2. Introduction and Overview of the Report

The field of antibody-drug conjugates (ADC) has seen an explosive growth during the last few years. The number of ADC companies evaluated for preparation of the present report was nearly triple that described in the previous edition of the ADC report in the year 2011. Similarly, the number of scientific publications found in PubMed for the search item „antibody-drug conjugate“ in the year 2013 was three-times that of 2011 or even 9-times higher than in the years before.

First generation ADC technology has matured as evidenced by the regulatory approval and marketing of the first two ADC products against hematologic and solid malignancies with the two main ADC technologies from ImmunoGen and Seattle Genetics. Both companies utilize cell-cycle dependent tubulin polymerization inhibitors (maytansine and auristatin derivatives) conjugated via cleavable or stable linkers to natural lysine or cysteine residues in the targeting antibody. As a result of this conjugation technology, the drug-antibody ratio may be variable and the product heterogenous with potential impact on efficacy, safety and pharmacokinetics.

Resistance of cancer cells to currently employed drug payloads of ADCs adds a further parameter for optimization of ADCs.

Based on the current state of the art, this report describes the emerging next generation ADC technologies regarding target selection, novel antibody and alternative targeting moiety formats, novel drugs and conjugation systems. The report pays special attention to the commercial relevance and value of these technologies and highlights those picked-up by Big Pharma setting a trend for the first wave of new ADCs based on next generation ADC technologies.

You will find in this report detailed profiles of nearly 100 companies active in the field including their financial history, deals, partnerships, technologies, success and failures of ADC projects and their profiles. Based on this basic information, the ADC pipeline, stakeholders in the field, ADC technologies and business opportunities are analyzed. An Addendum lists ADC projects categorized by various variables and business agreements for collaborations, licensing deals and M&A. Scientific references are provided and non-scientific sources of information are disclosed with hyperlinks.
Interestingly, Seattle Genetics abandoned its first generation ADC against CD70 (SGN-75) based on MMAF with a non-cleavable linker in phase I in favour of a next generation ADC with PBD as drug. Previously, Medarex (now BMS) had discontinued an anti-CD70 naked antibody in favour of an ADC using a minor-groove binding (MGB) toxic payload. Bristol-Myers Squibb completed the phase I study, but then did not proceed with development. The target does not seem to be easy.

Table 15: ADCs against CD20

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Target</th>
<th>Linker</th>
<th>Drug</th>
<th>Company</th>
<th>R&amp;D Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1302A-maytansinoid</td>
<td>Type III CD20</td>
<td></td>
<td>DM1 or DM4</td>
<td>ImmunoGen</td>
<td>Precl</td>
</tr>
<tr>
<td>EP-400</td>
<td>CD20</td>
<td></td>
<td>CLIP71</td>
<td>Esperance Pharmaceuticals</td>
<td>Res</td>
</tr>
</tbody>
</table>

Of the 36 marketed or clinical development ADCs with known target, ten of them (28%) are being developed for haematological malignancies. The ten ADCs are directed against eight different targets: CD30, CD22 (2x), CD79b, CD19 (2x), CD138, CD37, CD33 and CD74. This percentage for ADCs in haematological indications is higher if only ADCs in advanced clinical development are regarded: 5/11 (45%) which might indicate that the number of targets in haematological malignancies is limited as compared to those in solid tumors.

3.5 Companies with clinical stage ADCs

At present, there are 17 companies with marketed ADCs or ADCs in clinical development. (Table 16). The two major ADC technology providers Seattle Genetics and ImmunoGen have advanced in their process of converting from a mere technology company to a ADC product development company with each four clinical stage ADCs. Roche has a total of nine clinical ADCs. About half of the remaining companies with clinical activities in the ADC field are smaller biopharmaceutical companies. Big Pharma/Biotech has not yet fully advanced in R&D towards clinical stages, but the near future will show a strong push by entrance of more Big Pharma companies in clinical development with ADCs (Lilly, Novartis, GlaxoSmithKline, AstraZeneca, Daiichi Sankyo).
Table 26: Synopsis of site-specific conjugation technology companies – 2/2

<table>
<thead>
<tr>
<th>Company</th>
<th>Technology or Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mersana Therapeutics</td>
<td><strong>Fleximer polymers</strong> as a vehicle for drugs; Fleximer polymer is bound with the targeting moiety at cysteines (or lysines) by a different linker chemistry via only one linker; ADC collaborations with Adimab and Endo Pharmaceuticals</td>
</tr>
<tr>
<td>Quanta Biodesign</td>
<td>Discrete polyethylene glycol (dPEG) chemistries</td>
</tr>
<tr>
<td>Serina Therapeutics</td>
<td><strong>Polyoxazoline (POZ) polymer</strong> technology; research agreement with the Scripps Research Institute for development of polymer-antibody drug conjugates (Polymer-ADCs)</td>
</tr>
</tbody>
</table>

4.2.6 Companies with new payloads

Current state of the art cytotoxic payloads of ADCs are either auristatin- or maytansine-derived which both act only dividing cells via inhibition of tubulin polymerization inhibitor, and may be associated with drug resistance. New drugs for ADCs address this limitation by having a cell-cycle independent mechanism of action such directly acting on the DNA via binding to the minor groove. Representative drugs are pyrrolobenzodiazepine (PBD) or duocarmycins. PBD was mainly developed by Spirogen, which made the payload accessible to Seattle Genetics which in turn was first bringing a PBD-based ADC into a clinical trial. **Spirogen** recently was acquired by AstraZeneca for up to US$ 440 mln and therefore, probably, will be no longer available for future technology outlicensing, whereas Seattle Genetics does, as recently in an expanded deal with AbbVie, albeit with financial terms higher than previously with auristatin ADCs. **Synthon** is building its own pipeline of duocarmycin-based ADCs.

