A review of progress in the study of antibody-drug conjugates targeting HER2

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Abstract

This review article provides a comprehensive examination of the latest research advancements in HER2-targeted antibody-drug conjugates (ADCs) and their applications in cancer therapeutics. It begins by outlining the overexpression of HER2 receptors in different types of cancer and its correlation with cancer progression. It then provides an in-depth explanation of the structural components of ADCs (antibody, linker, and payload) and their mechanisms of action. It places particular emphasis on analyzing the clinical efficacy of the three FDA-approved HER2-targeting ADC drugs T-DM1, T-DXd and RC48, while also addressing current therapeutic challenges such as tumor heterogeneity and drug resistance. It outlines future research directions including optimizing ADC design, developing combination therapies and expanding indications. Ultimately, the article explores the potential of HER2-targeted ADCs to achieve high efficacy, low toxicity and broad-spectrum therapeutic outcomes.

Keywords: HER2; Antibody-drug conjugates (ADCs); Targeted therapy; T-DM1; T-DXd; RC48; Tumor heterogene ity; Drug resistance; Combination therapy; Precision medicine

1. Introduction

Human epidermal growth factor receptor 2 (HER2) constitutes a significant constituent of the epidermal growth factor receptor (EGFR) family, which is the property of the transmembrane tyrosine kinase receptor family and is located on the human chromosome 17q21. The receptor's molecular weight is estimated to be around 185kDa [1]. The HER family members include HER1 (EGFR), HER2, HER3, and HER4, which share the common characteristics of having a region that binds to an extracellular ligand, transmembrane region, and the presence of an intracellular complex kinase domain. It is evident that HER2 does not form complexes with ligands. Rather, it has been established that HER2 can constitute homodimers or heterodimers with other constituents of the HER family. These complexes then act as activators of signaling pathways, such as MAPK, PI3K/AKT and other key oncogenic pathways, which regulate cell growth, differentiation, angiogenesis and other biological processes [2].

It has been demonstrated that aberrant activation of the human epidermal growth factor receptor 2 (HER2) notably in the form of gene amplification and increased protein production — has a strong correlation with the onset of various malignancies. These include bladder cancer, breast cancer, cervical cancer, cholangiocarcinoma, colorectal cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, hepatocellular carcinoma, lung cancer, ovarian cancer and salivary gland cancer. A considerable body of research has indicated that HER2 is expressed in excess in 20-30% of diagnosed instances of breast cancer, gastric cancers, colon cancers, and other solid tumors, and the HER2-positive breast cancer (BC) subtype has been shown to be clinically aggressive, and there has recently been significant improvement in the prognosis of patients with this condition. This improvement can be attributed to advances in pathological diagnosis and molecular-targeted therapeutic techniques.

Adopting an advanced approach to cancer treatment, Antibody-deug conjugates (ADCs) represent a novel class of targeted anticancer therapies. These innovative therapies combine monoclonal tumor surface receptor-targeting antibodies with highly cytotoxic molecular payloads. The molecular payloads are bonded by specially designed cleavable or non-cleavable chemical connectors. The purpose of this bond is to achieve precise targeting and efficient killing of tumor cells. The result of this targeted and efficient killing by the payload is the potential for a significant improvement in the therapeutic index and a reduction in toxicity to normal tissues and has good clinical therapeutic value. Its therapeutic effect is influenced by various factors such as antibody selection, epitope affinity, linker type, payload type and the choice of drug-antibody coupling ratio (DAR). In recent years, Anticancer drugs, and therapeutic use and the study of new antibody drugs have been approved for some.

So far, the U.S. Food and Drug Administration (FDA) has approved several ADCs targeting HER2 to be marketed, including trastuzumab medenosum (trastuzumab emtansine, T-DM1), trastuzumab deruxtecan (trastuzumab deruxtecan, T-DXd), and RC48, this is a treatment that is used in HER2 tumors patients. In addition, clinical studies of ADC technology in a variety of solid tumors are advancing, showing a broad application prospect [3].

2. Antibody-drug coupling (ADC) targeting HER2

2.1 Composition and mechanism of action

As a new generation of targeted therapeutic drugs, the basic structure of an antibody-drug coupling (ADC) is composed of three parts: The pharmaceutical compound under consideration consists of three constituent elements: a monoclonal antibody that specifically recognizes tumor cells (the carrier), a highly effective cytotoxic drug (the payload), and a chemical connector that links the two. ADCs targeting HER2 have demonstrated significant efficacy in breast cancer treatment and are designed with the concept of achieving precise killing of tumor cells without increasing systemic toxicity.

