Antibody–Drug Conjugates as an Emerging Therapy in Oncodermatology

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Citation: Esnault, C.; Schrama, D.; Houben, R.; Guyénot, S.; Desgranges, A.; Martin, C.; Berthon, P.; Viaud-Massuard, M.-C.; Touzé, A.; Kervarrec, T.; et al. Antibody–Drug Conjugates as an Emerging Therapy in Oncodermatology. Cancers 2022, 14, 778. https://doi.org/10.3390/cancers14030778

Academic Editors: Céleste Lebbé and Maxime Battistella
Received: 4 January 2022
Accepted: 1 February 2022
Published: 2 February 2022

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Simple Summary: Currently, the therapeutic arsenal to fight cancers is extensive. Among these, antibody–drug conjugates (ADCs) consist in an antibody linked to a cytotoxic agent, allowing a specific delivery to tumor cells. ADCs are an emerging class of therapeutics, with twelve FDA- and EMA-approved drugs for hematological and solid cancers. In recent years, tremendous progress has been observed in therapeutic approaches for advanced skin cancer patients. ADCs appear as an emerging therapeutic option in oncodermatology. After providing an overview of ADC design and development, the goal of this article is to review the potential ADC indications in the field of oncodermatology.

Abstract: Antibody–drug conjugates (ADCs) are an emerging class of therapeutics, with twelve FDA- and EMA-approved drugs for hematological and solid cancers. Such drugs consist in a monoclonal antibody linked to a cytotoxic agent, allowing a specific cytotoxicity to tumor cells. In recent years, tremendous progress has been observed in therapeutic approaches for advanced skin cancer patients. In this regard, targeted therapies (e.g., kinase inhibitors) or immune checkpoint-blocking antibodies outperformed conventional chemotherapy, with proven benefit to survival. Nevertheless, primary and acquired resistances as well as adverse events remain limitations of these therapies. Therefore, ADCs appear as an emerging therapeutic option in oncodermatology. After providing an overview of ADC design and development, the goal of this article is to review the potential ADC indications in the field of oncodermatology.

Keywords: antibody–drug conjugates; oncodermatology; melanoma; skin squamous cell carcinoma; cutaneous T-cell lymphoma and Merkel cell carcinoma

1. Introduction

In 1909, the German chemist Paul Ehrlich [1] provided the first description of “targeted therapy”. He proposed the so called “magic bullet” concept, allowing the delivery...
of a therapeutic molecule to a specific target without affecting healthy tissues [2]. Currently, targeted therapies are used in daily oncology practice including oncodermatology. As such, tyrosine kinase inhibitors (TKIs) targeting BRAF and MEK proteins block the constitutive activation of the MAPK pathway in patients with BRAF-mutated melanoma [3], therefore reducing maintenance, development or dissemination of the cancer. Similarly, sonic hedgehog pathway inhibitors (sonidegib and vismodegib) act by inhibiting the smoothened protein involved in hedgehog signal transduction which plays a crucial role in basal cell carcinoma (BCC) development.

Among targeted therapies, antibody–drug conjugates (ADCs) combine a monoclonal antibody (mAb) with a highly cytotoxic molecule, allowing its specific delivery to tumor cells [4]. In recent years, optimization of ADC technologies in order to increase their therapeutic performances and overcome their limitations as well as evaluation of their effects in combination with currently approved drugs have significantly expanded their use in oncology [5,6]. Indeed, twelve ADCs have been approved by the FDA for treatment of hematologic malignancies (Table 1A) and solid tumors (Table 1B). Moreover, the number of ADCs in development is steadily increasing, with 195 ongoing clinical trials (https://www.beacon-intelligence.com/, accessed on 8 December 2021). Overall, ADCs are currently being applied in all oncology areas including skin cancers.

The aim of the present review is to highlight current developments of ADCs in oncodermatology and identify potential opportunities in this field.

Table 1. FDA-approved ADCs. A. Hematological malignancies. B. Solid tumors.

| Commercial Name | International Non-Proprietary Names (INN) | Target | Antibody Isotype | Bioconjugation Head (Antibody Amino Acid) | Linker | Drug (Therapeutic Class) | Indication |
|-----------------|------------------------------------------|--------|------------------|------------------------------------------|--------|--------------------------|------------|
| Adcetris®       | brentuximab vedotin                       | CD30   | Chimeric IgG1     | Maleimidocaproyl (Cysteine)              | Cleavable/ proteolytic (cathepsin B) | auristatin  | anaplastic large cell lymphoma + Hodgkin’s lymphoma |
| Polivy®         | polatuzumab vedotin-piiq                  | CD79b  | Humanized IgG1    | Maleimidocaproyl (Cysteine)              | Cleavable/ proteolytic (cathepsin B) | auristatin  | relapsed or refractory diffuse large B-cell lymphoma |
| Mylotarg®       | gemtuzumab ozogamicin                     | CD33   | Humanized IgG4    | Acetylbutyrate (Lysine)                  | Cleavable/hydrazone | calicheamicin | CD33-positive acute myeloid leukemia |
| Beponsa®        | inotuzumab ozogamicin                     | CD22   | Humanized IgG4    | Acetylbutyrate (Lysine)                  | Cleavable/proteolytic (furin) | Pseudomonas endotoxin A | lymphoblastic leukemia |
| Lumoxiti®       | moxetumomab pasudotox                     | CD22   | N/A              | N/A                                      | Cleavable/proteolytic (furin) | pyrolobenzodiazepine dimer (PBD) | hairy cell leukemia |
| Zynlonta®       | loncastuximab tesirine-lpyl              | CD19   | Humanized IgG1    | Maleimidocaproyl (Cysteine)              | Cleavable/proteolytic (cathepsin B) | auristatin  | relapsed/refractory diffuse large B-cell lymphoma |
| Blenrep®        | belantamab mafodotin                      | CD38   | Humanized IgG1k   | Maleimidocaproyl (Cysteine)              | Uncleavable          | auristatin  | relapsed/refractory multiple myeloma |
### 2. ADCs in Oncology

2.1. Structure of ADCs

ADCs consist in a cytotoxic drug, i.e., a payload bioconjugated through a linker to mAb-targeting tumor cell antigens [7] (Figures 1–2). The specific combination of these components determines both the therapeutic performance and safety of the ADC [4]. The following parts aim to provide a brief overview of the features of the different ADC components and how these can impact efficacy and safety.

#### Figure 1. Design of an antibody–drug conjugate and recommended biological properties. Characteristic of antigen, antibody, linker–antibody attachment, linker, linker–payload attachment and
payload are detailed. The antibody Fc part is implied in half-life and immunogenicity. The Fab part controls affinity and avidity to the targeted antigen.

**Figure 2.** Overview of ADC mode of action. 1. Binding of the ADC to the antigen expressed by the cancer cell. 2. Internalization of the ADC. 3. Degradation of the linker or antibody inside the lysosome induces the release of an active form of the payload. 4. The payload exerts cellular toxicity depending on its mode of action. 5. A bystander effect can occur.

### 2.2. Targets

Target identification is a crucial point in ADC development [8, 9]. Tumor-specific biomarkers previously used for diagnosis, as well as proteins overexpressed due to gene amplification or proteins involved in tumor aggressiveness [10] might be considered as potential ADC targets. Most ADCs bind to proteins expressed on the cell surface while targeting of intracellular tumor-associated proteins can also be achieved by using T-cell-receptor-like antibodies recognizing peptides in the context of presentation by MHC-I complexes [11]. In both cases, i.e., extra- and intracellular proteins, the specificity of the tumor antigen, antigen expression levels and antigen/ADC internalization [12] determine the performance of an ADC target [9].

To provide optimal payload delivery, high and homogenous expression of targeted antigens on the tumor cell surface is required [13]. By contrast, absent or low expression in healthy tissues [14] is expected in order to limit toxicities on physiologic cells (i.e., in order to avoid on-target off-tumor cytotoxicity). Nevertheless, several clinically approved ADCs such as brentuximab vedotin, targeting CD30 [15], polatuzumab vedotin, targeting CD79 [16], and inotuzumab ozogamicin, targeting CD22 [17], actually engage with ligands expressed by immune cells but still harbor therapeutic efficiency and acceptable tolerance. Moreover, most ADCs require internalization of the targeted surface antigen through receptor-mediated endocytosis and lysosomal degradation of the linker in order to deliver the payload [18]. One evasion mechanism that limits ADC performance is the
downregulation of the targeted antigen expression, which obviously affects ADC binding to the target cells [9].

While antigens present on the cell surface are the most frequent candidates for ADC targets [19], secreted proteins/soluble antigens might additionally offer new opportunities by being more accessible. As a consequence, linker and drug have to be designed to be active in this context [14]. Some ADCs targeting non-internalizing soluble antigens, such as Tenascin-C splice variants or fibronectin, with maytansinoid and auristatins as payloads, have already demonstrated antitumor activity [20,21]. Importantly, targeting soluble antigens in the tumor microenvironment (TME) might impact not only tumor cells but also tumor stroma, extracellular matrix and blood vessels. Moreover, an association between bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, and an ADC has provided improved outcomes compared to a combination of bevacizumab with standard chemotherapy, in a phase Ib clinical study including patients with platinum-resistant ovarian cancer [22].

2.3. Antibodies

mAbs used in ADC structures are mostly of the IgG1 or IgG4 subtypes, and are chimeric or humanized in order to decrease their immunogenicity [4]. Both parts of the mAbs, i.e., the fragment antigen-binding (Fab) and fragment crystallizable regions (Fc region), contribute to the performance of an ADC. While affinity of a mAb for its epitope is determined by the Fab portion [10], the Fc part is determinant for mAb stability and interactions with immune cells such as antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated phagocytosis (ADCP). To this end, the Fc part interacts with neonatal Fc receptor (FcRn) [23], a recycling receptor determining both IgG half-life and biodistribution [24], or complement (C1q) implied in CDC or Fc receptors on immune effector cells (FcγR), a family of receptors which may trigger an immune response upon Fc binding [25]. The ADC interactions with immune cells might either constitute an opportunity to induce an antitumor response, or represent a potential side effect, resulting in toxicity on immune cells [14]. Accordingly, to improve or avoid immune functions (ADCC, CDC, and ADCP), genetic engineering introducing mutations in the Fc domain of ADCs is used [14,26]. The Fc mutations aim to promote or impair interactions between ADCs and immune cells, Fc receptors or complement (C1q) in order to prevent or improve their activation, such as increased ADCC with ADC glyco-engineering (i.e., afucosylation) [27,28]. On the other hand, other Fc modifications have been proposed to increase ADC half-life via FcRn-mediated ADC recycling [9].

