ANTIBODY-DRUG CONJUGATES (ADCs) IN **ONCOLOGY DRUG DEVELOPMENT**

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THE ANTIBODY-DRUG CONJUGATE ONCOLOGY DRUG DEVELOPMENT CHALLENGE

Antibody-drug conjugates (ADCs) uniquely target cancer cells by combining the precision of monoclonal antibodies, which identify the cancer cells, with the potent cell-killing ability of cytotoxic agents. Both entities, namely the antibody and the cytotoxic agent, are already therapies for a certain type of cancer, but combining them enhances the efficacy and safety profiles. Breakthroughs in antibody engineering, novel linker chemistries and advanced payload design (more molecules per antibody) have catalyzed a surge in ADC development. This new generation of ADCs is achieving improved efficacy and more manageable side effects, making them a promising frontier for cancer treatment.

For example, Phase III clinical trial results show that trastuzumab deruxtecan, an ADC with eight molecules of deruxtecan linked to one trastuzumab molecule, approved for human epidermal growth factor receptor 2 (HER2)-positive breast cancer, results in significantly longer progression-free survival and overall survival in patients with HER2-low metastatic breast cancer compared to standard chemotherapy.

This white paper will explore the evolving landscape of ADCs, highlighting key technological advancements, regulatory considerations and clinical trends. It will also discuss challenges and opportunities in ADC development and how QPS' expertise can support the successful advancement of ADC programs.

WHAT IS AN ANTIBODY-DRUG CONJUGATE?

Antibody-drug conjugates (ADCs) are targeted cancer therapies that integrate three core components:

- **Antibodies:** These provide high specificity for tumor-associated antigens, ensuring that the therapeutic effect is focused on cancer cells while minimizing off-target effects.
- **Linkers:** These specialized chemical structures attach the cytotoxic payload to the antibody. Linkers are engineered to remain stable in the bloodstream, preventing premature release, yet are designed to break and release the payload once the ADC is internalized into the target cancer cell.
- **Cytotoxic Payloads:** Each antibody carries multiple molecules of these highly potent agents, capable of inducing cell death with minimal quantities per kg body weight. This strategy ensures that even a small number of targeted cancer cells are effectively destroyed.

EARLY ADCS: THE FOUNDATION FOR A RAPIDLY ADVANCING FIELD

The concept of arming antibodies with cytotoxic payloads to selectively target cancer cells dates back to the 1980s. The first ADC to gain FDA approval, gemtuzumab ozogamicin for acute myeloid leukemia, reached the market in 2000. However, it was voluntarily withdrawn in 2010 due to safety concerns before being reapproved in 2017 with an optimized dosing regimen. In 2011, the approval of brentuximab vedotin for Hodgkin's lymphoma marked an important milestone, ushering in a new wave of ADC development.

Since then, the pace of development has accelerated. Advancements in antibody engineering, linker chemistry and payload selection have dramatically improved ADC efficacy and safety. Worldwide, 17 ADCs have been approved (see Table), and hundreds more are in clinical development for various oncology indications.

KEY TECHNOLOGICAL ADVANCES IN ADC DEVELOPMENT

Recent technological innovations have addressed many historical challenges:

Antibody Engineering

Advances in target selection and antibody modifications have led to improved specificity and binding affinity. These refinements enable more precise tumor targeting, reducing adverse effects and improving therapeutic outcomes.

Linker Chemistry

Next-generation linkers exhibit significantly improved stability compared to earlier versions. Some utilize cleavable linkers activated by tumor-specific proteases, while others employ non-cleavable linkers that ensure the payload remains attached until internalized, minimizing systemic toxicity.

Payload Design and Conjugation

Developments in payload design and site-specific conjugation allow ADCs to deliver their cytotoxic load more efficiently. These advances boost the therapeutic index by reducing systemic toxicity while increasing on-target potency.

REGULATORY CONSIDERATIONS FOR ADCS

In March 2024, the US Food and Drug Administration (FDA) issued a Guidance for Industry on the Clinical Pharmacology Considerations for Antibody-Drug Conjugates. The FDA Guidance provides recommendations related to the development of ADCs with a cytotoxic small-molecule drug or payload. It includes considerations in the following areas: bioanalytical methods, dosing strategies, dose- and exposure-response analysis, intrinsic factors, QTc assessments, immunogenicity and drug-drug interactions.

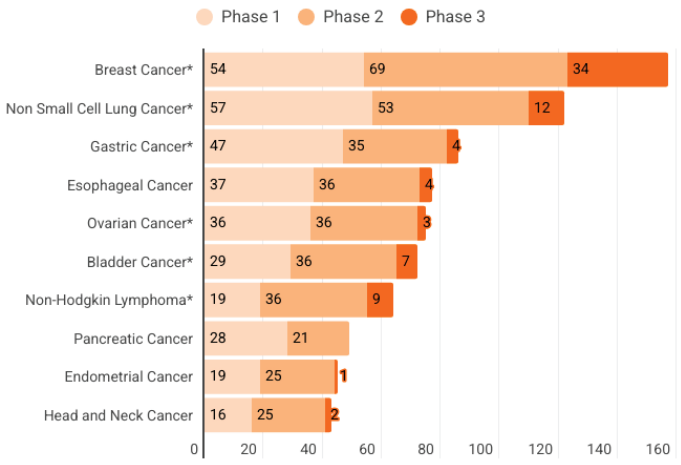
In December 2024, the National Medical Products Administration's Center for Drug Evaluation published a Technical Guideline for Antibody-Drug Conjugate Pharmaceutical Study and Evaluation in China. The European Medicines Agency has not published ADC-specific guidelines but does have Guidelines Relevant for Advanced Therapy Medicinal Products.