2.1.1 Antibody Component: Selective Recognition and Targeted Translocation

Antibodies in ADCs are used as guidance systems, similar to missile navigators, to recognize and bind specific antigens expressed externally by the presence of cancer cells. The ideal antibodies are those which meet specific criteria.1. The fundamental principles of this field are such that the materials must exhibit high stability and minimal immunogenicity: to reduce immune rejection in vivo.2. Antibodies must exhibit clear specificity for antigenic targets: the expression of antigens in neoplastic cells is typically elevated in comparison to that observed in normal tissues. This characteristic, when coupled with the antibody's capacity to precisely recognize these targets, facilitates the efficient accumulation of the therapeutic agent within tumor cells, thereby sparing healthy cells from potential harm. 3. Antibodies and antigens should have appropriate affinity and effective internalization: Antibodies need to be rapidly endocytosed by tumor cells after binding to antigens. It has been established that higher antibody affinity has the capacity to enhance the efficiency of internalization. Conversely, an excess of antigen affinity has the potential to impede penetration into solid tumors, thereby diminishing the efficacy of the drug within the tumor. Therefore, the antibody should exhibit reasonable affinity for the antigen in order to ensure a rapid uptake by the target cells [4].4. The half-life of antibodies in the plasma is of significance. Humanized or chimeric immunoglobulin G (IgG) antibodies are the antibodies most commonly used, with IgG1 being the most prevalent option as the foundation for the design of ADCs, due to its strong immune effect and stability.

2.1.2 Linker: Stability and Controlled Release

Linkers play a fundamental role in ADCs as intermediaries between the payload and the antibody. The linker's chemical properties affect how drug delivery works as well as the pharmacokinetics, efficacy and safety of the ADC are all important considerations. The junction connecting the antibody to the payload must be highly stable in the bloodstream. This is to avoid premature release of toxicity and at the same time capable of being cleaved by specific enzymes or acidic environments within the tumor cells to trigger drug release. The types of junctions are usually classified as cleavable (e.g., enzyme-sensitive peptides) or non-cleavable, and the different designs affect the release pathway and the capacity of the drug to have a "bystander effect". Cleavable junctions characteristically exhibit stability within blood but rapidly break down and the active compounds in question are released in environments with low pH level, protease-rich lysosomes, or elevated glutathione concentrations. The non-cleavable linker constitutes a novel development and boasts superior plasma stability in comparison with the cleavable linker. On-cuttable connectors have the potential to impede off-target toxicity while concurrently offering a plethora of therapeutic interventions due to their elevated stability and safety [5].

2.1.3 Payload: efficient killing and system stability

Cytotoxicity payload is an indispensable element for ADCs to achieve antitumor activity and plays a pivotal role in determining the efficiency of ADC pharmaceuticals, which are usually small molecule anti-microtubule drugs or DNA-damaging drugs. In order to achieve optimal tumor suppression, the employment of agents of a cytotoxic nature must be subject to a series of specific requirements.:

1. Low immunogenicity and good solubility: It has been demonstrated by preceding studies that the entry of toxic molecules into cells is contingent upon their solubility within an aqueous buffer solution, for easy coupling.

2. High cytotoxicity: The fundamental property of non-immunogenic cytotoxic agents is that they must exhibit stability and non-toxicity when circulating in the bloodstream, and after entering tumor cells the induction of cellular toxicity by these substances occurs at concentrations well below the nanomolar range. Moreover, these substances are known to exert

a pronounced biological effect on tumor cells. It is therefore imperative that these substances are clearly released within the tumor cell environment [6].

3. Suitable lipid solubility and half-life: to ensure uniform distribution and stable metabolism in vivo.

4. Innovative mechanisms: payloads under development in recent years are mostly equipped with novel mechanisms of action, which are able to break through the barrier of resistance to conventional chemotherapy, thus increasing the therapeutic response rate.

2.2 ADC anti-tumor mechanism: target binding to apoptosis

The purpose of an antibody-drug conjugate (ADC) is to deliver cytotoxic compounds directly to specific tumor cells. The antitumor effect of HER2-targeted ADCs can be summarized in four stages, namely, "target binding - endocytosis - drug release - induced cell death". "The process is as follows:

1. ADC is recycled from plasma into tissues.

2. The antibody constituent of the ADC has been demonstrated to bind to the antigen known as HER2, which is specifically expressed on tumor cells.

