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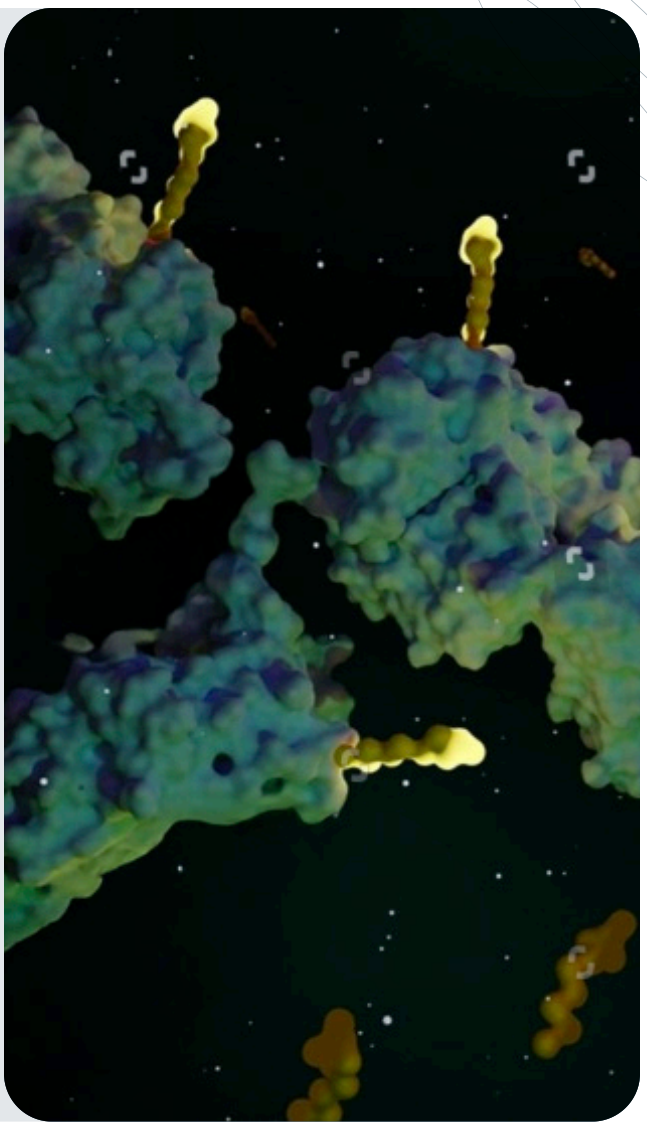
BIOPHARMA STRATEGY



ESMO Congress Report
October 2025

Trends in ADC development: **Expanding the ADC arsenal**

Executive summary

Antibody–drug conjugates (ADCs) continue to reshape treatment across solid tumors. At ESMO 2025, we saw movement of approved ADCs into earlier lines of therapy as well as new agents targeting previously untapped biology. These advances highlight the growing importance of optimizing treatment sequencing and understanding emerging resistance mechanisms as patients are increasingly exposed to multiple ADCs over their disease course. Key unmet needs now include strategies to overcome payload-related resistance. In response, developers are pursuing innovation through dual-payload designs and novel payload classes intended to evade current resistance pathways while maintaining tumor-selective cytotoxicity.

What did we learn about ADCs at ESMO 2025?

Established ADCs advance to early treatment settings

In recent years, ADCs have transformed the oncology treatment landscape. Several ADCs have been approved by the FDA for various metastatic solid cancers (**Figure 1**). But so far, trastuzumab emtansine (T-DM1) remains the only FDA-approved ADC for adjuvant treatment. T-DM1 showed significant benefit in HER2-positive early breast cancer over trastuzumab alone.[1] Building on this success, other ADCs are being explored in early settings. Several late-stage trials recently achieved positive outcomes and were given the spotlight at the ESMO 2025 Presidential Symposium.

First up, neoadjuvant trastuzumab deruxtecan (T-DXd) followed by taxane-based chemotherapy + trastuzumab + pertuzumab improved pathologic complete response in the DESTINY-Breast11 trial compared to the anthracycline-containing control arm (67% versus 56%, 95% confidence interval [CI] 4.0–18.3, P=0.003) while also showing reduced cardiac toxicity. Similarly, the DESTINY-Breast05 phase 3 trial demonstrated a significant reduction in recurrence or death by 53% with adjuvant T-DXd versus T-DM1 in high-risk patients with residual invasive disease after surgery and neoadjuvant treatment.[2]

The KEYNOTE-905 study in cisplatin-ineligible muscle-invasive bladder cancer further highlighted the potential of ADCs in curative-intent care. In this trial, enfortumab vedotin combined with pembrolizumab both before and after surgery significantly improved event-free survival by 60%, increased pathological complete response (57% versus 9%, 95% CI 39.5–56.5, P<0.000001), and reduced the risk of death by 50% compared with surgery alone.[3]