The Wilex subsidiary **Heidelberg Pharma** recently gained interest by its collaboration with Roche to evaluate the use of its alpha-amanitin toxic payload for conjugation with Roche antibodies. α-Amanitin is a bicyclic peptide which exhibits comparable activity against proliferating and resting tumor cells. The Roche group has also a collaboration with **Nerviano Medical Sciences** about the novel cytotoxic agents. One group of such molecules are nemarubicin metabolites which were shown to be effective in auristatin-resistant cells.
cells, mediates binding and uptake via endocytosis. Within the cancer cell, AEZS-138 is cleaved and Disorazol Z can deploy its potent anti-proliferative activity.

AEZS-138 possesses cytotoxicity at low nanomolar concentrations in a highly diverse panel of various tumor cell lines. AEZS-138 inhibits tubulin polymerization, shows pro-apoptotic properties and arrests cancer cells in G2 stage of the cell cycle. In animal studies AEZS-138 is well tolerated and demonstrates promising antitumor efficacy in mice xenograft experiments. A joint research project of a consortium in Germany is being funded by a US$1.5 million grant from the German Ministry of Education and Research. Goal of the project is to further investigate the mode-of-action, to optimize fermentation and drug supply and to evaluate the in vivo potential of AEZS-138 (Aeterna Zentaris Homepage Nov 26, 2013).

Assessment:

The company is leveraging its know how in endocrine peptides for creating peptide-drug conjugates with different cytotoxic drugs. Specifically, LHRH receptor overexpressing tumors are suitable targets for LHRH analog peptides conjugated with drugs. The technology so far has been limited to LHRH receptor targeted peptide-drug conjugates.

Affinicon

The Danish biotech company is developing an antibody-drug conjugate technology platform for targeted delivery of known drugs to macrophages. The development of receptor-targeted therapeutics will focus on the macrophage specific receptor CD163, the most abundant transport receptor on macrophages. Affinicon acquired all intellectual property rights from Cytoguide as of October 2013, and continues the project of Cytogudies (Affinicon Homepage Nov 29, 2013). Affinocor exploits CD163 uptake of conjugate drugs for specific targeting of macrophages.

They have developed a new biodegradable anti-CD163 ADC that specifically targets the glucocorticoid, dexamethasone, to the hemoglobin scavenger receptor CD163 in macrophages. The conjugate, that in average contains four dexamethasone molecules per antibody, exhibits
in patients with relapsed and/or refractory multiple myeloma: clinical activity in Len/Dex-refractory patients

55th Annual Meeting of the American Society of Hematology; New Orleans, LA, USA; December 7-10, 2013: abstract 758

Kurkjian C, LoRusso P, Sankhala KK et al.
A phase I, first-in-human study to evaluate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of IMGN853 in patients (Pts) with epithelial ovarian cancer (EOC) and other FOLR1-positive solid tumors
J Clin Oncol 2013; 31 (suppl): abstract 2573

Letsch M, Schally AV, Szepeshazi K et al.
Preclinical evaluation of targeted cytotoxic luteinizing hormone-releasing hormone analogue AN-152 in androgen-sensitive and insensitive prostate cancers
Clin Cancer Res 2003; 9: 4504-4513
(http://clincancerres.aacrjournals.org/content/9/12/4505.full.pdf+html )

Leuschner C, Giardina C, Coulter A et al.
Nucleolin targeting oncolytic peptide for treatment of cancer
Cancer Res 2010; 70 (suppl 1): abstract LB-292

Lhospice F, Bregeon D, Belmant C et al.
Towards homogeneous ADCs: a new site-specific antibody conjugation using bacterial transglutaminase
World ADC Summit; San Francisco, CA, USA; October 14-17, 2013 - Poster

Li D, Poon KA, Yu SF et al.
DCDT2980S, an anti-CD22-monomethyl auristatin E antibody-drug conjugate, is a potential treatment for non-Hodgkin lymphoma
Mol Cancer Ther 2013; 12: 1255-1265
### ADCs with Auristatin Derivatives – 13/13

<table>
<thead>
<tr>
<th>ID No.</th>
<th>Product Name</th>
<th>Target / Mechanism of Action</th>
<th>Class of Compound</th>
<th>Company</th>
<th>Product Category</th>
<th>Indication</th>
<th>R&amp;D Stage</th>
<th>Message</th>
</tr>
</thead>
<tbody>
<tr>
<td>1713</td>
<td>h15H3-vcMMAE and h15H3-mcMMAF</td>
<td>Alphav/beta6 integrin inhibitor with auristatin payload</td>
<td>Rec humanized monoclonal antibody conjugated with either monomethyl auristatin E with a protease-cleavable linker (vcMMAE) or monomethyl auristatin F (mcMMAF),</td>
<td>Seattle Genetics</td>
<td>Antibody</td>
<td>Cancer</td>
<td>Res</td>
<td><a href="#">Seattle Genetics PR Apr 4, 2012</a> - Integrin alpha-v-beta6 is a promising new target antigen expressed at high levels on multiple solid tumors, including cancers of the lung, pancreas and head and neck. An anti-alphavbeta6 ADC demonstrated antitumor activity in multiple preclinical models <a href="#">AACR abstract</a></td>
</tr>
</tbody>
</table>