3. Triggered internalization stimulates the development of early endosomes, followed by entry into late endosomes and eventual fusion with lysosomes.

4. The ADC receptor complex releases cytotoxins after degrading them.

5. Cytotoxic drugs are known to bind to their targets.

6. Cytotoxicity leads to DNA strand breaks and microtubule disruption, preventing tumor cells from dividing and thus hypothesized that this process may induce apoptosis (programmed cell death) [7].

7.(1) The release of the drug is initiated at the antibody following its binding to the antigen and subsequent endocytosis, the drug is released from the cellular space due to the elevated permeability of the drug membrane exerts its effect on the adjacent, targeted or untargeted cells. It has been demonstrated that this results in enhanced killing efficiency of ADC in cancers characterized by low or heterogeneous expression of target antigen. (2) As an alternative hypothesis, cleavable junctions may serve to facilitate the release of a segment of the payload. Let this segment go into the extracellular environment in anticipation of subsequent internalization following antigen binding. This process would result in the immediate initiation of cytotoxic activity.

8. It has been established that certain antibodies can induce the death of cancer cells. This process occurs through the binding of the antibodies to immune effector cells within the ADC, thereby triggering anti-tumor immunity through the mechanism of antibody-dependent cell-mediated toxicity [4].

2.3 HER2 structural features and ADC selectivity mechanism

The HER2 receptor belongs to the ErbB receptor family and structurally the entity under consideration is comprised of three domains: firstly, an extracellular ligand-binding domain; secondly, a transmembrane domain; and thirdly, A tyrosine kinase domain located within the cell[17].Despite the absence of a known ligand for HER2, it has been identified as the primary dimerization chaperone for other HER proteins, in particular HER3. HER2 overexpression, otherwise known as gene amplification, is a condition characterized by the unregulated formation of dimers, resulting in aberrant signaling. This phenomenon has been observed to occur in conjunction with increased signaling through a process known as ligand-dependent heterodimerization [8].

In HER2-positive tumors, HER2 is an ideal ADC target. On the one hand, its high expression properties are conducive to enhancing ADC targeting and internalization efficiency; on the other hand, its intracellular signaling activation mechanism provides cytotoxic drugs and the potential to interfere with key signaling pathways, thereby stimulating cell proliferation and growth, while concomitantly suppressing apoptosis, is of considerable significance.

3. Representative HER2-targeted ADC drugs and clinical studies

With the development of HER2-targeted therapeutic strategies, a variety of anti-HER2 ADC drugs have been introduced and have demonstrated good efficacy in a variety of malignant tumors. Among them, T-DM1, T-DXd and RC48 are the most researched and widely used drugs.

3.1 Trastuzumab Emtansine (T-DM1)

T-DM1, the first ADC drug to receive FDA approval for HER2-positive metastatic breast cancer, consists of the anti- HER2 monoclonal antibody trastuzumab (trastuzumab) linked to the cytotoxic agent DM1 via a non-cleavable thioethylene junction.DM1 is a meditating derivative, a derivative, which binds to microtubule proteins and inhibits their polymerization, which may result in cell cycle arrest and, indeed, apoptosis[9].On average, 3-4 DM1 molecules are attached to each antibody.

The mode of action of DM1 is characterized by its capacity to interact with microtubule proteins, thereby impeding their process of polymerization. This interaction consequently triggers cell cycle arrest and apoptosis induction. Upon entry into the circulation, trastuzumab partially recognizes and it is initiated upon binding of the ligand to the extracellular structural domain IV of the HER2 receptor. This is followed by receptor-mediated endocytosis of the ligand-binding domain within the tumor cell. In the lysosome, the antibody component is degraded and DM1 is released into the cytoplasm, inhibition of the activation of signaling pathways, including PI3K/Akt and MAPK, has been demonstrated. Thus, inhibiting tumor cell proliferation and inducing cell death [10]. T-DM1 has been proposed as a first-line therapeutic option, has been shown to have a significant advantage which is that prolongation of survival is possible for patients diagnosed with HER2-positive breast cancer, as indicated by the results of numerous clinical studies.

