease cleavable)</td>
<td>NHL, renal cancer</td>
<td>Medarex, Inc.</td>
<td>I</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
<td>Antibody</td>
<td>Target</td>
<td>Linker Type</td>
<td>Cancer Type</td>
<td>Company</td>
<td>Phase</td>
<td>Reference</td>
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<td>MEDI-4276 (16)</td>
<td>HER-2</td>
<td>Tubulysin</td>
<td>Breast and stomach cancer</td>
<td>Med-Immune, LCC</td>
<td>II</td>
<td>(de Goeij and Lambert 2016)</td>
<td></td>
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<tr>
<td>Milatuzumab doxorubicin (IMMU-110) (19)</td>
<td>CD74</td>
<td>Doxorubicin</td>
<td>SMCC-hydrazone (pH cleavable)</td>
<td>CLL</td>
<td>Immuno-medics, Inc.</td>
<td>II</td>
<td>(de Goeij and Lambert 2016) (Stein et al. 2010)</td>
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<tr>
<td>Mirvetuximab soravtansine (IMGN853) (6)</td>
<td>Folate receptor α</td>
<td>DM-4</td>
<td>Sulfo-SPDB (gluthation cleavable)</td>
<td>Platinum resistant ovarian cancer</td>
<td>ImmunoGen, Inc.</td>
<td>III</td>
<td>(Moore et al. 2017)</td>
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<tr>
<td>PCA-062 (2) P-cadherin</td>
<td>DM-1</td>
<td>SMCC (non-cleavable)</td>
<td>Breast cancer</td>
<td>Novartis International AG</td>
<td>I</td>
<td>(Trail et al. 2018)</td>
<td></td>
</tr>
<tr>
<td>PF-062635-07 (5) 5T4</td>
<td>MMAF</td>
<td>mc (non-cleavable)</td>
<td>Breast cancer</td>
<td>Pfizer, Inc.</td>
<td>I</td>
<td>(Shapiro et al. 2017)</td>
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</tr>
<tr>
<td>PF-066508-08 (1) Notch3</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Breast, lung and ovarian cancer</td>
<td>Pfizer, Inc.</td>
<td>I</td>
<td>(Pfizer, Inc., n.d.)</td>
<td></td>
</tr>
<tr>
<td>Pinatuzumab vedotin (1)</td>
<td>CD22</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>CLL</td>
<td>Genentech, Inc.</td>
<td>II</td>
<td>(de Goeij and Lambert 2016) (Kim, 2015)</td>
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<tr>
<td>Polatuzumab vedotin (RG7596) (1)</td>
<td>CD79b</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>B-cell lymphoma</td>
<td>Genentech, Inc.</td>
<td>II</td>
<td>(de Goeij and Lambert 2016) (Palanca-Wessels et al. 2015)</td>
</tr>
<tr>
<td>ADC Code</td>
<td>Target</td>
<td>Payload</td>
<td>ADC Description</td>
<td>Disease</td>
<td>Company</td>
<td>Phase</td>
<td>Reference</td>
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<tr>
<td>PSMA ADC 1301EXT (1)</td>
<td>PSMA</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Prostate cancer</td>
<td>Progenics Pharmaceuticals, Inc.</td>
<td>Phase II</td>
<td>(Wang et al. 2011)</td>
</tr>
<tr>
<td>RC48-ADC (1)</td>
<td>HER-2</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Breast cancer</td>
<td>RemeGen, Inc.</td>
<td>Phase II</td>
<td>(Hong and Fang 2017)</td>
</tr>
<tr>
<td>Rovalpituzumab tesirine (Rova-T®) (4)</td>
<td>DLL-3</td>
<td>PBD dimer</td>
<td>mp-PEG8-VA-PABC (protease cleavable)</td>
<td>SCLC, Large-cell neuroendocrine carcinoma</td>
<td>AbbVie, Inc.</td>
<td>Phase III</td>
<td>(Rudin et al. 2017)</td>
</tr>
<tr>
<td>Sacituzumab govitocan (IMMU-1332) (17)</td>
<td>TROP-2</td>
<td>SN-38</td>
<td>CL2A (pH cleavable)</td>
<td>Several epithelial cancers</td>
<td>immunoMedics, Inc.</td>
<td>Phase III</td>
<td>(Starostub et al. 2015)</td>
</tr>
<tr>
<td>SAR-408701 (14)</td>
<td>CEA-CAM5</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>CEACAM5-positive tumours</td>
<td>Sanofi S.A.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
<td>SAR-428926 (14)</td>
<td>LAMP-1</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>Neoplasm malignant</td>
<td>Sanofi S.A.</td>
<td>Phase I</td>
<td>(Trail et al. 2018)</td>
</tr>
<tr>
<td>SAR-566658 (14)</td>
<td>CA6</td>
<td>DM-4</td>
<td>SPDB (glutathione cleavable)</td>
<td>CA6-positive metastatic TNBC</td>
<td>Sanofi S.A.</td>
<td>Phase II</td>
<td>(de Goeij and Lambert 2016)</td>
</tr>
<tr>
<td>SGN-CD-19B (12)</td>
<td>CD19</td>
<td>PBD dimer</td>
<td>mc-VA-modified PABC (protease cleavable)</td>
<td>NHL</td>
<td>Ligand Pharmaceuticals; Seattle Genetics</td>
<td>Phase I</td>
<td>(Ryan et al. 2017)</td>
</tr>
<tr>
<td>SGN-LIVIA (1)</td>
<td>LIV-1</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Metastatic breast cancer</td>
<td>Seattle Genetics, Inc.</td>
<td>Phase I</td>
<td>(Trail et al. 2018)</td>
</tr>
<tr>
<td>SYD-985 (9)</td>
<td>HER-2</td>
<td>Duo-carmycin</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Breast cancer</td>
<td>Synthon Holding BV</td>
<td>Phase I</td>
<td>(Trail et al. 2018)</td>
</tr>
<tr>
<td>-------------</td>
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</tr>
<tr>
<td>Tisotumab vedotin (HuMax®-TF-ADC) (1)</td>
<td>HER-2</td>
<td>MMAE</td>
<td>mc-VC-PABC (protease cleavable)</td>
<td>Cervical cancer</td>
<td>Genmab A/S, Seattle Genetics, Inc.</td>
<td>Phase II</td>
<td>(Concin et al. 2017)</td>
</tr>
<tr>
<td>Trastuzumab emtansine (Kadcyla®) (2)</td>
<td>HER-2</td>
<td>DM-1</td>
<td>SMCC (non-cleavable)</td>
<td>Metastatic breast cancer</td>
<td>Roche Registra- tion GmbH.</td>
<td>Approved: USA, EU, Japan 2013</td>
<td>(Lambert and Chari 2014)</td>
</tr>
<tr>
<td>U3-1402 (10)</td>
<td>HER-3</td>
<td>DX-8951</td>
<td>GGFG (protease cleavable)</td>
<td>Breast cancer and NSCLC</td>
<td>Daiichi Sankyo Co., Ltd.</td>
<td>Phase II</td>
<td>(Kogawa et al. 2017)</td>
</tr>
<tr>
<td>XMT-1522 (13)</td>
<td>HER-2</td>
<td>MMAF</td>
<td>mp-polymer ester (non-cleavable)</td>
<td>Breast cancer</td>
<td>Mersana Therapeutics, Inc.</td>
<td>Phase I</td>
<td>(Trail et al. 2018)</td>
</tr>
</tbody>
</table>