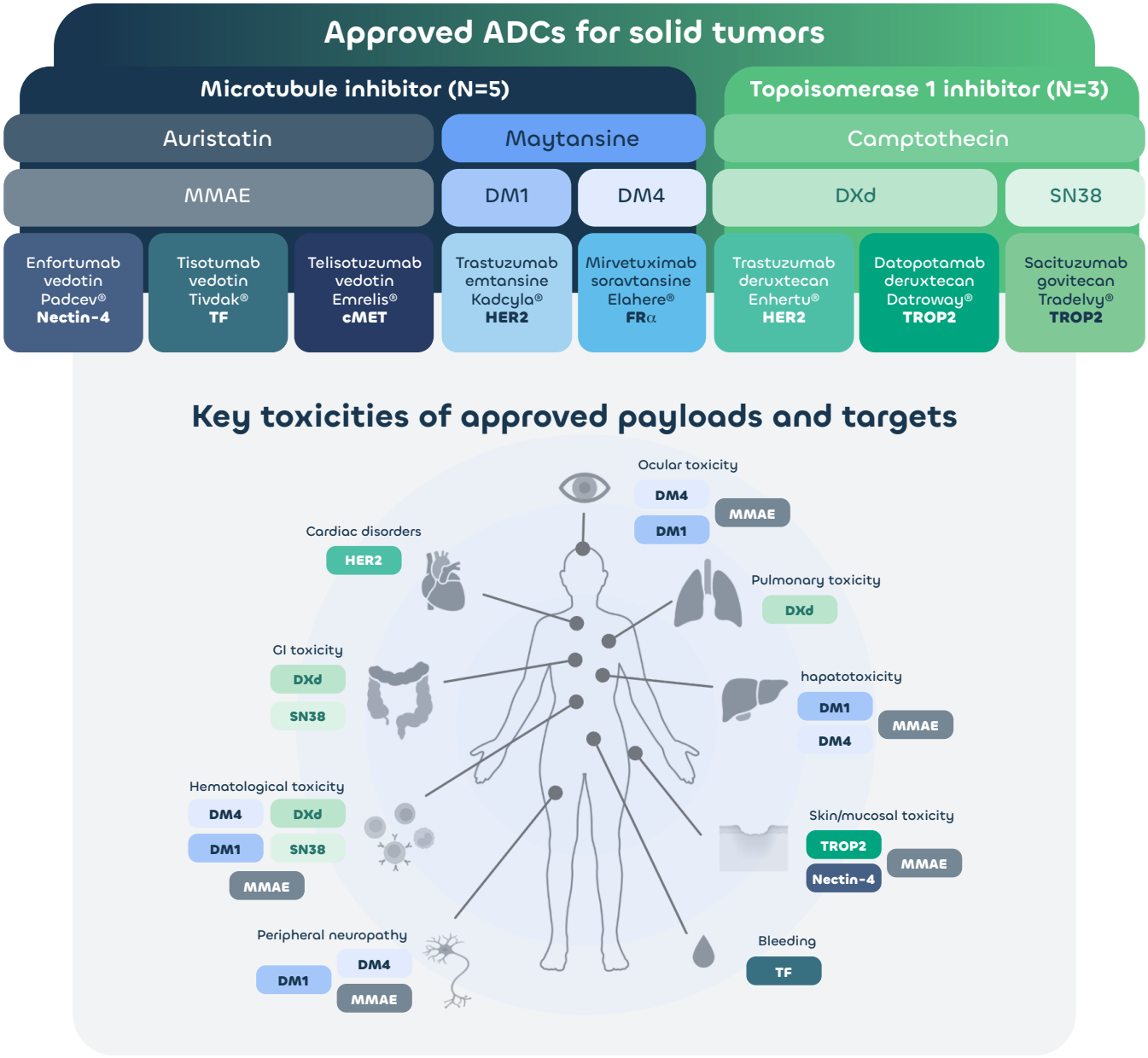


Figure 1. (**A**) Overview of approved ADCs for solid tumors and (**B**) key toxicities of approved ADC payloads and targets. All FDA-approved ADCs for solid tumors use one of two payload mechanisms. Abbreviations: cMET – Cellular mesenchymal-epithelial transition factor. DXd – Deruxtecan. FRα – Folate receptor alpha. HER2 – Human epidermal growth factor receptor 2. MMAE – Monomethyl auristatin E. TF – Tissue factor. TROP2 – Tumor-associated calcium signal transducer 2.