Additional factors related to the payload and linker affect ADC pharmacokinetics (PK) and pharmacodynamics (PD) [29]. Notably, ADC hydrophobicity is associated with shorter half-life in serum [30] and because most of the payloads are hydrophobic, attachment to a hydrophilic antibody remains a challenge [31]. To overcome hydrophobicity and ADC aggregation, the most common ADC modification consists in glycosylation, a naturally occurring post-translational modification influencing the solubility, antigenicity and stability of proteins [32]. PEGylation, the addition of polyethylene glycol (PEG) to the linker in order to mask payloads hydrophobicity and to improve the PK of ADCs (i.e., reduction in aggregation, improvement in solubility and half-life [31]), has also been proposed [32].

2.4. Payloads

While radionucleotides, toxins [33] and cytokines [34] have been suggested as ADC payloads [35–37], most preclinical and FDA/EMA-approved ADCs are bioconjugated with small cytotoxic molecules [38] with a broad range of structures and mechanisms of action [4]. Among these, duocarmycins and pyrrolobenzodiazepines (PBD) dimers induce DNA alkylation by linking alkyl residues to AT-rich regions or guanine, leading to cell apoptosis [38]. Cell death can also be induced by calicheamicins inducing DNA double-
strand breaks [38]. Maytansine derivatives (including DM1 and DM4) [39] and auristatins (monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF)) [7] are poisons which inhibit microtubule polymerization by targeting tubulins, resulting in G2/M arrest and apoptosis. A third family of cytotoxic agents inhibit the topoisomerase enzymes, which control DNA structure changes. Topoisomerase inhibitors block the cell cycle ligation step, which generates DNA single- and double-strand breaks, leading to apoptotic cell death [40]. Trastuzumab deruxtecan and sacituzumab govitecan are both approved topoisomerase inhibitor ADCs [40]. Currently, auristatins, maytansine derivatives and PBD/PNU (anthracyclines family) represent 29%, 25% and 2% of the global active ADCs, respectively (https://www.beacon-intelligence.com/, accessed on 8 December 2021). Overall, MMAE remains the most frequent payload used for ADC development, involved in 19% of active ADCs for which the payload is disclosed (https://www.beacon-intelligence.com/, accessed on 8 December 2021).

Beyond their direct cytotoxic tumor-targeted activity, highly membrane-permeable payloads, such as MMAE or calicheamicin, are able to induce a “bystander effect” [41] due to drug release from the primary target cells into the TME. The bystander effect enhances ADC efficacy by targeting not only stromal cells, which do not express the targeted antigen, but also antigen-negative tumor cells in cases of intratumoral heterogeneity [12] (Figure 2). By contrast, MMAF, another auristatin derivate, has low cell permeability due to its negative charge. While such properties limit the off-target toxicity of MMAF ADCs, their bystander activity remains low [12]. Regarding this limit, MMAF ADCs require high tumor expression of target antigen [42]. Nevertheless, a MMAF-conjugated ADC, belantamab mafodotin, was approved in 2020 by the FDA and the EMA for relapsed or refractory multiple myeloma treatment [43,44].

2.5. Linker

The linker is the ADC portion that connects antibody and drug. Depending on the payload and antibody properties, either cleavable or non-cleavable linkers are used. Cleavable linkers are used in combination with payloads being only fully active after lysosomal degradation (e.g., MMAE or calicheamicin) [38]. To prevent the cleavage of the linker in blood circulation resulting in unspecific cytotoxicity, the ADC linker has to be stable until the ADC reaches its target cell. To this end, cleavable linkers are usually sensitive to conditions specifically found in lysosomes (e.g., acidic condition or lysosomal proteases (cathepsin B, glycosidase, phosphatase)) or high intracellular glutathione concentrations [38] and thereby release the payload only after endocytosis is achieved, leading to death of the target cell [38] (Figure 2).

Regarding non-cleavable linkers, the drug is active after internalization and enzymatic digestion of the antibody into the lysosome, allowing the release of an active metabolite, amino acid–linker–drug complex (e.g., trastuzumab emtansine) [7]. Non-cleavable linkers allow increased ADC stability, leading to reduced toxicity in non-target tissues [7]. Payloads such as MMAF or DM1 are classically used in this setting.

2.6. Linker–Antibody Conjugation

The drug to antibody ratio (DAR), defined as the number of drug molecules attached to one mAb, is another important determinant for ADC performance [38]. The optimal DAR depends on the nature of the payload [45]. The paradigm that a DAR value of 4 is optimal for pharmacokinetics has been challenged by the recent approval of DAR 8 antibodies, in particular in light of improved hydrophobicity-masking technologies [46,47]. The technology connecting the mAb to the linker is crucial to obtain a homogeneous and controlled DAR (i.e., position of drugs and loading) [48]. Chemical linkers involving functional groups (i.e., bioconjugation head) are used to bind to mAb amino acids. First-generation bioconjugation technologies involved either N-hydroxysuccinimide (NHS) ester
bioconjugation heads binding to lysine residues, or hydrazones, maleimides and thi-others binding to cysteines [49]. However, those bioconjugation heads led to the generation of heterogeneous ADCs, presenting a high variability of the DAR in the range of 0–8, and to multiple different linker positions [38].

More recently, site-specific conjugation, i.e., engineered cysteine residues, unnatural amino acids, or enzymatic conjugation through glycosyltransferases have been applied to obtain more homogeneous ADCs [7]. Indeed, site-specific conjugation of antibodies has been shown to improve the therapeutic index because it improves ADC pharmacokinetics by reducing the hydrophobicity of the linker–payload as well as prevent the release of payload in blood [48]. Moreover, site-specific conjugation with rebridging of antibody disulfide bonds results in stable and homogeneous ADCs with a controlled number and position of payload, and higher stability characteristics [50].

Interestingly, Van Geel et al. has shown that it is possible to link a payload to the native N-glycan residing at asparagine 297 and demonstrated in vitro and in vivo efficacy [51].

To conclude, ongoing optimization of ADC technology is likely to expand their application in oncology in the upcoming years, as illustrated below with ADCs currently approved or investigated in the field of oncodermatology.

3. ADCs in Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) was the first skin cancer for which a therapeutic ADC was approved. CTCLs are a group of extra-nodal non-Hodgkin’s lymphomas with primary cutaneous infiltration of malignant monoclonal T lymphocytes. Mycosis fungoides (MF) is the most common form of CTCLs, characterized by slow progression from patches to infiltrating plaques and eventually to cutaneous and extracutaneous tumors. Among CTCLs, Sézary syndrome (SS) is characterized by erythroderma, lymphadenopathy and systemic dissemination of malignant Sézary T cells [52]. Although rare, SS displays an aggressive course, with a median survival of 1 to 5 years [53]. In the case of advanced MF and SS, the only potentially curative treatment is allogenic hematopoietic stem cell transplantation [54]. CD30, a proliferation-promoting member of the TNF receptor family [54], is expressed in 12 to 23% of SS and MF cases [55]. Since CD30 expression is restricted in healthy human tissues to activated T, B and NK cells, it was chosen as a potential ADC target for treating advanced CTCLs [10] (Figure 3A). Accordingly, brentuximab vedotin (adcetris®), consisting of an anti-CD30 MMAE-conjugated ADC, with a cathepsin B cleavable linker, was developed (Table 2). Clinical benefit of brentuximab vedotin was demonstrated in CTCLs (stage IV SS and MF) with clinical objective response rates (ORR) of 70% [56,57]. Moreover, brentuximab vedotin achieved more durable responses (56% ORR lasting 4 months) than conventional treatments with methotrexate or bexarotene (12% ORR lasting 4 months) (Table 3). Consequently, brentuximab vedotin was approved by the FDA and the EMA in 2017 to treat CD30+ CTCLs after at least one line of systemic therapy.

Table 2. Preclinical and clinical trials of ADCs in cutaneous lymphoma.

| Commercial Name | Target | Percentage of Positivity | Antibody | Antibody Isotype | Bioconjugation Head (Antibody Amino Acid) | Linker | Drug | Phase |
|-----------------|--------|--------------------------|----------|-----------------|------------------------------------------|--------|------|-------|
| Brentuximab vedotin | CD30 | 75% | Activated T, B and NK cells | Brentuximab | Chimeric IgG1 | Maleimidocaproyl (Cysteine) | Cleavable/proteolytic (cathepsin B) | MMAE | Approved |
### Table 3. Results of brentuximab vedotin clinical trials in cutaneous lymphoma.

| Study       | Phase | Patient Number | Response Rate | Survival                  |
|-------------|-------|----------------|---------------|----------------------------|
| Duvic et al. | II    | 48 (28 with MF, 9 with LyP, 2 with pcALCL) | ORR 73% ORR 54% in MF group ORR 100% in other subgroups CR 2/28, PR 13/28 in MF subgroup | PFS 1.1 years (95% CI 0.9–1.4) Median PFS not reached at 12 months |
| Kim et al.  | II    | 32 (MF and SS) | ORR in 21/30 (70%, 90% CI 53–83) CR in 1/30 PR in 20/30SD in 4/30 | Median EFS > 6 months 61% event free at 6 months 28% event free at 12 months |
| Prince et al. | III  | 123 (97 with MF, 31 with pcALCL) with 64 in BV group, 64 in PC group | ORR 56.3% (BV group) versus 12.5% (PC group), with \( p < 0.0001 \) ORR 67% in BV group CR 16% ORR 20% in PC group CR 2% | Median PFS 16.7 months (BV group) versus 3.5 months (PC group), with \( p < 0.0001 \) |

Objective response rate: ORR; mycosis fungoides: MF; Sézary syndrome: SS; complete response: CR; partial response: PR; lymphomatoid papulosis: LyP; primary cutaneous anaplastic large cell lymphoma: pcALCL; progression-free survival: PFS; brentuximab vedotin: BV; physician’s choice: PC; event-free survival: EVS.
Figure 3. ADC targets in oncodermatologic indications and implication of antigen expression in cancer aggressiveness. (A) Cutaneous T-cell lymphoma. (B) Melanoma. (C) Carcinoma: squamous cell carcinoma and Merkel cell carcinoma.

However, resistance to MMAE was observed upon brentuximab vedotin treatment [58]. To overcome this resistance mechanism, a DM1-conjugated anti-CD30 ADC is currently in development. The anti-CD30 antibody is conjugated to DM1, a tubulin inhibitor, through antibody lysines by NHS ester non-cleavable linker (Table 2). This ADC has shown similar antitumoral effects to brentuximab vedotin without acquisition of payload resistance mechanism; moreover, the payload-bioconjugation modifications may have safety advantages comparing to brentuximab vedotin, without retro-Michael instability of maleimide. This ADC is currently evaluated in an ongoing clinical trial of patients with recurrent or refractory CD30+ hematological malignancies (NCT03894150).