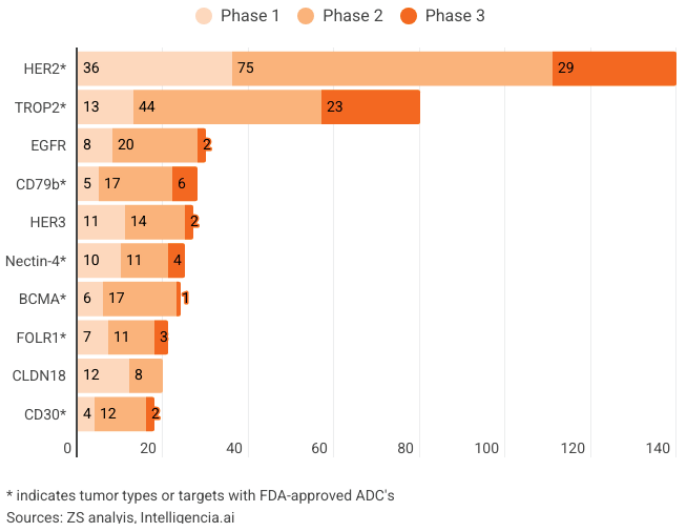
CURRENT PHARMACEUTICAL COMPANY ACTIVITY IN ADC DEVELOPMENT

The clinical trial landscape for ADCs is rapidly evolving. Hundreds of ADCs are currently in clinical development, evaluating therapies against a range of tumor types, as shown in Figures 1 and 2. The current inventory of ADCs in development reflects the market landscape, with non-small-cell lung, breast, ovarian, gastric and esophageal cancers at the forefront. This trend is not surprising, considering the proven effectiveness of ADCs in the market.

Safety and Off-Target Toxicity

While advanced linker chemistries have improved payload delivery, it is essential to ensure that cytotoxic agents are released exclusively within tumor cells. Continued efforts in biomarker-driven patient selection and optimized dosing regimens will help to further reduce adverse events and increase the success rate for efficacy.





Figures 1 and 2: ADC tumor types and targets by phase of development

Drug Resistance

Cancer cells can develop resistance mechanisms to ADC therapies, like the resistance that occurs in response to other targeted cancer therapies. Resistance can arise when cancer cells downregulate target antigen expression or alter intracellular trafficking. Researchers are addressing this by developing ADCs with dual-targeting capabilities and evaluating combination therapies to counteract resistance mechanisms.

Regulatory Complexity

The regulatory environment for ADCs continues to evolve. Due to their hybrid biological-chemical composition and high toxicity payload, each component introduces specific development and regulatory considerations. For example, the stability of the linker and controlled payload release are essential in ADC development. Premature release leads to toxicity, while inadequate release reduces efficacy.

ADCs must navigate both biologics and small molecule regulatory guidelines due to their dual nature, complicating the approval process. ADC clinical trial designs need to demonstrate targeted delivery, controlled release and the minimization of systemic toxicity. Adaptive trial designs incorporating biomarker-driven patient selection and efficacy endpoints are increasingly favored by regulatory agencies to expedite approvals.

THE EXPANDING ADC COMPETITIVE LANDSCAPE

The number of ADC candidates in clinical development has increased significantly in recent years. Current data (see figures) show how the expanding pipeline of ADC clinical trials includes both early-phase exploratory studies and later-stage confirmatory trials.

Innovations such as bispecific ADCs, which target two antigens simultaneously, and ADCs developed through integrated genomic and proteomic insights, are pushing the boundaries further, providing new strategies to address tumor heterogeneity and resistance mechanisms.

QPS: YOUR PROVEN PARTNER FOR ADC DEVELOPMENT

QPS is a leading full-service global contract research organization with extensive experience in ADC research. Our dedicated global team provides expert support across all phases of ADC development, from preclinical studies to bioanalysis and clinical trials.

Our Capabilities Include:

- **Global Clinical Team:** Our team includes board-certified oncologists, experienced clinical research coordinators, project managers and skilled data analysts, ensuring deep expertise in ADC development.
- **Patient-Centric Approach:** We leverage strong collaborations with study sites across Europe, the US and Asia, employing innovative patient recruitment strategies and partnerships.
- **State-of-the-Art Facilities:** Our advanced bioanalysis laboratories utilize cutting-edge technology for precise method development and assay execution. We have extensive experience conducting pharmacokinetic and immunogenicity ADC projects using ELISA, ECL and (Hybrid) LC-MS/MS techniques.
- **Customized Oncology Solutions:** We design tailored study protocols to meet the unique needs of oncology research, including biomarker analysis, imaging services and specialized assay development.
- **Proven Track Record:** We have successfully conducted global Phase I-IV oncology studies, covering a broad range of cancers such as breast, head and neck, lung and prostate.

ADVANCING ADCS INTO THE FUTURE

The rapid evolution of ADC technology is setting a new standard in targeted cancer therapy. With significant advancements in antibody design, linker stability and payload potency, the next generation of ADCs is poised to deliver greater clinical efficacy and safety. As the ADC pipeline continues to grow and diversify, QPS remains a trusted partner, offering the specialized expertise and integrated solutions needed to navigate this complex landscape. Together, we can accelerate the development of transformative therapies that offer renewed hope for patients worldwide.

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