3.2 Trastuzumab Deruxtecan (T-DXd)

T-DXd represents a pioneering HER2-targeted ADC composed of an anti-HER2 antibody, a cleavable tetrapeptide junction (GGFG), and a topoisomerase I inhibitor payload that is membrane-permeable [11]. In comparison with T-DM1, T-DXd has been found to exhibit a higher drug-antibody. Furthermore, T-DXd has been demonstrated in order to facilitate more efficacious penetration of the cell membrane, producing a stronger "bystander effect". It is evident that there are a number of other factors. These contribute to the effectiveness of T-DXd. A higher drug-antibody ratio is included, which facilitates increased delivery of the payload to the target cell. In addition, there is high plasma stability after intravenous infusion, and reactivity is maintained.

After T-DXd enters HER2-expressing tumor cells via endocytosis, the junction breaks in the lysosome and the released DXd not only exerts DNA damaging effects on the target cells, moreover, spreads to neighboring cells to exert cytotoxicity, notwithstanding the presence of low HER2 expression or heterogeneity in these cells. This feature enables T-DXd to show excellent efficacy in HER2-low or HER2-heterogeneous tumors, which breaks the limitation of traditional ADCs that rely on high HER2 expression [12]. Therefore, the T-DXd has been shown to be effective in treating a range of HER2-positive tumors.

In 2021, T-DXd received approval from the U.S. Food and Drug Administration (FDA) for the treatment of patients diagnosed with HER2-positive gastric cancer. Moreover, T-DXd has demonstrated its effectiveness in treating HER2-low gastric cancer. (ClinicalTrials.gov identifier NCT04379596), with an objective remission rate of 26.3% [13]. And in cases of gastric cancer. And in cases of breast cancer. With low or heterogeneous expression of HER2, studies have shown that T - DXd is also an effective way of treating.

3.3 Disitamab Vedotin (RC48)

RC-48 consists of the humanised monoclonal antibody herceptin, which is part of a new generation of highly specific anti-Her2 monoclonal antibodies, and a cytotoxic payload, monomethyl auristatin E (MMAE), the cleavable tetrapeptide junction (maleimide-cysteine-valine-citrulline-citrulline-p-aminobenzyloxycarbonyl (MC - VC - PABC)) is linked in order to form the ADC drug[4].Hertuzumab has a high affinity and specificity for HER2 proteins, whereas MMAE effectively disrupts microtubule structure and induces cell cycle G2/M blockade and apoptosis.

Upon uptake by target cells, RC48 releases MMAE by junction breakage in a lysosomal environment. payload subsequently interferes with microtubule assembly in tumor cells, inhibiting their division and inducing cell death. In addition, RC48 may inhibit tumor-associated signal transduction and transcriptional processes, further enhancing its anti-tumor activity. Clinical studies have shown that RC48 has some efficacy against gastric and breast cancers exhibiting low HER2 expression represent a significant research focus, particularly in the context of developing HER2-targeted ADC drugs.

4. Challenges and strategies in HER2-ADC therapy

Although HER2-targeted antibody-drug couplings (ADCs) have shown significant therapeutic promise with regard to the treatment of breast cancer., their clinical application still faces many challenges. First, the heterogeneity and dynamic

changes of HER2 expression in tumor tissues can lead to decreased targeting precision, which in turn affects ADC efficacy. In addition, ADCs are increasingly used in clinical experimental studies, and acquired resistance has gradually become an important factor limiting efficacy, whose mechanisms include a decrease in expression levels of the HER2 receptor is observed. In addition, receptor internalization and degradation are impaired, altered lysosomal function, and activation of drug efflux pumps.

In terms of payload selection, a significant proportion of the ADCs currently in clinical use are more than fifty per cent of the total use carry microtubule protein inhibitors or DNA damage analogues. It is imperative to consider combinations of ADCs with other drugs that have proven efficacy in the treatment of tumors. These include immune checkpoint inhibitors, tyrosine kinase inhibitors and chemotherapeutic agents, with the objective of enhancing the activity of ADCs. In principle, ADCs are characterized by an enhanced safety profile, attributable to stable linker design which engenders an optimized therapeutic profile. Nevertheless, implementing them successfully is often a real challenge[14].However, these conventional cytotoxic agents still have limitations in terms of efficacy and safety, and are particularly prone to induce hematological toxicity, neurotoxicity, and hepatic impairment with toxic side effects similar to those of conventional chemotherapeutic agents[15].Therefore, the development of new efficient payloads with diverse mechanisms of action, as well as the optimization of the joint structure to enhance the stability and bystander effect of the drug, have become the focus of current research.