Another approach includes the combination of brentuximab vedotin with other therapeutics in order to improve efficacy and/or circumvent resistance. For instance, combination with the PD-1 blocking antibody nivolumab is currently being investigated in two phase I/II trials [59] (NCT02581631 and NCT01703949). Similarly, a phase I study is currently investigating the association between brentuximab vedotin and romidepsin, a histone deacetylase inhibitor which is FDA approved as a monotherapy for CTCL patients (NCT02616965).

Since patients treated with brentuximab vedotin do not achieve improvements in long-term outcomes, new CTCL targets were identified and new ADCs were developed. Inducible Co-Stimulator (ICOS) is a T-cell costimulatory receptor involved in the development of CTCLs. High ICOS expression in CTCLs suggested it as a suitable target to develop an anti-ICOS MMAE-conjugated ADC [60]. Interestingly, a comparison between brentuximab vedotin and an anti-ICOS MMAE-conjugated ADC in a preclinical model of a CTCL xenograft showed a longer overall survival of mice [60]. Recently, cell surface proteome analysis on CTCL cell lines identified cell surface heat shock protein 70 (scHSP70) as highly expressed compared with normal T cells [61]. Then, an anti-scHSP70 MMAE-conjugated ADC was developed, and in vitro comparison with brentuximab vedotin showed similar activity against MS and SS cell lines [61]. However, under hypoxic conditions, such as a tumor microenvironment, scHSP70 expression was higher and cells were obviously more sensitive to the ADC—this result suggests an advantage over brentuximab vedotin [61].
4. ADCs in Melanoma

While BRAF/MEK inhibitors or immune checkpoint inhibitors (ICI) have revolutionized the treatment of patients with metastatic melanoma, approximately 50% of patients still experience fatal outcomes. Although 70% of patients with metastatic melanoma respond upon treatment with a combination of BRAF and MEK inhibitors [62], acquired resistance is frequent, especially in those with high tumoral burden at baseline. Acquired resistance to MAPK pathway inhibition is frequently associated with reactivation of the MAPK pathway due to secondary genetic (NRAS mutation, BRAF amplification, and MEK mutations) or epigenetic changes (Akt amplification, loss of PTEN, amplification of HGF, RTK (receptor tyrosine kinase), PDGFRβ, and IGF 1R) [3]. Metastatic melanoma patients can be treated with ICI such as the anti-PD1 antibodies pembrolizumab or nivolumab as monotherapies [63] or nivolumab combined with ipilimumab, an antibody targeting CTLA-4 on T cells [63]. Overall, primary resistance occurs in 40 to 65% of metastatic melanoma cases either treated with targeted therapies, i.e., BRAF/MEK inhibitors or ICI [64], highlighting the need for new therapeutic options [65]. In this context, several ADC strategies targeting tumor cell membrane proteins, mostly tyrosine kinase receptors, or soluble proteins, have been developed in recent years (Table 4). ADCs developed against melanoma are presented in three parts depending on their target types (Figure 3B).

Table 4. Preclinical and clinical trials of ADCs in melanoma.

| Commercial Name | Target          | Percentage of Positivity | Expressions in Healthy Tissues | Antibody | Antibody Isotype | Bioconjugation | Linker          | Drug     | Phase  |
|-----------------|-----------------|-------------------------|-------------------------------|----------|------------------|----------------|-----------------|----------|--------|
| Glembatumumab vedotin gpNMB | 86% (n = 21) | Skin, bones             | Glembatumumab                 | Human IgG2 | Maleimidocaproyl (Cysteine) | Cleavable/proteolytic | MMAE              | Phase I/II |
| N/A PMEL17     | 64% (n = 58)  | Melanocytes             | 17A9 Mouse N/A N/A            | N/A       | Cleavable/proteolytic | MMAE          | Preclinical     |
| EV20/MMAF ADC  | HER3           | 65% (n = 130)           | EV20 Humanized Maleimidocaproyl (Cysteine) | Un cleavable | MMAF             | Preclinical |
| DEDN6526 A ETµR | Majority of tumors (% N/A) | Liver, cortex, medulla | MEDN6000A Humanized Maleimidocaproyl (Cysteine) | Cleavable/proteolytic | MMAE | Phase I |
| LOP628 c-KIT   | 66% to 88%     | Skin epithelial cells, breast, neurons | LMJ Humanized IgG1 Ester NHS (Lysine) | Un cleavable | DM1    | Phase I (stopped) |
| Enapotamab vedotin AXL | N/A | Muscle, testis | Enapotamab Human IgG1 Maleimidocaproyl (Cysteine) | Cleavable/proteolytic | MMAE | Phase I/II |

Unprovided data: N/A. gpNMB: glycoprotein-NMB; PMEL17: premelanosome protein 17; HER3: human epidermal growth factor receptor 3; ETµR: endothelin B receptor; c-KIT: tyrosine-protein kinase; AXL: Anexelekto.

4.1. Membrane Protein as Targets

Glycoprotein-NMB (gpNMB) is a transmembrane glycoprotein involved in tumor growth, tumor invasion and metastasis. Moreover, gpNMB exerts a direct inhibitory effect
on activated T cells, impairing antitumor immunity and allowing immune evasion [66]. Accordingly, high gpNMB tumor expression levels are associated with poor clinical outcome [66]. In melanoma, 87% of tumors demonstrate membrane expression of gpNMB [67,68]. By contrast, in normal cells, gpNMB is restricted to intracellular compartments, therefore suggesting gpNMB as a promising ADC target in melanoma [66]. Accordingly, glembatumumab vedotin, a gpNMB-targeted MMAE-conjugated ADC [69], resulted in a 39% ORR in a phase I/II study conducted among patients with advanced melanoma refractory to ICI and BRAF/MEK inhibition, with acceptable toxicity (NCT00412828) [70]. In line with the observation that gpNMB expression is induced by the inhibition of MAPK pathway [71], combination of glembatumumab vedotin with MAPK pathway inhibitors demonstrated a synergistic therapeutic effect in a melanoma mouse model [71].

High and homogeneous expression levels of HER3, a tyrosine kinase receptor, have been observed in 65% of cutaneous melanomas [72]. HER3 is a member of the HER/EGFR family, and heterodimerization of HER3 with other HER family members (e.g., EGFR or HER2) leads to the activation of the PI3K/AKT pathway [73]. Accordingly, HER3 expression promotes tumor growth, and its overexpression was associated with impaired survival in melanoma [8,73]. Moreover, BRAF/MEK inhibitors induce FOXD3 expression, a transcription factor triggering HER3 expression. Hence, upregulation of HER3 by FOXD3 can promote adaptive resistance to BRAF inhibitors [74]. As a consequence, co-targeting HER3 and BRAF/MEK appears as an interesting option to overcome therapeutic resistances in BRAF-mutated melanoma [74]. However, unconjugated anti-HER3 antibodies have only shown limited antitumor activity justifying the use of anti-HER3 ADCs [75]. Indeed, an anti-HER3 MMAE-conjugate exhibited complete and durable antitumor responses in xenograft mice models [76]. Another anti-HER3 topoisomerase I inhibitor-conjugated ADC [77] is evaluated as monotherapy in phase I/II clinical trials for melanoma (NCT02980341).

Finally, Chen and collaborators identified the melanosomal protein, PMEL17, as a highly expressed marker restricted to melanoma cells. Accordingly, they generated an anti-PMEL17 MMAE-conjugated ADC which was cytotoxic in vitro and in vivo in a preclinical model [78].

4.2. Tyrosine Kinase Receptor

Endothelin B receptor (ETαR) is a member of the G protein-coupled receptor superfamily mediating tissue differentiation, growth, and repair, through the MAPK pathway [79]. ETαR has been reported to be overexpressed in metastatic melanoma compared to normal melanocytes [80]. ETαR signaling has been implicated in malignant transformation of melanocytes, suggesting it as an oncogenic driver for melanoma development [81]. Importantly, ETαR blockade results in inhibition of melanoma growth in vitro and in vivo [81], rendering ETαR as a possible target for an ADC [82]. Accordingly, an anti-ETαR MMAE-conjugated ADC is currently evaluated in a phase I clinical trial in patients with metastatic or unresectable melanoma (n = 53) (NCT01522664) [83]. Upon treatment, 32% of patients had stable disease beyond 6 months, irrespective of BRAF status [83]. Interestingly, in a preclinical model, combination of a single dose of ADC and daily intake of MAPK pathway inhibitors increased expression of ETαR and enhanced the therapeutic response [84].

Anexelekto (AXL) is a tyrosine kinase receptor frequently expressed in melanoma [85]. Its tumoral expression has been associated with a more invasive phenotype [85]. Antitumor activity of an anti-AXL MMAE-conjugated ADC was observed in a preclinical model, and again combination with BRAF/MEK inhibitors improved antitumoral cytotoxicity [66]. Importantly, a BRAF/MEK inhibitor-resistant but high-AXL-expressing tumor sub-population was killed by the anti-AXL ADC, while BRAF/MEK inhibition was specifically cytotoxic for the low-AXL-expressing tumor cells [86]. Following this promising
preclinical study, a phase I/II clinical trial is ongoing to evaluate this ADC (called enapotamab vedotin) in solid tumors including melanoma (NCT02988817). Moreover, AXL could also be an interesting target for squamous cell carcinoma [87].

c-KIT is a tyrosine kinase receptor engaged by a ligand called stem cell factor. c-KIT is involved in regulation of apoptosis, differentiation and proliferation [88]. In cancer, c-KIT mutation or gene amplification results in uncontrolled proliferation and resistance to apoptosis [88]. High c-KIT expression is observed in 64 to 88% of melanomas [88]. So far, c-KIT-targeted tyrosine kinase inhibitors only showed limited clinical benefit in Kit-mutated metastatic melanoma, due to the emergence of secondary mutations [89]. Preclinical studies revealed a potent antitumor activity of an anti-c-KIT DM1-conjugated ADC on several c-KIT-positive solid cancers including melanoma and leukemia [90]. Nevertheless, in a phase I clinical trial (NCT02221505), acute hypersensitivity reactions triggered by degranulation of c-KIT-expressing mast cells led to the termination of the trial [90].

4.3. Soluble Target for ADCs

Non-internalizing ADCs are also investigated for melanoma treatment using an ADC targeting the galectin-3-binding protein (Gal-3BP), a metastasis-associated secreted protein [91] which is abundant in the TME [92]. Following treatment with anti-Gal-3BP ADC, complete tumor regression was achieved in a xenograft mouse melanoma model [91].

5. ADCs in Skin Carcinomas

ADC strategies have also been developed for treating skin carcinomas which are prone to display an aggressive course, mostly squamous cell carcinoma (SCC) and Merkel cell carcinoma (MCC).

