ADCs
The year in review and 2018 outlook

Schematic for the structure of an antibody–drug conjugate (ADC). Adapted from reference [1]

INTRO
Antibody-drug conjugates (ADCs), are agents that consists of an immune substance, such as a monoclonal antibody, antigen or an immunoglobulin, and covalently bound to other molecule(s), usually either a toxin, a radioisotope, or a cytotoxic agent. Immunoconjugates allow for specific delivery of certain substances to specific cells or tissues for diagnostic or therapeutic purposes.[2] The majority of the ADCs currently under development or in clinical trials are oncology and hematology indications, although some drug developers are also looking to expanding the application to other important areas such as infectious diseases.[3]

The primary objective to develop ADCs as a antineoplastic platform is to generate compounds that are “better than chemotherapy”, by targeting the cytotoxic payload selectively to tumors to improve efficacy while avoiding the off-target toxicities that frequently limited the use of chemotherapy during prolonged treatment periods.[4–6]

APPROVALS
Before 2017, Brentuximab Vedotin (Adcetris®) and Trastuzumab Emtansine (Kadcyla®) were the only two ADCs approved respectively for CD30 positive hematologic malignancies and for Her2
positive advanced or metastatic breast cancer. 

In 2017 two more ADCs have been approved:

- Gemtuzumab ozogamicin (Mylotarg®) which was previously approved but voluntarily withdrawn in 2010, was reintroduced in September 2017 in the US market after approval by the FDA for the treatment of CD33 positive acute myeloid leukemia based on the positive results of three studies: ALFA-0701 (NCT00927498), Study AML-19 (NCT00091234) and Study MyloFrance-1.

- Inotuzumab ozogamicin (Besponsa®) was approved first by the European Commission and later by the US FDA for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL) based on data from INO-VATE ALL (NCT01564784).

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**RESEARCH TRENDS**

There is a plethora of ADCs, over 90 [2] and currently there are over 70 ADCs in clinical development, surpassing the 59 reported as in 2016 [7]. Eighty eight and 54 clinical trials are ongoing for Brentuximab Vedotin and Trastuzumab Emtansine respectively (8), but many new ADCs are being investigated in early phase trials, emerging data of which appears promising. Table 1 shows a selection of the most promising ADCs in clinical development based both on the maturity of the studies and in the reported results available in pubmed and press releases.

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**Table 1: Top ADCs in pipeline (as of January 2018)**

<table>
<thead>
<tr>
<th>ADC (manufacturer)</th>
<th>Target Antigen</th>
<th>Therapeutic Area</th>
<th>Ongoing Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glembatumumab Vedotin (Celldex)</td>
<td>gpNMB</td>
<td>Breast cancer (special focus in TNBC), NSCLC - squamous, Osteosarcoma, Melanoma (special focus in uveal melanoma), other solid tumors</td>
<td>Phase I and II (6 studies)</td>
</tr>
<tr>
<td>Mirvetuximab Soravtansine (ImmunoGen)</td>
<td>FOLR-1</td>
<td>Ovarian Cancer, Endometrial Cancer, Breast Cancer</td>
<td>Phase I, II and III (6 studies)</td>
</tr>
<tr>
<td>Polatuzumab vedotin (Genentech)</td>
<td>CD79B</td>
<td>Non-Hodgkin Lymphoma</td>
<td>Phase I, II and III (7 studies)</td>
</tr>
<tr>
<td>Anetumab Ravtansine (Bayer)</td>
<td>Mesothelin</td>
<td>Pancreatic cancer, Mesothelioma, Lung cancer and other solid tumors</td>
<td>Phase I and II (9 studies)</td>
</tr>
<tr>
<td>SGM-101 (Surgimab)</td>
<td>CEA</td>
<td>Digestive cancer, Breast cancer</td>
<td>Phase I and II (2 studies)</td>
</tr>
<tr>
<td>Panitumumab - iRDye800 (Eben Rosentha)</td>
<td>EGFR</td>
<td>Head and Neck Cancer, Pancreatic cancer</td>
<td>Phase I and II (2 studies)</td>
</tr>
<tr>
<td>MOC31PE (Creative Biolabs)</td>
<td>tumor-associated epithelial cell adhesion molecule</td>
<td>Colorectal peritoneal metastasis</td>
<td>Phase I and II (2 studies)</td>
</tr>
</tbody>
</table>
DMUC4064A (Genentech) | MUC16 | Ovarian Cancer | Phase I (1 study)
---|---|---|---
SYD985 (Synthon Biopharmaceuticals BV) | Her2 | Breast cancer | Phase I and III (2 studies)
Camidanlumab Tesirine (ADC Therapeutics S.A) | CD 25 | Hematological neoplasms | Phase I (2 studies)
GSK2857916 (GlaxoSmithKline) | BCMA | Multiple Myeloma | Phase I (1 study)
Ladiratuzumab vedotin (Seattle Genetics) | LIV-1 | Breast cancer | Phase I and II (2 studies)
Sacituzumab govitecan (Imunomedics) | TROP-2 | Breast cancer and Gastrointestinal cancer | Phase I, II and III (3 studies)
Indatuximab Ravtansine (Biotest) | CD138 | Multiple Myeloma, TNBC, Bladder Cancer | Phase I and II (2 studies)

**Abbreviations**: TNBC (Triple Negative Breast Cancer), NSCLC (Non-Small Cell Lung Cancer). **Ongoing Clinical Trials**: includes Not yet recruiting, Recruiting and Active, not recruiting trials.