To overcome the resistance problem faced by ADC monotherapy, combination therapy strategies are being widely explored. For instance, a combination of HER2-ADC with immune checkpoint inhibitors, tyrosine kinase inhibitors (TKIs), DNA damage repair inhibitors, or statins is expected to enhance tumor cell killing through multi-mechanism synergism while reducing the incidence of single-drug resistance. Especially in patients exhibiting low or heterogeneous HER2 expression, enhancing the bystander effect of ADCs, boosting the drug-antibody ratio (DAR), and introducing dual-target or multi-target ADC designs (e.g., HER2/HER3 dual-targeting) have been considered as important strategies to improve the efficacy of the therapy.

In the future, the research and development of HER2-ADCs should focus on (1) optimizing the junction and load structure to enhance stability and membrane permeability; (2) enhancing the efficiency of cytotoxic load delivery and expanding the therapeutic window; and (3) designing multifunctional ADC molecules to adapt to tumor types in cases of low or heterogeneous HER2 expression of the HER2 protein to extend both progression-free survival and overall survival rates among patients. Through continuous molecular optimization and precise drug combination, HER2-ADC is expected to further enhance clinical value in the context of precision treatment strategies for breast cancer.

5. Development trends and outlook

In recent years, HER2-targeted therapy has made substantial progress in both basic and clinical studies, especially in HER2 overexpression, which is evident in both breast and gastric cancers. Although the research on anti-HER2 therapy has not yet achieved any breakthrough, antibody-drug coupling (ADC), as a new generation of precision therapeutic strategy, shows strong clinical potential and development prospects. Taking RC48-ADC as an example, the treatment has been found to demonstrate a satisfactory safety profile and efficacy, when administered to patients with HER2-positive metastatic uroepithelial cancer (mUC) who have failed first-line chemotherapy. The antibody utilised in this pharmaceutical compound exhibits a higher binding affinity for the HER2 receptor in comparison to trastuzumab, significantly enhancing the selective recognition and killing of tumor cells.

Looking ahead, the following key directions should be given primary focus in research on HER2-targeted ADCs:

1. innovations in ADC structural design: The development of innovative payload platforms is imperative, coupling strategies and junction structures to enhance therapeutic efficacy and reduce systemic toxicity. High DAR (drug-to-antibody ratio), intelligent release mechanisms and connector designs with greater tissue selectivity will be the focus of research.

2. Delivery system optimization: through engineered recombinant antibody technology, the target delivery efficiency and lysosomal transport capacity of ADCs in cancer cells can be improved to enhance drug release and cytotoxicity.

3. Toxicity control and expansion of therapeutic window: while enhancing anti-tumor activity, optimize the safety configuration of ADCs, and reduce adverse reactions such as hematology, hepatotoxicity and neurotoxicity as much as possible.

4. In-depth analysis of drug resistance mechanism: further elucidation of primary and acquired drug resistance mechanisms in HER2-ADC treatment, providing theoretical basis and new target support for overcoming clinical drug resistance.

5. Development of combination therapy strategies: to explore the synergistic combination of HER2-ADC with immune checkpoint tyrosine kinase inhibitors (TKIs) and DNA repair inhibitors, etc., with the aim of enhancing the efficacy, delaying the drug resistance, and broadening the scope of indications.

6. Expansion to HER2 low expression population: Enhancing the uptake efficiency and therapeutic responsiveness of ADCs to HER2 low expression tumors is an important direction to achieve broad-spectrum anti-HER2 therapy [4].

6. Conclusion

The utilization of antibody-drug couplings (ADCs) in the therapeutic management of HER2-positive tumors has been demonstrated to hold considerable promise. These findings suggest the capacity to address the limitations exhibited by conventional HER2-targeted therapies, such as trastuzumab, thereby offering a promising therapeutic intervention. A considerable number of ongoing clinical trials have demonstrated the exciting efficacy of ADCs in a broad spectrum of HER2-positive solid tumors. A significant development has transpired in the field of oncology, as three HER2-targeted ADC drugs – T-DM1, DS-8201a (T-DXd) and RC48 – have been approved for the treatment of HER2-positive malignant tumors. This represents a pivotal shift, progressing from theoretical research to clinical application, thereby marking a new era in the therapeutic management of these malignancies.