5.1. Squamous Cell Carcinoma

SCC is a common skin cancer frequently induced by cumulative exposure to ultraviolet radiation [93]. SCC prognosis is mostly favorable after complete tumor resection while poor outcome is observed at the metastatic stage, with no demonstrated benefit of conventional chemotherapies or EGFR inhibitors on patient survival [93]. Recently, one PD-1 inhibitor, cemiplimab, was shown to provide a 47% ORR in patients with advanced or metastatic cutaneous SCCs, with durable responses in 61% of them [94,95]. PD-1 inhibitors are currently recommended as first-line treatment of advanced SCCs which are not candidates for surgery or radiation therapy [96].

Several targets have been identified as candidates for ADC therapy in lung or cervical SCCs [97] (Figure 3C). Most of the studies evaluated ADCs in head and neck SCCs. Overexpression of tissue factor (TF)—a transmembrane protein activating pro-survival pathways [98]—has been associated with high metastatic potential and poor outcome in various solid tumors [99]. High TF expression levels are also associated with increased expression of VEGF, enhancing tumor angiogenesis [98]. Tisotumab vedotin, a MMAE-conjugated anti-TF ADC with a protease-cleavable linker (Table 5A), demonstrated a 16% ORR (95% CI 10.2–22.5) in a phase I/II study with 147 patients with multiple solid tumors, including SCCs of the head and neck. The safety profile appeared manageable although 27% of patients had a treatment-emergent serious adverse event related to the drug, and one death from pneumonia possibly related to the treatment [100]. A phase II study is ongoing to determine the efficacy and safety of tisotumab vedotin after failure of first-line standard of care therapy, in solid tumors including head and neck SCCs (NCT03485209).
### Table 5. Preclinical and clinical trials of ADCs in carcinoma. A. Squamous cell carcinoma. B. Merkel cell carcinoma.

#### Squamous Cell Carcinoma

| Commercial Name       | Target                   | Percentage of Positivity | Expression in Healthy Tissues                | Antibody          | Antibody Isotype | Bioconjugation Head (Antibody Amino Acid) | Linker | Drug   | Phase          |
|-----------------------|--------------------------|--------------------------|---------------------------------------------|--------------------|------------------|-----------------------------------------|--------|--------|----------------|
| Tisotumab vedotin TF  | TF                       | 75% (n = 20)             | Brain, heart, intestine, kidney, lung, placenta, uterus | Tisotumab          | Human IgG1       | MaleimidocaproCleavable/proteolytic MMAE | Phase I/II |
|                       |                          |                          | Skin                                       |                    |                  |                                         |        |        |                 |
|                       |                          |                          | keratinocytes, cervix, cornea, tonsil       | Bivatuzumab        | Humanize d IgG1  | Disulfide linker Cleavable/hydrazone DM1 | Phase I | (stopped) |
|                       |                          |                          | Hair follicles, tonsil, stomach, spleen, osteoblasts | (or BIWA 4)        |                  |                                         |        |        |                 |
| Samrotamab vedotin (ABBV-085) | LRRC15                   | 64% (n = 115)            |                                              | Ab1                | Humanize d IgG1  | MaleimidocaproCleavable/protolytic MMAE | Phase I |

#### Merkel Cell Carcinoma

| Commercial Name       | Target                   | Percentage of Positivity | Expression in Healthy Tissues                | Antibody          | Antibody Isotype | Bioconjugation Head (Antibody Amino Acid) | Linker | Drug   | Phase          |
|-----------------------|--------------------------|--------------------------|---------------------------------------------|--------------------|------------------|-----------------------------------------|--------|--------|----------------|
| Lorvotuzumab mertansine (IMGN901) | CD56 | 88% (n = 64)            | NK cells, neuroendocrine cells, neurons     | Lorvotuzumab       | Humanize d IgG1  | Disulfide linker SPP (Lysine) Cleavable/hydrazone DM1 | Phase I |
|                       |                          |                          |                                             | (huN901)           |                  |                                         |        |        |                 |
|                       |                          |                          |                                             |                    |                  |                                         |        |        |                 |
| ADCitmer®             | CD56                     | 66% (n = 90)             | NK cells, neuroendocrine cells, neurons     | m906               | Human IgG1       | MaleimidocaproCleavable/protolytic MMAE | Phase Preclinical |

TF: tissue factor; LRRC15: leucine-rich repeat containing 15.

Leucine-rich repeat containing 15 (LRRC15) is a marker of cancer-associated fibroblasts [101]. TGF-β, an immunosuppressive cytokine frequently expressed by tumor cells, induces LRRC15 expression in activated fibroblasts in the TME [102,103]. Targeting cancer-associated fibroblasts through LRRC15 in order to reduce immunosuppressive properties of the TME could overcome therapeutic resistances [104]. In line with the frequent LRRC15 expression in SCC cancer-associated fibroblasts (81% of cases) [101], an anti-LRRC15 MMAE-conjugated ADC, ABBV-085, triggered complete response in SCC xenograft (PDX) models [101]. Moreover, combination of this drug with an anti-PD1 antibody (mouse IgG2a, 17D2 clone) has shown potent activity in tumor models [101]. This ADC is currently being investigated in a phase I clinical trial including head and neck SCCs (NCT02001623) (Table 5A). Of note, LRRC15 is also expressed by melanoma tumor cells, which could constitute an additional application field for this ADC [101].

The major issue of ADCs targeting a molecule expressed by healthy tissues is illustrated by the outcome of the program development of bivatuzumab mertansine (Table 5A). This anti-CD44v6 DM1-conjugated ADC, CD44v6 being an aggressive variant of...
CD44, was assessed in four clinical trials including one enrolling head and neck SCC patients. After occurrence of a case of fatal toxic epidermal necrolysis together with other skin-related adverse events, clinical development of the ADC was discontinued [105]. This severe adverse event probably occurred due to CD44v6 expression by both SCC and normal squamous epithelium [105].

5.2. Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is an aggressive skin cancer induced either by UV light or the Merkel cell polyomavirus [106,107]. Until 2017, only cytotoxic chemotherapies, mostly platin salts and etoposide, were available for patients with advanced disease. In recent years, avelumab, an anti PD-L1 antibody, was shown to provide a 33% ORR in patients with metastatic disease, after failure of a first-line chemotherapy—most of these responses being durable. Avelumab was approved by the FDA and the EMA for treating patients with advanced metastatic MCCs [108]. Pembrolizumab was assessed in the first-line setting and was approved by the FDA in 2018 for treating advanced MCCs [109,110]. Although responses to ICI may be long-lasting, more than 50% of patients do not respond or develop secondary resistance [108].

CD56 has recently been suggested as a suitable target for antibody-dependent cellular cytotoxicity in MCCs, as it is expressed on the tumor cell surface by the majority of MCCs [111] (Figure 3C). Accordingly, an anti-CD56 DM1-conjugated ADC, lorvotuzumab mertansine (LM, also known as IMGN901), has been developed by covalently coupling the DM1 to the humanized anti-CD56 mAb, lorvotuzumab (huN901) (Table 5B). In a phase I clinical trial, this ADC demonstrated acceptable safety and tolerability in different CD56-expressing tumors [112,113]. Moreover, signs of clinical activity were especially detected in the four MCC-tested patients with two objective responses [112]. The following phase I/II clinical trial investigated the combination of carboplatine/etoposide/LM versus carboplatine/etoposide alone in patients with small-cell lung cancer [114]. This trial was first modified by a reduction in the dose of carboplatine/etoposide and finally discontinued because of safety concerns (NCT01237678) [114].

Recently, a new CD56-targeting MMAE-conjugated ADC, Adcitmer®, using a new bioconjugation approach has shown the control of MCC tumor growth in a mouse preclinical model [115].

Delta-like protein 3 (DLL3) is an inhibitory ligand of NOTCH receptors and is involved in neurogenesis during early embryonic development. DLL3 is upregulated in neuroendocrine tumor and has a minimal expression in normal tissues [116]. DLL3 expression was found in 91% of MCC patients [117] and high expression of DLL3 was associated with virus-positive MCCs [118]. Rovalpituzumab tesirine, an anti-DLL3 PBD-conjugated ADC [118], showed modest antitumor activity in patients with small-cell lung carcinoma treated in third lines [119] (NCT02674568), but such anti-DLL3 ADCs could represent a potential strategy for treating viro-positive MCCs.

6. Strengths and Weaknesses of ADCs: Challenges and Perspectives

When compared to other cancer therapies, notably conventional cytotoxic treatment, the use of ADCs is a vectorized therapy with low off-target toxicity. Nevertheless, ADCs could also have some drawbacks, due to recognition of the target on non-tumor cells, leading to “on-target off-tumor cytotoxicity”, limiting the therapeutic window in which ADCs can be applied [14]. Moreover, unspecific linker cleavage can cause drug delivery without antibody recognition, resulting in systemic toxicity, which represents another important limitation of ADCs [120]. Improvements in the production process as well as modifications in ADC structures may counteract these constraints [14]. In order to obtain stable ADCs, engineering of the bioconjugation head might contribute to linker stability improvement [9]. As an example, maleimide residue either included in the linker or the bioconjugation head might react with free thiol of plasma, e.g., albumin, resulting in the so-called “retro-Michael reaction”. Hence, this retro-Michael reaction induces an unspecific
release of the linker and drug in the plasma, which not only impacts the efficacy of the ADCs but also leads to off-target toxicity [120].

Several resistance mechanisms to ADCs have been described such as target antigen downregulation or mutations, and impairment of lysosomal degradation pathways. Moreover, ADC payloads can be rejected from tumor cells though multidrug resistance transporter efflux [121]. For instance, loss of CD30 expression can be observed in cutaneous CD30-positive lymphoid neoplasm treated with brentuximab vedotin [58,122]. Trogocytosis, i.e., the extraction of the antibody–epitope complexes by monocytes may induce resistance to the ADC in CD30-positive lymphoma [122].

A wide number of ADC optimizations have been developed to improve ADC performance. A new class of therapy aiming to improve the tumor specificity of mAbs, named probodies, consists in the optimization of mAbs used for ADC technology [123]. These antibodies are modified in order to mask the Fab paratopes, thereby limiting their activity in healthy tissue. By contrast, in the TME, high protease activity removes the masking peptide, allowing paratope–epitope recognition. Enhancement of the therapeutic index by such probody-based therapy was demonstrated in an EGFR-overexpressing mouse model [125]. The use of probodies in ADCs to enhance tumor cell-specific delivery of drugs has recently been tested [124]. In this respect, an anti-CD166 probody–drug conjugate has shown on-target on-tumor specificity in a preclinical study on lung cancer [125].