Shared features of the most recent studies reflect 2018 outlook and the 5 top trends on the ADC development:

1. **Investigate the expression levels of the target antigen**

Predictive biomarkers are essential to ensure that the ADCs will be offered to the group of patients most likely to benefit from them. Whenever feasible, studies are including the development of specific tests that will determine the chances of responding to treatment to an ADC by investigating the level of expression of the target antigen. Illustrative examples are:

- CD123 expression levels in patients with relapsed or refractory acute myeloid leukemia (AML) receiving SGN-CD123A
- Her2 overexpression in patients with refractory breast cancer receiving DS-8201
- AG7 antigen expression in patients with chemo-refractory locally advanced, recurrent or metastatic gastric, colorectal or pancreatic adenocarcinoma receiving AbGn-107
- Mesothelin expression in patients with lung adenocarcinoma receiving Anetumab Ravtansine

2. **Test combinations**

Among the most promising are combinations of ADC and Immuno Oncology compounds (IO). It has been reported [9-10] that synergistic activities between IOs and ADCs may increase the formation of tumor specific immunological memory, ultimately leading to durable responses in a larger fraction of cancer patients. Indeed, many of the current classes of payloads employed for ADCs were previously reported to have very significant immunostimulatory activities. The identification of optimal combination regimens between ADC- and IO compounds holds strong promise to overcome the current limitations of immune checkpoint inhibitors, by increasing the recruitment of CD8+ effector T-cells to the tumor core.

Illustrative examples are the combinations tested with the more mature drugs
Brentuximab Vedotin and Trastuzumab Emtansine:

Brentuximab Vedotin is being combined with pembrolizumab, ipilimumab, nivolumab, TGR-1202, TAK228, imatinib, rituximab, ceritinib, bevacizumab, ibrutinib, alsertib, lenalidomide, bendamustine, ABVD, ICE, romidepsin, gemcitabine.

Trastuzumab Emtansine is being combined with pembrolizumab, atezolizumab, lapatinib, pertuzumab, tucatinib, neratinib, BYL719, ribociclib, capecitabine, vinorelbine, temozolomide, endocrine therapy, utomilumab, vemurafenib, alectinib, abraxane, cetuximab, taselisib.

3 – New linker technology

Increase delivery efficiency by using linkers that suit the particular antibody and cytotoxic being used, provide stability before entering the cell, and provide efficient payload release once inside the target cell. On this effort it is emphasized [7] the importance of expanding on the three most frequently employed classes of linker types, including the protease cleavable peptide linker, the reductively cleavable disulfide linkages, and thioether linkages. One example is the discovery of the novel, nonpeptidic ADC linkers (Peptidomimetic ADCs) which have been reported to improve the selectivity of ADCs by showing enhanced protease specificity [11]. In the search of more effective drug delivery and increased antitumor activity, new high-affinity molecules as cytotoxic payload carriers instead of ADCs have been proposed such as folic acid, growth hormones, diabodies, and minibodies [12]. However, this approach will also limit the pharmacokinetic benefits of an ADC resulting in more rapid clearance and larger volume of distribution.

4 – Target antigens not expressed in normal tissues

5 – Overcome the problem of heterogeneity of target antigen expression in the tumor

RESEARCH HIGHLIGHTS

Among the most destacable highlights in 2017:

Interim phase I data from Camidanlumab Tesirine (ADCT-301) shows encouraging preliminary safety and efficacy results in refractory lymphoma [13-14]

GSK2857916 demonstrates 60% response rate in heavily pre-treated relapsed/refractory multiple myeloma [15]

Polatuzumab Vedotin + Bendamustine and Rituxan increased complete response rates in patients with previously treated aggressive lymphoma [16]

Phase III ECHELON-1 clinical trial of Brentuximab Vedotin + ABVD meets primary endpoint and demonstrates a statistically significant improvement in modified-PFS against ABVD in frontline therapy of patients with advanced classical hodgkin lymphoma [17]
Updated data from an ongoing phase I clinical trial evaluating ladiratuzumab vedotin (SGN-LIV1A) in patients with metastatic triple negative breast cancer (mTNBC), show 29% objective response rate (ORR) at the recommended dose in patients with heavily pretreated disease. [18]

Treatment with sacituzumab govitecan (IMMU-132) elicited an objective response rate (ORR) of 34% in patients with heavily pretreated metastatic triple-negative breast cancer (mTNBC), according to updated findings from a phase II study [19]

In conclusion, ADCs are an emerging novel class of anticancer treatment agents that combines the selectivity of targeted treatment with the cytotoxic potency of chemotherapy drugs. It is expected that an increasing number of ADCs will likely become viable treatment options as single agents or in combination in the near future.

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