T-DM1, T-DXd and RC48, as a case in point, HER2-targeted ADC drugs have exhibited remarkable anti-tumor activity in different HER2 expression levels and drug-resistant backgrounds by optimizing antibody screening, linker structure and payload type. These results not only promote the therapeutic progress of HER2-associated tumors such as breast cancer but also establish a robust foundation for the prospective advancement of precision medicine.

Looking forward, the development of HER2-targeted ADCs will continue to evolve in the direction of high efficiency, low toxicity and broad spectrum. With the continuous development of novel linker design, intelligent delivery systems, and biomarker screening technologies, HER2-ADCs are expected to further improve efficacy while expanding to tumor patients with low or heterogeneous expression of HER2, thus achieving a wider range of individualized therapeutic applications.

REFERENCES

[1] Zhou L, Zhang Y, Zhang J, Wang H, Zhao B, Cai Y, Qu Y, Li X, Zhang D. Clinical characteristics and therapeutic direction of HER2 low-expression breast cancer. Front Oncol. 2025 Feb 27; 15:1484103. Doi: 10.3389/fonc.2025.1484103. PMID: 40083869; PMCID: PMC11903420.
[2] Hansel DE, Swain E, Dreicer R, Tubbs RR. HER2 overexpression and amplification in urothelial carcinoma of the bladder is associated with MYC coamplification in a subset of cases. Am J Clin Pathol. 2008 Aug;130(2):274-81.
[3] Chau CH, Steeg PS, Figg WD. Antibody-drug conjugates for cancer. Lancet 2019; 394:793e804.
[4] A. Beck, L. Goetsch, C. Dumontet, N. Corvaïa, Strategies and challenges for the next generation of antibody-drug conjugates, Nat. Rev. Drug Discov. 16 (5) (2017) 315-337.
[5] E. Ferraro, J.Z. Drago, S. Modi, Implementing antibody-drug conjugates (ADCs) in HER2-positive breast cancer: state of the art and future directions, Breast Cancer Res 23 (1) (2021) 84.
[6] Carter, P.J.; Lazar, G.A. Next Generation Antibody Drugs: Pursuit of the "High-Hanging Fruit". Nat. Rev. Drug Discov. 2018, 17, 197-223.
[7] Staudacher, A. H. & Brown, M. P. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? Br. J. Cancer 117, 1736-1742 (2017).
[8] Tebbutt, N., Pedersen, M. W. & Johns, T. G. Targeting the ERBB family in cancer: couples therapy. Nat. Rev. Cancer 13, 663e73 (2013).
[9] Baselga, J. & Swain, S. M. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nat. Rev. Cancer 9, 463-475 (2009).
[10] M. M. Moasser, The oncogene HER2: its signalling and transforming functions and its role in human cancer pathogenesis, Oncogene 26 (45) (2007) 6469 -6487.

[11] Lewis Phillips, G.D.; Li, G.; Dugger, D.L.; Crocker, L.M.; Parsons, K.L.; Mai, E.; Blättler, W.A.; Lambert, J.M.; Chari, R.V.J.; Lutz, R.J.; et al. Targeting HER2-Positive Breast Cancer with Trastuzumab-DM1, an Antibody-Cytotoxic Drug Conjugate. Cancer Res. 2008, 68, 9280-9290.

[12] Suzuki, M.; Yagishita, S.; Sugihara, K.; Ogitani, Y.; Nishikawa, T.; Ohuchi, M.; Teishikata, T.; Jikoh, T.; Yatabe, Y.; Yonemori, K.; et al. Visualisation of Intratumor Pharmacokinetics of [Fam-] Trastuzumab Deruxtecan (DS-8201a) in HER2 Heterogeneous Model Using Phosphor-Integrated Dots Imaging Analysis. Clin. Cancer Res. 2021, 27, 3970-3979.

[13] Hagemann, U. B. et al. Advances in precision oncology: targeted thorium-227 conjugates as a new modality in targeted alpha therapy. Cancer Biother. Radiopharm. 35, 497-510 (2020).

[14] asters, J.C.; Nickens, D.J.; Xuan, D.; Shazer, R.L.; Amantea, M. Clinical Toxicity of Antibody Drug Conjugates: a Meta-Analysis of Payloads. Investig. New Drugs 2018, 36, 121-135. [CrossRef]

[15] Fuentes-Antrás, J.; Genta, S.; Vijenthira, A.; Siu, L.L. Antibody-Drug Conjugates: In Search of Partners of Choice. Trends Cancer 2023, 9, 339-354.