ADC antitumor effect could be optimized by the use of innovative payloads or a new bioconjugation strategy. As an example, trastuzumab emtansine is indicated as second-line treatment for HER2-positive metastatic breast cancer. Interestingly, a second anti-HER2 ADC, trastuzumab deruxtecan [126], with eight topoisomerase inhibitors conjugated to trastuzumab through a cleavable linker was recently approved by the FDA and the EMA—which this ADC has shown higher efficacy than trastuzumab emtansine, demonstrating the involvement of a payload and bioconjugation strategy in ADC performance [126].

Among the challenges, ADC toxicity (i.e., thrombocytopenia, neutropenia or peripheral neuropathy) should be known and controlled, for example by dose modulation [127]. Moreover, unexpected combinatorial effects, in particular atypical ocular toxicities of bleomycin and brentuximab vedotin observed for Hodgkin’s lymphoma, should be considered for future combination strategies [127].

7. Conclusions

Several targets in skin cancers are currently being investigated as candidates for ADC therapy, which allows the targeted delivery of a drug. ADC is a growing class of therapeutics in oncology, including one ADC approved for cutaneous T-cell lymphoma. In preclinical and clinical trials, further ADCs are currently evaluated for the treatment of CTCLs, melanoma, SCCs or MCCs. Various combinations of ADCs with other therapeutics are investigated to overcome limitations of these drugs due to intrinsic or acquired resistance. Increased knowledge on critical ADC features, such as target, antibody, linker and drug choice, allows a steady improvement in ADC design and better management of side effects.

Author Contributions: Conceptualization, C.E., T.K. and M.S.; methodology, C.E, T.K. and M.S.; validation, C.E., A.D., C.M., T.K. and M.S.; writing—original draft preparation, C.E., T.K. and M.S.; writing—review and editing, C.E., D.S., R.H., S.G., A.D., C.M., P.B., M.-C.V.-M., A.T., T.K. and M.S.; supervision, T.K. and M.S. All authors have read and agreed to the published version of the manuscript.

Funding: This work did not receive any funding.

Conflicts of Interest: A.D., C.M. and M.C.V.M. are employees of McSAF, who is the owner of the patent Adcitmer®. A.T., T.K. and M.S. filed this patent. T.K. is A.D.’s husband. The other authors declare no conflict of interest.
Abbreviations:
- ADC: antibody–drug conjugate
- CTCL: cutaneous T-cell lymphoma
- DAR: drug to antibody ratio
- EtsR: endothelin B receptor
- FcRn: neonatal Fc receptor
- FDA: food and drug administration
- Gal-3BP: galectin-3-binding protein
- gpNMB: glycoprotein-NMB
- ICI: immune checkpoint inhibitors
- LRRC15: leucine-rich repeat containing 15 mAb: monoclonal antibody
- MCC: Merkel cell carcinoma
- MF: mycosis fungoides
- MMAE: monomethyl auristatin E
- MMAF: monomethyl auristatin F
- PBD: pyrrolobenzodiazepines
- PDX: patient-derived xenograft
- RTK: receptor tyrosine kinase
- SCC: squamous cell carcinoma
- SS: Sézary syndrome
- TF: tissue factor
- TME: tumor microenvironment

References

1. Schwartz, R.S. Paul Ehrlich’s Magic Bullets. N. Engl. J. Med. 2004, 350, 1079–1080, https://doi.org/10.1056/NEJMcp048021.
2. Strebhardt, K.; Ullrich, A. Paul Ehrlich’s Magic Bullet Concept: 100 Years of Progress. Nat. Rev. Cancer 2008, 8, 473–480, https://doi.org/10.1038/nrc2394.
3. Kakadia, S.; Yarlagadda, N.; Awad, R.; Kundranda, M.; Niu, J.; Naraev, B.; Mina, L.; Dragovich, T.; Gimbel, M.; Mahmoud, F. Mechanisms of Resistance to BRAF and MEK Inhibitors and Clinical Update of US Food and Drug Administration-Approved Targeted Therapy in Advanced Melanoma. OncoTargets Ther. 2018, 11, 7095–7107, https://doi.org/10.2147/OTT.S182721.
4. Chau, C.H.; Steeg, P.S.; Figg, W.D. Antibody-Drug Conjugates for Cancer. Lancet 2019, 394, 793–804, https://doi.org/10.1016/S0140-6736(19)31774-X.
5. Tong, J.T.W.; Harris, P.W.R.; Brimble, M.A.; Kavianinia, I. An Insight into FDA Approved Antibody-Drug Conjugates for Cancer Therapy. Molecules 2021, 26, 5847, https://doi.org/10.3390/molecules26195847.
6. Joubert, N.; Beck, A.; Dumontet, C.; Deneuville-Sabourin, C. Antibody–Drug Conjugates: The Last Decade. Pharmaceuticals 2020, 13, 245, https://doi.org/10.3390/molecules26195847.
7. Beck, A.; Goetsch, L.; Dumontet, C.; Corváia, N. Strategies and Challenges for the next Generation of Antibody-Drug Conjugates. Nat. Rev. Drug Discov. 2017, 16, 315–337, https://doi.org/10.1038/nrd.2016.268.
8. Boni, V.; Sharma, M.R.; Patnaik, A. The Resurgence of Antibody Drug Conjugates in Cancer Therapeutics: Novel Targets and Payloads. Am. Soc. Clin. Oncol. Educ. Book Am. Soc. Clin. Oncol. Annu. Meet. 2020, 40, e58–e74, https://doi.org/10.1200/EDBK_281107.
9. Amani, N.; Dorkoosh, F.A.; Mobedi, H. ADCs, as Novel Revolutionary Weapons for Providing a Step Forward in Targeted Therapy of Malignancies. Curr. Drug Deliv. 2020, 17, 23–51, https://doi.org/10.2174/15670261206661911221145109.
10. Teicher, B.A. Antibody-Drug Conjugate Targets. Curr. Cancer Drug Targets 2009, 9, 982–1004, https://doi.org/10.2174/15680090979012365.
11. Lai, J.; Wang, Y.; Wu, S.-S.; Ding, D.; Sun, Z.-Y.; Zhang, Y.; Zhou, J.; Zhou, Z.; Xu, Y.-C.; Pan, L.-Q.; et al. Elimination of Malignoma by Sortase A-Generated TCR-like Antibody-Drug Conjugates (TL-ADCs) Targeting Intracellular Malignoma Antigen MART-1. Biomaterials 2018, 178, 158–169, https://doi.org/10.1016/j.biomaterials.2018.06.017.
12. Staudacher, A.H.; Brown, M.P. Antibody Drug Conjugates and Bystander Killing: Is Antigen-Dependent Internalisation Required? Br. J. Cancer 2017, 117, 1736–1742, https://doi.org/10.1038/bjc.2017.367.
13. Damelin, M.; Zhong, W.; Myers, J.; Sapra, P. Evolving Strategies for Target Selection for Antibody-Drug Conjugates. Pharm. Res. 2015, 32, 3494–3507, https://doi.org/10.1007/s11195-015-1624-3.
14. Hoffmann, R.M.; Combe, B.G.T.; Josephs, D.H.; Mele, S.; Ilieva, K.M.; Cheung, A.; Tutt, A.N.; Spicer, J.F.; Thurston, D.E.; Crescioli, S.; et al. Antibody Structure and Engineering Considerations for the Design and Function of Antibody Drug Conjugates (ADCs). Oncoimmunology 2018, 7, e1395172, https://doi.org/10.1080/2162402X.2017.1395172.
15. Vakilas, C.; Forero-Torres, A. Safety and Efficacy of Brentuximab Vedotin in Patients with Hodgkin Lymphoma or Systemic Anaplastic Large Cell Lymphoma. Ther. Adv. Hematol. 2012, 3, 209–225, https://doi.org/10.1177/2040620712443076.
16. Sehn, L.H.; Herrera, A.F.; Flowers, C.R.; Kamdar, M.K.; McMillan, A.; Hertzberg, M.; Assouline, S.; Kim, T.M.; Kim, W.S.; Ozcan, M.; et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2020, 38, 155–165, https://doi.org/10.1200/JCO.19.00172.

17. Fayad, L.; Offner, F.; Smith, M.R.; Verhoeef, G.; Johnson, P.; Kaufman, J.L.; Rohatiner, A.; Advani, A.; Foran, J.; Hess, G.; et al. Safety and Clinical Activity of a Combination Therapy Comprising Two Antibody-Based Targeting Agents for the Treatment of Non-Hodgkin Lymphoma: Results of a Phase I/II Study Evaluating the Immunoconjugate Inotuzumab Ozogamicin With Rituximab. J. Clin. Oncol. 2013, 31, 573–583, https://doi.org/10.1200/JCO.2012.42.7211.

18. Sievers, E.L.; Senter, P.D. Antibody-Drug Conjugates in Cancer Therapy. Annu. Rev. Med. 2013, 64, 15–29, https://doi.org/10.1146/annurev-med-050311-201823.

19. Thomas, A.; Teicher, B.A.; Hassan, R. Antibody–Drug Conjugates for Cancer Therapy. Lancet Oncol. 2016, 17, e254–e262, https://doi.org/10.1016/S1470-2045(16)30030-4.

20. Perrino, E.; Steiner, M.; Krall, N.; Bernardes, G.J.L.; Pgetto, F.; Casi, G.; Neri, D. Curative Properties of Noninternalizing Antibody–Drug Conjugates Based on Maytansinoids. Cancer Res. 2014, 74, 2569–2578, https://doi.org/10.1158/0008-5472.CAN-13-2990.

21. Gébéux, R.; Stringhini, M.; Casanova, R.; Soltermann, A.; Neri, D. Non-Internalizing Antibody–Drug Conjugates Display Potent Anti-Cancer Activity upon Proteolytic Release of Monomethyl Auristatin E in the Subendothelial Extracellular Matrix. Int. J. Cancer 2017, 140, 1670–1679, https://doi.org/10.1002/ijc.30569.

22. O’Malley, D.M.; Matulonis, U.A.; Birrer, M.J.; Castro, C.M.; Gilbert, L.; Vergote, I.; Martin, L.P.; Manta-Maldone, G.M.; Martin, A.G.; Bratos, R.; et al. Phase Ib Study of Mirvetuxumab Soravtansine, a Folate Receptor Alpha (FRa)-Targeting Antibody-Drug Conjugate (ADC), in Combination with Bevacizumab in Patients with Platinum-Resistant Ovarian Cancer. Gynecol. Oncol. 2020, 157, 379–385, https://doi.org/10.1016/j.ygyno.2020.01.037.