7.2 Structures
Below are the structures, corresponding to the above list. They were drawn in BIOVIA Draw 2018.
7.3 Terminated ADCs
Below is a brief list of ADCs found to be terminated, with a reference for further reading.

Table 3. List of terminated ADCs.

<table>
<thead>
<tr>
<th>Terminated</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABBV-838</td>
<td>(Clinicaltrials.gov, 2018)</td>
</tr>
<tr>
<td>ASG-5ME</td>
<td>(Adis Insight, 2018)</td>
</tr>
<tr>
<td>AVE9633</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>BAY-1187982</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>BAY-794620</td>
<td>(Adis Insight, 2014)</td>
</tr>
<tr>
<td>Bivatuzumab mertansine</td>
<td>(Adis Insight, 2014)</td>
</tr>
<tr>
<td>Cantuzumab mertansine</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>Cantuzumab ravtansine</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>DEDN6526A</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>IMGN388</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>MEDI-547</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>MLN2704</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>LOP2628</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>RG-7600 (DMOT4039A)</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>PF-06647263</td>
<td>(Adis Insight, 2018)</td>
</tr>
<tr>
<td>Pinatuzumab vedotin</td>
<td>(Adis Insight, 2018)</td>
</tr>
<tr>
<td>SGN-15</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>SGN-CD70A</td>
<td>(Adis Insight, 2018)</td>
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<tr>
<td>Sofituzumab Vedotin</td>
<td>(Moek et al., 2017)</td>
</tr>
<tr>
<td>Vorsetuzumab mafodotin</td>
<td>(Seattle Genetics Inc., 2013)</td>
</tr>
<tr>
<td>Vadastuximab talirine (SGN-CD33A)</td>
<td>(GenEngNews, 2017)</td>
</tr>
<tr>
<td>Vandortuzumab vedotin</td>
<td>(Moek et al., 2017)</td>
</tr>
</tbody>
</table>

-monotherapy-multiple-myeloma/ [Accessed 2018/04/18]


SEATTLE GENETICS, INC. (2013) Seattle Genetics Reports Third Quarter 2013 Financial Results Available from:


WANG, X et al. (2011) In Vitro and In Vivo Responses of Advanced Prostate Tumors to PSMA ADC, an Auristatin-Conjugated Antibody to Prostate-Specific Membrane Antigen, Molecular Cancer Therapeutics, 10 (9), pp. 1728-1739.

