Dual-Payload ADCs enter the Clinic: A New Cancer Therapy Frontier

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ABSTRACT

antibody–drug conjugates (ADCs) are an emerging strategy in targeted cancer therapy, offering enhanced efficacy by delivering two distinct cytotoxic agents simultaneously. This approach addresses key limitations of single-payload ADCs, such as tumor heterogeneity, drug resistance, and limited potency. Advances in linker chemistry such as hetero trifunctional linkers, site-specific conjugation, and click chemistry have enabled the development of homogeneous dual-payload ADCs with defined drug-to-antibody ratios (DAR), improved pharmacokinetics, and reduced off-target toxicity. Preclinical studies show superior efficacy of dual payload ADCs over single-payload or combination therapies. Clinically, KH815 has received IND clearance, and IBI3020 is in Phase I trials, marking early translation into the clinic. While promising, challenges remain in manufacturing, DAR control, pharmacokinetics, and toxicity. With growing biotech innovation in the Asia Pacific region, regional efforts may significantly contribute to advancing this next-generation cancer therapy.

Keywords: *Payload synergy; Tumor microenvironment; Controlled DAR; Immunogenic; Heterogeneous tumors*

1. Introduction

Antibody–drug conjugates (ADCs) have emerged as a powerful class of targeted cancer therapeutics, capable of delivering highly potent cytotoxic agents directly to tumor cells while minimizing systemic toxicity[1, 2]. By harnessing the specificity of monoclonal antibodies and the potency of small-molecule drugs, ADCs offer a unique mechanism for precision oncology. However, conventional single-payload ADCs often face significant limitations, including tumor antigen heterogeneity, the emergence of drug resistance, and insufficient bystander killing of antigen-low tumor cells[1, 3]. To address these challenges, dual-payload ADCs have been developed as an advanced therapeutic strategy. By incorporating two distinct cytotoxic agents into a single antibody platform, these next-generation constructs provide a multifaceted approach to tumor eradication [3, 4]. This dual-mechanism design enables synergistic cell killing, circumvents established resistance pathways, and extends therapeutic reach to both antigen-high and antigen-low tumor populations [2, 5].Recent advancements in conjugation technologies—including site-specific conjugation, hetero trifunctional linkers, and click chemistry have further enhanced the feasibility and precision of dual-payload ADC construction [4-6]. These innovations are crucial in achieving homogeneous drug-to-antibody ratios (DAR), optimized pharmacokinetics, and minimized off-target toxicity.

The rise of dual-payload ADCs reflects a broader shift toward more complex, multi-modal cancer therapies. This review explores the rationale, design strategies, preclinical validation, and emerging clinical applications of dual-payload ADCs—highlighting their potential to redefine the future landscape of targeted cancer treatment.

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2. Design & Construction Strategies

2.1 Payload Combinations & Linker Technology

- Dual-payload ADCs frequently utilize combinations of microtubule inhibitors (e.g., MMAE or MMAF) alongside DNA-damaging agents such as PBD dimers or topoisomerase inhibitors. This strategy enables simultaneous engagement of distinct cytotoxic mechanisms to address tumor heterogeneity and resistance[7].
- New conjugation systems, including as hetero trifunctional and chemo-enzymatic linkers, allow for the precise site-specific attachment of multiple payloads, enabling specific drug-to-antibody ratios like 2+2, 4+2, or even 8+8 combinations. These linker methods improve stability and pharmacokinetic performance by providing exquisite control over DAR distribution[8].

2.2 Site- specific Conjugation

- It is possible to create homogenous ADCs with consistent drug-to-antibody ratios (DAR) by using site-specific conjugation techniques, such as engineered cysteines, glycoengineering, and the addition of artificial amino acids. In contrast to conventional heterogeneous ADCs, these homogeneous conjugates exhibit increased stability, better pharmacokinetics, less off-target toxicity, and decreased immunogenicity[9, 10]
- In order to enable extremely effective and site-specific payload attachment, click chemistry techniques such as strain-promoted azide-alkyne cycloaddition (SPAAC) and copper-catalyzed azide-alkyne cycloaddition (CuAAC) have also been widely used. Under mild, aqueous circumstances, these bioorthogonal processes enable accurate conjugation, enabling scalable, reproducible manufacturing and contributing to constant ADC quality[11, 12]

3. Preclinical Evidence: Efficacy & Mechanism

3.1 Enhanced Tumor Regression in Heterogeneous Models

A dual-payload anti-HER2 ADC providing MMAE + MMAF induced complete tumor remission in HER2-heterogeneous and T-DM1-resistant xenograft models (e.g., JIMT-1/MDA-MB-231 mixed tumors), greatly outperforming both single-payload ADCs and their co-administration. In this situation, the co-conjugated MMAE can provide a diffusible bystander effect that kills nearby antigen-negative cells because MMAF, which is more potent, efficiently destroys resistant, HER2-high tumor cells. Mechanistically, MMAF is restricted to the target cells, resulting in a precise and powerful cytotoxic activity, whereas MMAE can spread to neighboring cells and kill them[13, 14].