23. Castaneda, D.C.; Brachet, G.; Goupille, C.; Ouldamer, L.; Gouilleux-Gruart, V. The Neonatal Fc Receptor in Cancer. Cancer Med. 2020, 9, 4736–4742, https://doi.org/10.1002/cam4.3067.

24. Chen, N.; Wang, W.; Fauty, S.; Fang, Y.; Hamuro, L.; Hussain, A.; Prueksaritanont, T. The Effect of the Neonatal Fc Receptor on Human IgG Biodistribution in Mice. mAbs 2014, 6, 502–508, https://doi.org/10.4161/mabs.27765.

25. Nimmerjahn, F.; Ravetch, J.V. Fcgamma Receptors as Regulators of Immune Responses. Nat. Rev. Immune. 2008, 8, 34–47, https://doi.org/10.1038/nri2206.

26. Aguier, S.; Dias, J.; Manuel, A.M.; Russo, R.; Gois, P.M.P.; da Silva, F.A.; Goncalves, J. Chimeric Small Antibody Fragments as Strategy to Deliver Therapeutic Payloads. Adv. Protein Chem. Struct. Biol. 2018, 112, 143–182, https://doi.org/10.1016/bs.apsesb.2018.03.002.

27. Carter, P.J. Potent Antibody Therapeutics by Design. Nat. Rev. Immune. 2006, 6, 343–357, https://doi.org/10.1038/nri1837.

28. Gauzy-Lazo, L.; Sassoon, I.; Brun, M.-P. Advances in Antibody-Drug Conjugate Design: Current Clinical Landscape and Future Innovations. SLAS Discov. Adv. Sci. Drug Discov. 2020, 25, 843–868, https://doi.org/10.1177/247275520912955.

29. Lucas, A.T.; Robinson, R.; Schorzan, A.N.; Piscitelli, J.A.; Razo, J.F.; Zamboni, W.C. Pharmacologic Considerations in the Disposition of Antibodies and Antibody-Drug Conjugates in Preclinical Models and in Patients. Antibodies Basel Switz. 2019, 8, 3, https://doi.org/10.3390/antib8010003.

30. Hamblet, K.J.; Senter, P.D.; Chace, D.F.; Sun, M.M.C.; Lenox, J.; Cerveny, C.G.; Kissler, K.M.; Bernhardt, S.X.; Kopcha, A.K.; Zabinski, R.F.; et al. Effects of Drug Loading on the Antitumor Activity of a Monoclonal Antibody Drug Conjugate. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2004, 10, 7063–7070, https://doi.org/10.1158/1078-0432.CCR-04-0789.

31. Buecheler, J.W.; Winzer, M.; Weber, C.; Gieseler, H. Alteration of Physicochemical Properties for Antibody-Drug Conjugates and Their Impact on Stability. J. Pharm. Sci. 2019, 109, 161–168, https://doi.org/10.1016/j.xphs.2019.08.006.

32. Buettner, M.J.; Shah, S.R.; Saeui, C.T.; Ariss, R.; Yarema, K.J. Improving Immunotherapy Through Glycodelign. Front. Immunol. 2018, 9, 2485, https://doi.org/10.3389/fimmu.2018.02485.

33. Schrama, D.; Reisfeld, R.A.; Becker, J.C. Antibody Targeted Drugs as Cancer Therapeutics. Nat. Rev. Drug Discov. 2006, 5, 147–159, https://doi.org/10.1038/nrd1957.

34. King, D.M.; Albertini, M.R.; Schalch, H.; Hank, J.A.; Gan, J.; Sufius, J.; Mahvi, D.; Schiller, J.H.; Warner, T.; Kim, K.; et al. Phase I Clinical Trial of the Immunocytokine EMD 273063 in Melanoma Patients. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2004, 22, 4463–4473, https://doi.org/10.1200/JCO.2004.11.035.

35. Teicher, B.A.; Chari, R.V.J. Antibody Conjugate Therapeutics: Challenges and Potential. Clin. Cancer Res. 2011, 17, 6389–6397, https://doi.org/10.1158/1078-0432.CCR-11-1417.

36. Wu, A.M.; Senter, P.D. Arming Antibodies: Prospects and Challenges for Immunomonomer. Nat. Biotechnol. 2005, 23, 1137–1146, https://doi.org/10.1038/nbt1141.

37. Milenic, D.E.; Brady, E.D.; Brechbiel, M.W. Antibody-Targeted Radiation Cancer Therapy. Nat. Rev. Drug Discov. 2004, 3, 488–499, https://doi.org/10.1038/nrd1413.

38. Leung, D.; Wurst, J.M.; Liu, T.; Martinez, R.M.; Datta-Mannan, A.; Feng, Y. Antibody Conjugates-Recent Advances and Future Innovations. Antibodies 2020, 9, 2, https://doi.org/10.3390/antib9010002.

39. Yaghoubi, S.; Karimi, M.H.; Lotfinia, M.; Gharibi, T.; Mahi-Birjand, M.; Kavi, E.; Hosseini, F.; Sepher, K.S.; Khatami, M.; Bagheri, N.; et al. Potential Drugs Used in the Antibody–Drug Conjugate (ADC) Architecture for Cancer Therapy. J. Cell. Physiol. 2020, 235, 31–64, https://doi.org/10.1002/jcp.28967.

40. Thomas, A.; Pommier, Y. Targeting Topoisomerase I in the Era of Precision Medicine. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2019, 25, 6581–6589, https://doi.org/10.1158/1078-0432.CCR-19-1089.
41. Abdollahpour-Alitappeh, M.; Lotfia, M.; Gharibi, T.; Mardaneh, J.; Farhadihosseinabadi, B.; Larki, P.; Fahghfournia, B.; Sepehr, K.S.; Abbaszadeh-Goudarzi, K.; Abbaszadeh-Goudarzi, G.; et al. Antibody–Drug Conjugates (ADCs) for Cancer Therapy: Strategies, Challenges, and Successes. J. Cell. Physiol. 2019, 234, 5628–5642, https://doi.org/10.1002/jcp.27419.

42. Smith, L.M.; Nesterova, A.; Alley, S.C.; Torgov, M.Y.; Carter, P.J. Potent Cytotoxicity of an Auristatin-Containing Antibody-Drug Conjugate Targeting Melanoma Cells Expressing Melanotransferrin/P97. Mol. Cancer Ther. 2006, 5, 1474–1482, https://doi.org/10.1158/1535-7163.MCT-06-0026.

43. Tai, Y.-T.; Mayes, P.A.; Acharya, C.; Zhong, M.Y.; Cea, M.; Cagnetta, A.; Craigen, J.; Yates, J.; Gliddon, L.; Fiesle, W.; et al. Novel Anti-B-Cell Maturation Antigen Antibody-Drug Conjugate (GSK2857916) Selectively Induces Killing of Multiple Myeloma. Blood 2014, 123, 3128–3138, https://doi.org/10.1182/blood-2013-10-535088.

44. Lonial, S.; Lee, H.C.; Badros, A.; Trudel, S.; Nooka, A.K.; Char, A.; Abdallah, A.-O.; Callender, N.; Sborov, D.; Suvannasanka, A.; et al. Longer Term Outcomes with Single-Agent Belantamab Mafodotin in Patients with Relapsed or Refractory Multiple Myeloma: 13-Month Follow-up from the Pivotal DREAMM-2 Study. Cancer 2021, 127, 4198–4212, https://doi.org/10.1002/cncr.33809.

45. Walsh, S.J.; Bargh, J.D.; Dannheim, F.M.; Hanby, A.R.; Seki, H.; Counsell, A.J.; Ou, X.; Fowler, E.; Ashman, N.; Takada, Y.; et al. Site-Selective Modification Strategies in Antibody–Drug Conjugates. Chem. Soc. Rev. 2021, 50, 1305–1353, https://doi.org/10.1039/D0CS0310G.

46. Burke, P.J.; Hamilton, J.Z.; Jeffrey, S.C.; Hunter, J.H.; Doronina, S.O.; Okeley, N.M.; Miyamoto, J.B.; Anderson, M.E.; Stone, I.J.; Ulrich, M.L.; et al. Optimization of a PEGylated Glucuronide-Monomethylauristatin E Linker for Antibody-Drug Conjugates. Mol. Cancer Ther. 2017, 16, 116–123, https://doi.org/10.1158/1535-7163.MCT-16-0343.

47. Viricel, W.; Fournet, G.; Beaulm, S.; Perrial, E.; Papot, S.; Dumontet, C.; Joseph, B. Monodisperse Polysaccharide-Based Highly-Loaded Antibody-Drug Conjugates. Chem. Sci. 2019, 10, 4048–4053, https://doi.org/10.1039/C9SC0285E.

48. Junutula, J.R.; Raab, H.; Clark, S.; Bhakta, S.; Leipold, D.D.; Weir, S.; Chen, Y.; Simpson, M.; Tsai, S.P.; Dennis, M.S.; et al. Site-Specific Conjugation of a Cytotoxic Drug to an Antibody Improves the Therapeutic Index. Nat. Biotechnol. 2008, 26, 925–932, https://doi.org/10.1038/nb7140.

49. Bargh, J.D.; Isidro-Llobet, A.; Parker, J.S.; Spring, D.R. Cleavable Linkers in Antibody–Drug Conjugates. Chem. Soc. Rev. 2019, 48, 4361–4374, https://doi.org/10.1039/C9CS00676H.

50. Juen, L.; Baltus, C.B.; Géli, C.; Feuillâtre, O.; Desgranges, A.; Viaud-Massuard, M.-C.; Martin, C. Innovative Bioconjugation Technology for Antibody-Drug Conjugates: Proof of Concept in a CD30-Positive Lymphoma Mouse Model. Bioconjugate Chem. 2021, 32, 595–606, https://doi.org/10.1021/acs.bioconjchem.1c00058.

51. Van Geel, R.; Wijdeven, M.A.; Heesbeen, R.; Verkade, J.M.M.; Wasiel, A.A.; van Berkel, S.S.; van Delft, F.L. Chemoenzymatic Conjugation of Toxic Payloads to the Globally Conserved N-Glycan of Native MAbs Provides Homogeneous and Highly Efficient Antibody–Drug Conjugates. Bioconj. Chem. 2015, 26, 2233–2242, https://doi.org/10.1021/bc500224v.

52. Willemze, R.; Cerroni, L.; Kempf, W.; Berti, E.; Fachetti, F.; Swerdlo, S.H.; Jaffe, E.S. The 2018 Update of the WHO-EORTC Classification for Primary Cutaneous Lymphomas. Blood 2019, 133, 1703–1714, https://doi.org/10.1182/blood-2018-11-881268.

53. Scarsbrick, J.J.; Prince, H.M.; Vermeer, M.H.; Quaglinio, P.; Horwitz, S.; Forcu, P.; Stadler, R.; Wood, G.S.; Beylot-Barry, M.; Pham-Ledard, A.; et al. Cutaneous Lymphoma International Consortium Study of Outcome in Advanced Stages of Mycosis Fungoides and Sézary Syndrome: Effect of Specific Prognostic Markers on Survival and Development of a Prognostic Model. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2015, 33, 3766–3773, https://doi.org/10.1200/JCO.2015.61.7142.

54. Welborn, M.; Duvic, M. Antibody-Based Therapies for Cutaneous T-Cell Lymphoma. Am. J. Clin. Dermatol. 2019, 20, 115–122, https://doi.org/10.1007/s40257-018-0402-5.

55. Pierce, J.M.R.; Mehta, A. Diagnostic, Prognostic and Therapeutic Role of CD30 in Lymphoma. Expert Rev. Hematol. 2017, 10, 29–37, https://doi.org/10.1080/17474086.2017.1270202.

56. Mehrara, T.; Ikenberg, K.; Moos, R.M.; Benz, R.; Nair, G.; Schanz, U.; Haralambieva, E.; Hoezsteenecker, W.; Dummer, R.; French, L.E.; et al. Brentuximab as a Treatment for CD30+ Mycosis Fungoides and Sézary Syndrome. JAMA Dermatol. 2015, 151, 73–77, https://doi.org/10.1001/jamadermatol.2014.1629.

57. Kim, Y.H.; Tavallae, M.; Sundram, U.; Salva, K.A.; Wood, G.S.; Li, S.; Rozati, S.; Nagpal, S.; Krathen, M.; Reddy, S.; et al. Phase II Investigator-Initiated Study of Brentuximab Vedotin in Mycosis Fungoides and Sézary Syndrome with Variable CD30 Expression Level: A Multi-Institution Collaborative Project. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2015, 33, 3750–3758, https://doi.org/10.1200/JCO.2014.60.3969.

58. Chen, R.; Hou, J.; Newman, E.; Kim, Y.; Donohue, C.; Liu, X.; Thomas, S.H.; Forman, S.J.; Kane, S.E. CD30 Downregulation, MAAE Resistance, and MDR1 Upregulation Are All Associated with Resistance to Brentuximab Vedotin. Mol. Cancer Ther. 2015, 14, 1376–1384, https://doi.org/10.1158/1535-7163.MCT-15-0036.

59. Merli, M.; Ferrario, A.; Maffioli, M.; Olivares, C.; Stasia, A.; Arcaini, L.; Passamonti, F. New Uses for Brentuximab Vedotin and Novel Antibody Drug Conjugates in Lymphoma. Expert Rev. Hematol. 2016, 9, 767–780, https://doi.org/10.1080/17474086.2016.1205949.

60. Amatore, F.; Ortonne, N.; Lopez, M.; Barré, M.; Orlanducci, F.; Castellano, R.; Ingen-Housz-Oro, S.; De Croos, A.; Gorvel, L.; Goubard, A.; et al. ICOS Is Widely Expressed in Cutaneous T-Cell Lymphoma and Its Targeting Promotes Potent Killing of Malignant Cells. Blood 2021, 138, 790, https://doi.org/10.1182/blood-2021-150677.
61. Choudhary, R.K.; Jones, R.J.; Kuiatse, I.; Wang, H.; Vega, F.; Bouska, A.C.; Lone, W.G.; Iqbal, J.; Orlowski, R.Z. A Novel Antibody Drug Conjugate (ADC) Targeting Cell Surface Heat Shock Protein 70 (CshSP70) Is Active Against Pre-Clinical Models of Peripheral T-Cell Lymphoma (PTCL). *Blood* **2021**, *138*, 870–870, https://doi.org/10.1182/blood-2021-150842.

62. Seth, R.; Messersmith, H.; Kaur, V.; Kirkwood, J.M.; Kuchadkar, R.; McQuade, J.L.; Provenzano, A.; Swami, U.; Weber, J.; Alluri, K.C.; et al. Systemic Therapy for Melanoma: ASCO Guideline. *J. Clin. Oncol.* **2020**, *38*, 3947–3970, https://doi.org/10.1200/JCO.20.0198.

63. Albittar, A.A.; Alhalabi, O.; Oliva, I.C.G. Immunotherapy for Melanoma. *Adv. Exp. Med. Biol.* **2020**, *1244*, 51–68, https://doi.org/10.1007/978-3-030-41008-7_3.

64. Gide, T.N.; Wilmott, J.S.; Scolyer, R.A.; Long, G.V. Primary and Acquired Resistance to Immune Checkpoint Inhibitors in Metastatic Melanoma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2018**, *24*, 1260–1270, https://doi.org/10.1158/1078-0432.CCR-17-2267.

65. Kuske, M.; Westphal, D.; Wöhner, R.; Schmitz, M.; Beissert, S.; Praetorius, C.; Meier, F. Immunomodulatory Effects of BRAF MEK Inhibitors: Implications for Melanoma Therapy. *Pharmacol. Res.* **2018**, *136*, 151–159, https://doi.org/10.1016/j.phrs.2018.08.019.

66. Rose, A.A.N.; Biondini, M.; Curiel, R.; Siegel, P.M. Targeting GPNMB with Glembatumumab Vedotin: Current Developments and Future Opportunities for the Treatment of Cancer. *Pharmacol. Ther.* **2017**, *179*, 127–141, https://doi.org/10.1016/j.pharmthera.2017.05.010.

67. Williams, M.D.; Esmaeili, B.; Soheili, A.; Simantov, R.; Gombos, D.S.; Bedikian, A.Y.; Hwu, P. GPNMB Expression in Uveal Melanoma: A Potential for Targeted Therapy. *Melanoma Res.* **2010**, *20*, 184–190, https://doi.org/10.1097/CMR.0b013e3283364a08.

68. Taya, M.; Hammers, S.R. Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB) and Cancer: A Novel Potential Therapeutic Target. *Stereoids* **2018**, *133*, 102–107, https://doi.org/10.1016/j.steroids.2017.10.013.

69. Tse, K.F.; Jeffers, M.; Pollack, V.A.; McCabe, D.A.; Shadish, M.L.; Khramtsov, N.V.; Hackett, C.S.; Shenoy, S.G.; Kuang, B.; Boldog, F.L.; et al. CR011, a Fully Human Monoclonal Antibody-Auristatin E Conjugate, for the Treatment of Melanoma. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2006**, *12*, 1373–1382, https://doi.org/10.1158/1078-0432.CCR-05-2018.

70. Ott, P.A.; Hamid, O.; Pavlick, A.C.; Kluger, H.; Kim, K.B.; Boasberg, P.D.; Simantov, R.; Crowley, E.; Green, J.A.; Hawthorne, T.; et al. Phase II/II Study of the Antibody-Drug Conjugate Glembatumumab Vedotin in Patients with Advanced Melanoma. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2014**, *32*, 3659–3666, https://doi.org/10.1200/JCO.2013.54.8115.

71. Rose, A.A.N.; Annis, M.G.; Frederick, D.T.; Biondini, M.; Dong, Z.; Kwong, L.; Chin, L.; Keler, T.; Hawthorne, T.; Watson, I.R.; et al. MAPK Pathway Inhibitors Sensitize BRAF-Mutant Melanoma to an Antibody-Drug Conjugate Targeting GPNMB. *Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res.* **2016**, *22*, 6088–6098, https://doi.org/10.1158/1078-0432.CCR-16-1192.

72. Ocana, A.; Vera-Badillo, F.; Seruga, B.; Templeton, A.; Pandiella, A.; Amir, E. HER3 Overexpression and Survival in Solid Tumors: A Meta-Analysis. *J. Natl. Cancer Inst.* **2013**, *105*, 266–273, https://doi.org/10.1093/jnci/djs501.

73. Liu, X.; Liu, S.; Lyu, H.; Riker, A.I.; Zhang, Y.; Liu, B. Development of Effective Therapeutics Targeting HER3 for Cancer Treatment. *Biol. Proced. Online* **2019**, *21*, 5, https://doi.org/10.1186/s12575-019-0093-1.

74. Abel, E.V.; Basile, K.J.; Kugel, C.H.; Witkiewicz, A.K.; Le, K.; Amaravadi, R.K.; Karakousis, G.C.; Xu, X.; Xu, W.; Schuchter, L.M.; et al. Melanoma Adapts to RAF/MEK Inhibitors through FOXO3-Mediated Upregulation of ERBB3. *J. Clin. Investig.* **2013**, *123*, 2155–2168, https://doi.org/10.1172/JCI716780.

75. Zhang, N.; Chang, Y.; Rios, A.; An, Z. HER3/ErbB3, an Emerging Cancer Therapeutic Target. *Acta Biochim. Biophys. Sin.* **2016**, *48*, 39–48, https://doi.org/10.1093/abbs/gmv103.

76. Capone, E.; Lamolinaro, A.; D’Agostino, D.; Rossi, C.; De Laurenzi, V.; Iezzi, M.; Iacobelli, S.; Sala, G. EV20-Mediated Delivery of Cytotoxic Auristatin MMAF Exhibits Potent Therapeutic Efficacy in Cutaneous Melanoma. *J. Control. Release Off. J. Control. Release Soc.* **2018**, *277*, 48–56, https://doi.org/10.1016/j.jconrel.2018.03.016.

77. Hashimoto, Y.; Koyama, K.; Kamai, Y.; Hirofani, K.; Ogitani, Y.; Zembutsu, A.; Abe, M.; Kaneda, Y.; Maeda, N.; Shiouse, Y.; et al. A Novel HER3-Targeting Antibody–Drug Conjugate, U3-1402, Exhibits Potent Therapeutic Efficacy through the Delivery of Cytotoxic Payload by Efficient Internalization. *Clin. Cancer Res.* **2019**, *25*, 7151–7161, https://doi.org/10.1158/1078-0432.CCR-19-1745.

78. Chen, Y.; Chalouni, C.; Tan, C.; Clark, R.; Venook, R.; Ohri, R.; Raab, H.; Firestein, R.; Mallet, W.; Polakis, P. The Melanosomal Protein PMEL17 as a Target for Antibody Drug Conjugate Therapy in Melanoma. *J. Biol. Chem.* **2012**, *287*, 24082–24091, https://doi.org/10.1074/jbc.M112.361485.

79. Nelson, J.; Bagnato, A.; Battistini, B.; Nisen, P. The Endothelin Axis: Emerging Role in Cancer. *Nat. Rev. Cancer* **2003**, *3*, 110–116, https://doi.org/10.1038/nrc990.