3.2 Synergy & Bystander Effects

The contrasting physicochemical properties of MMAE and MMAF lend complementary cytotoxic effects when paired in ADCs. MMAE, being cell-permeable and membrane diffusible, generates a strong bystander killing effect, enabling elimination of neighboring antigen-negative cells. In contrast, MMA Fbearing a charged C-terminal group is non-diffusible and restricts its activity to target antigen–high cells, reducing off-target toxicity[15].

3.3 Broader Payload Pairings

Dual-payload ADCs that combine topoisomerase inhibitors with PBD dimers or pair cytotoxins like MMAF with immune agonists such as TLR7/8 agonists demonstrate enhanced antitumor activity. These combinations not only exert direct cytotoxic effects but also promote immunogenic cell death and modulate the tumor microenvironment, leading to improved efficacy in resistant and heterogeneous cancer models.

Dual-payload ADCs combining topoisomerase inhibitors with PBD dimers or a cytotoxin like MMAF with immune agonists such as TLR7/8 activators show promise by both inducing potent cytotoxicity and modulating the tumor

microenvironment. For instance, a CD276-targeting DualADC delivering MMAF along with a TLR agonist induced tumor regression and enhanced immune infiltration in TNBC models[16]. Similarly, ADCs integrating topoisomerase inhibitors with DNA– crosslinking agents (e.g., PBD dimers) have demonstrated synergistic efficacy by combining DNA damage pathways[7].

4. Early Clinical Translation

4.1 First- in-Class Dual- Payload Clinic Candidates

- The first dual-payload ADC to begin clinical testing is KH815—a new dual-payload TROP2-targeted ADC that co-delivers an RNA polymerase II inhibitor and a topoisomerase I inhibitor—which started a Phase I solid tumor trial on April 30, 2025 (NCT06885645). In addition to showing strong antitumor efficacy and a manageable safety profile (the highest non-severely toxic dose of 40 mg/kg in cynomolgus monkeys), preclinical research indicates that KH815 decreased the expression of resistance-related proteins such as P-glycoprotein (P-gp) and HSP70, pointing to a potential way to overcome ADC resistance [17].
- IBI3020: CEACAM5-targeted ADC with undisclosed dual-payloads. Phase I trial began Q1 2025, with first patient dosed (NCT06963281).

4.2 Emerging Platforms & Preclinical Pipelines

- Multiple biotech firms including Araris Biotech, Sutro Biopharma, Acepodia, and othersare actively advancing dual-payload ADC constructs in preclinical development, targeting antigens such as HER2, NaPi2b, GPC3, and even exploring tri-payload configurations[18, 19]

5. Opportunities & Challenges

5.1 Opportunities

- Dual-payload ADCs co-deliver drugs that target several tumor survival pathways, utilizing synergistic methods to increase antitumor activity and decrease resistance[20].
- Targeting antigen-negative tumor cells is made possible by the bystander effect made possible by cell-permeable payloads, which successfully addresses intratumoral heterogeneities[21].
- To increase anticancer immunity, immune agonists (such as TLR activators) with cytotoxic payloads increase immunogenic cell death and alter the tumor microenvironment[21].

5.2 Challenges

- Complex manufacturing: To ensure stability and batch-to-batch consistency, engineering dual-payload ADCs with exact drug-to-antibody ratios (DAR) calls for sophisticated conjugation processes [1].
- Pharmacokinetics and distribution: To prevent premature drug release and reduce off-target toxicity, it is essential to balance the different chemical characteristics and release kinetics of two payloads [22].
- Regulatory and safety obstacles: Dual-payload structures could increase the danger of systemic toxicity. Strict information on DAR homogeneity, biodistribution profiles, and linker chemistry (cleavable vs. non-cleavable) is needed by regulatory agencies[22].
- Translational validation: Sturdy clinical trials, such as biomarker-driven patient selection and head-to-head comparisons with current ADCs, are required to validate preclinical superiority[1]

6. Conclusion

Dual-payload ADCs mark a significant advance in targeted oncology by merging complementary cytotoxic mechanisms into a single biologic molecule. Preclinical data in refractory and heterogeneous tumor models show superior efficacy versus conventional ADCs. Early clinical entry of agents like KH815 and IBI3020 bring promisebut realizing their full potential will demand improvements in conjugation technology, careful toxicity control, and

thoughtful clinical trial design. Future work should focus on detailed Phase I/II data, robust biomarker strategies, and expansion into dual-payload combinations that include immune modulatory agents. If successful, dual- payload ADCs may redefine next- generation ADC therapeutics.

7. Conflict of Interest

The authors declare no conflicts of interest.

8. References

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