80. Saldana-Caboverde, A.; Kos, L. Roles of Endothelin Signaling in Melanocyte Development and Melanoma. *Pigment. Cell Mela-noina Res.* **2010**, *23*, 160–170, https://doi.org/10.1111/j.1755-148X.2010.00678.x.

81. Bagnato, A.; Rosano, L.; Spinella, F.; Di Castro, V.; Tecc, R.; Natali, P.G. Endothelin B Receptor Blockade Inhibits Dynamics of Cell Interactions and Communications in Melanoma Cell Progression. *Cancer Res.* **2004**, *64*, 1436–1443, https://doi.org/10.1158/0008-5472.can-03-2244.

82. Asundi, J.; Reed, C.; Arca, J.; McCutcheon, K.; Ferrando, R.; Clark, S.; Luis, E.; Tien, J.; Firestein, R.; Polakis, P. An Antibody Drug Conjugate Targeting the Endothelin B Receptor for the Treatment of Melanoma. *Clin. Cancer Res Off. J. Am. Assoc. Cancer Res.* **2011**, *17*, 965–975, https://doi.org/10.1158/1078-0432.CCR-10-2340.

83. Sandhu, S.; McNeil, C.M.; LoRusso, P.; Patel, M.R.; Kabbarah, O.; Li, C.; Sanabria, S.; Flanagan, W.M.; Yeh, R.-F.; Brunstein, F.; et al. Phase I Study of the Anti-Endothelin B Receptor Antibody-Drug Conjugate DEDN6526A in Patients with Metastatic or
106. Feng, H.; Shuda, M.; Chang, Y.; Moore, P.S. Clonal Integration of a Polyomavirus in Human Merkel Cell Carcinoma. Science 2008, 319, 1096–1100, https://doi.org/10.1126/science.1152586.

107. Becker, J.C.; Stang, A.; DeCaprio, J.A.; Cerroni, L.; Lebbé, C.; Veness, M.; Nghiem, P. Merkel Cell Carcinoma. Nat. Rev. Dis. Primers 2017, 3, 1707, https://doi.org/10.1038/nrdp.2017.77.

108. D’Angelo, S.P.; Bhativa, S.; Brohl, A.S.; Hamid, O.; Mehniert, J.M.; Terheyden, P.; Shih, K.C.; Brownell, I.; Lebbé, C.; Lewis, K.D.; et al. Avelumab in Patients with Previously Treated Metastatic Merkel Cell Carcinoma: Long-Term Data and Biomarker Analyses from the Single-Arm Phase 2 JAVELIN Merkel 200 Trial. J. Immunother. Cancer 2020, 8, e00674, https://doi.org/10.1136/jitc-2020-00674.

109. Nghiem, P.T.; Bhativa, S.; Lipson, E.J.; Kudchadkar, R.R.; Miller, N.J.; Annamalai, L.; Berry, S.; Chartash, E.K.; Daud, A.; Fling, S.P.; et al. PD-1 Blockade with Pembrolizumab in Advanced Merkel-Cell Carcinoma. N. Engl. J. Med. 2016, 374, 2542–2552, https://doi.org/10.1056/NEJMoai1603702.

110. Nghiem, P.; Bhativa, S.; Lipson, E.J.; Sharfman, W.H.; Kudchadkar, R.R.; Brohl, A.S.; Friedlander, P.A.; Daud, A.; Kluger, H.M.; Reddy, S.A.; et al. Durable Tumor Regression and Overall Survival in Patients with Advanced Merkel Cell Carcinoma Receiving Pembrolizumab as First-Line Therapy. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2019, 37, 693–702, https://doi.org/10.1200/JCO.18.01896.

111. Ollier, J.; Kervarrec, T.; Samimi, M.; Benlama, H.; Aumont, P.; Vivien, R.; Touzé, A.; Labarrière, N.; Vié, H.; Clémenceau, B. Merkel Cell Carcinoma and Cellular Cytotoxicity: Sensitivity to Cellular Lysis and Screening for Potential Target Antigens Suitable for Antibody-Dependent Cellular Cytotoxicity. Cancer Immunol. Immunother. 2018, 67, 1209–1219, https://doi.org/10.1007/s00262-018-2176-2.

112. Shah, M.H.; Lorigan, P.; O’Brien, M.E.R.; Fossella, F.V.; Moore, K.N.; Bhativa, S.; Kirby, M.; Woll, P.J. Phase I Study of IMGN901, a CD56-Targeting Antibody-Drug Conjugate, in Patients with CD56-Positive Solid Tumors. Invest. New Drugs 2016, 34, 290–299, https://doi.org/10.1007/s10637-016-0336-9.

113. Ailawadhi, S.; Kelly, K.R.; Vesco, R.A.; Jagannath, S.; Wolf, J.; Gharibio, M.; Sher, T.; Bojanini, L.; Kirby, M.; Chanan-Khan, A. A Phase I Study to Assess the Safety and Pharmacokinetics of Single-Agent Lorvotuzumab Mertansine (IMGN901) in Patients with Relapsed and/or Refractory CD-56-Positive Multiple Myeloma. Clin. Lymphoma Myeloma Leuk. 2019, 19, 29–34, https://doi.org/10.1016/j.clml.2018.08.018.

114. Socinski, M.A.; Kaye, F.J.; Spigel, D.R.; Kudrik, F.J.; Ponce, S.; Ellis, P.M.; Majem, L.; Lorigan, P.; Gandhi, L.; Gutierrez, M.E.; et al. Phase 1/2 Study of the CD56-Targeting Antibody-Drug Conjugate Lorvotuzumab Mertansine (IMGN901) in Combination With Carboplatin/Etoposide in Small-Cell Lung Cancer Patients With Extensive-Stage Disease. Clin. Lung Cancer 2017, 18, 68–76.e2, https://doi.org/10.1016/j.cct.2016.09.002.

115. Esnault, C.; Leblond, V.; Martin, C.; Desgranges, A.; Baltus, C.B.; Aubrey, N.; Lakhrif, Z.; Lajoie, L.; Lantier, L.; Clémenceau, B.; et al. Adcetris®, a New CD56-Targeting Monomethyl Auristatin E-Conjugated Antibody, Is a Potential Therapeutic Approach in Merkel Cell Carcinoma. Br. J. Dermatol. 2021, https://doi.org/10.1111/bjd.20770.

116. Lashari, B.H.; Vallatharasu, Y.; Kolandra, L.; Hamid, M.; Upreti, D. Rovalpituzumab Tesirine: A Novel DLL3-Targeting Antibody-Drug Conjugate. Drugs RD 2018, 18, 255–258, https://doi.org/10.3254/drugsRD18-088-01247-7.

117. Rand, J.; Balzer, B.L.; Frishberg, D.P.; Essner, R.; Shon, W. Prevalence of Delta-Like Protein 3 Expression in Merkel Cell Carcinoma. J. Am. Acad. Dermatol. 2019, 85, 749–750, https://doi.org/10.1016/j.jaad.2019.09.069.

118. Xie, H.; Kaye, F.J.; Isse, K.; Sun, Y.; Ramoth, J.; French, D.M.; Flotte, T.J.; Luo, Y.; Saunders, L.R.; Mansfield, A.S. Delta-like Protein 3 Expression and Targeting in Merkel Cell Carcinoma. Oncol. 2020, 25, 810–817, https://doi.org/10.1634/theoncologist.2019-0877.

119. Morgensztern, D.; Besse, B.; Greillier, L.; Santana-Davila, R.; Ready, N.; Hann, C.L.; Glisson, B.S.; Farago, A.F.; Dowlati, A.; Rudin, C.M.; et al. Efficacy and Safety of Rovalpituzumab Tesirine in Third-Line and Beyond Patients with DLL3-Expressing, Relapsed/Refractory Small-Cell Lung Cancer: Results From the Phase II TRINITY Study. Clin. Cancer Res. Off. J. Am. Assoc. Cancer Res. 2019, 25, 6958–6966, https://doi.org/10.1158/1078-0432.CCR-19-1133.

120. Szijj, P.A.; Bahou, C.; Chuhasama, V. Minireview: Addressing the Retro-Michael Instability of Maleimide Bioconjugates. Drug Discov. Today Technol. 2018, 30, 27–34, https://doi.org/10.1016/j.ddct.2018.07.002.

121. Parslow, A.C.; Parakh, S.; Lee, F.-T.; Gan, H.K.; Scott, A.M. Antibody-Drug Conjugates for Cancer Therapy. Biomedicines 2016, 4, 14, https://doi.org/10.3390/biomedicines4030014.

122. Goyal, A.; Patel, S.; Goyal, K.; Morgan, E.A.; Foreman, R.K. Variable Loss of CD30 Expression by Immunohistochemistry in Recurrent Cutaneous CD30+ Lymphoid Neoplasms Treated with Brentuximab Vedotin. J. Cutan. Pathol. 2019, 46, 823–829, https://doi.org/10.1111/1345-13551.1511.

123. Desnoyers, L.R.; Vasiljeva, O.; Richardson, J.H.; Yang, A.; Menendez, E.E.M.; Liang, T.W.; Wong, C.; Bessette, P.H.; Kamath, K.; Moore, S.J.; et al. Tumor-Specific Activation of an EGFR-Targeting Probody Enhances Therapeutic Index. Sci. Transl. Med. 2013, 5, 207ra144, https://doi.org/10.1126/scitranslmed.3006682.

124. Autio, K.A.; Boni, V.; Humphrey, R.W.; Naing, A. Probody Therapeutics: An Emerging Class of Therapies Designed to Enhance On-Target Effects with Reduced Off-Target Toxicity for Use in Immuno-Oncology. Clin. Cancer Res. 2020, 26, 984–989, https://doi.org/10.1158/1078-0432.CCR-19-1457.

125. Chomet, M.; Schreurs, M.; Nguyen, M.; Howong, B.; Villanueva, R.; Krimm, M.; Vasiljeva, O.; van Dongen, G.A.M.S.; Vugts, D.J. The Tumor Targeting Performance of Anti-CD16 Probody Drug Conjugate CX-2009 and Its Parental Derivatives as Monitored by 89Zr-Immuno-PET in Xenograft Bearing Mice. Theranostics 2020, 10, 5815–5828, https://doi.org/10.7150/thno.44334.
126. Modi, S.; Saura, C.; Yamashita, T.; Park, Y.H.; Kim, S.-B.; Tamura, K.; Andre, F.; Iwata, H.; Ito, Y.; Tsurutani, J.; et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer. *N. Engl. J. Med.* 2020, 382, 610–621, https://doi.org/10.1056/NEJMoa1914510.

127. Donaghy, H. Effects of Antibody, Drug and Linker on the Preclinical and Clinical Toxicities of Antibody-Drug Conjugates. *mAbs* 2016, 8, 659–671, https://doi.org/10.1080/19420862.2016.1156829.