Novel targets and bispecifics are coming into sight

In addition, other clinical trial readouts demonstrated the expanding breadth of ADC targets and their potential in the treatment of cancer patients. For example, Tubulis' TUB-040, directed at NaPi2b, produced a 50% confirmed overall response rate in platinum-resistant ovarian cancer patients (N=46) with a median of four lines of prior therapy while exhibiting favorable tolerability.[4,5] The bispecific EGFR × HER3 ADC Izalontamab Brengitecan (Iza-Bren), co-developed by SystImmune and Bristol Myers Squibb, delivered a 55% overall response rate in an early trial in metastatic non-small cell lung cancer (N=20) and improved progression-free survival from 4.8 to 8.5 months versus chemotherapy in refractory nasopharyngeal cancer (N=234) with at least two prior lines of therapy, although hematologic toxicity requires further monitoring.[6,7]

A range of other clinical-stage ADCs directed at novel targets were presented, demonstrating continued growth in target innovation; however, almost all of these ADCs remain reliant on established payload classes.

Changing the target might not be enough

As ADCs move to earlier lines of therapy and the spectrum of available targets broadens, questions around optimal sequencing of ADCs become increasingly complex.

ADC resistance can occur when tumor cells reduce or alter antigen expression, as seen with HER2 in breast cancer or Nectin-4 in urothelial carcinoma.[8] Antigen-related resistance might be driven by downregulation, truncation or masking of the antigen. Tumor cells under treatment may also experience selective pressure, leading to the emergence of clones with reduced antigen expression. In these cases payloads with bystander effect would be of significant benefit. One example of the bystander effect compensating for heterogeneous antigen expression is seen in HER2-low breast cancers, where HER2-ADCs with appropriate payloads can still be effective. However, other mechanisms, including payload release by TME-specific proteases, may substantially contribute to ADC efficacy in tumors with heterogeneous antigen expression.[9]

In addition to antibody-related resistance, tumors can become resistant to the cytotoxic payload itself. Initial studies on sequential ADC use suggest that response duration diminishes when ADCs with the same payload class are administered one after another, even if their targets differ or other therapies are used in between (**Figure 2**).[10]

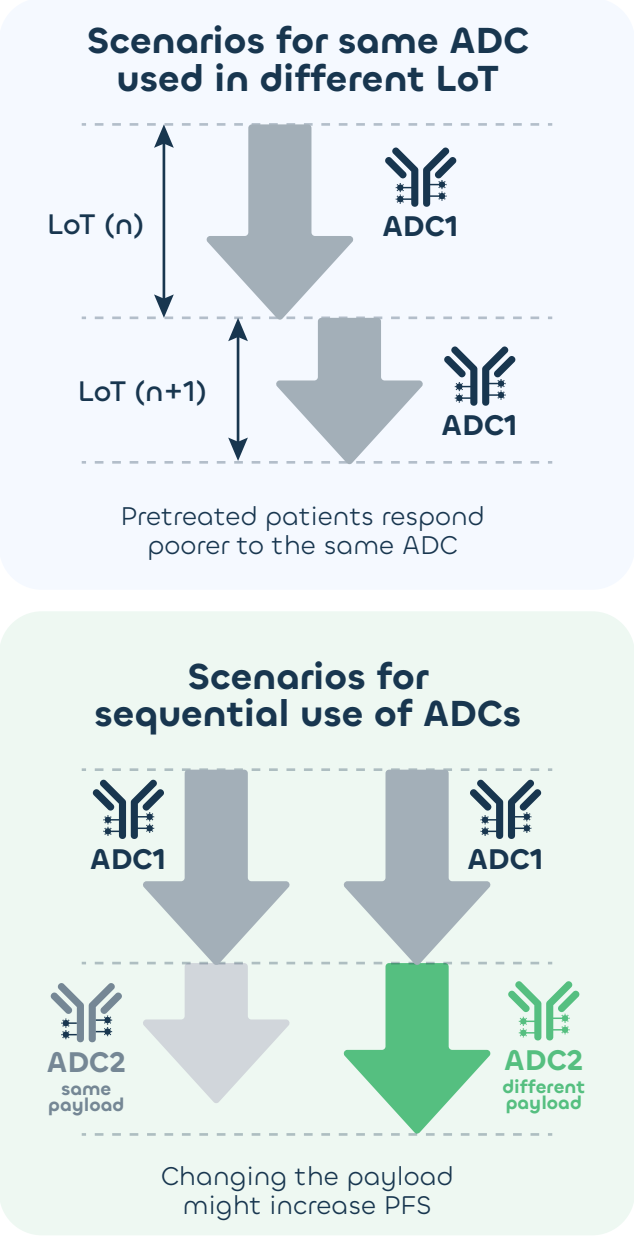


Figure 2. Schematic overview for different options to use ADCs sequentially. In general, using the same ADC sequentially reduces efficacy, while changing the payload may increase efficacy.

From chemotherapy, we have learned that resistance to certain cytotoxic agents can lead to greater cross-resistance within a chemotherapy class, reflecting the complexity of developing multi-resistant cancer phenotypes.[11] In these cases, switching therapeutic targets can overcome resistance by targeting alternative pathways.[12] Thus, adding a second ADC with a different payload class could benefit patients (**Figure 2**).[13]

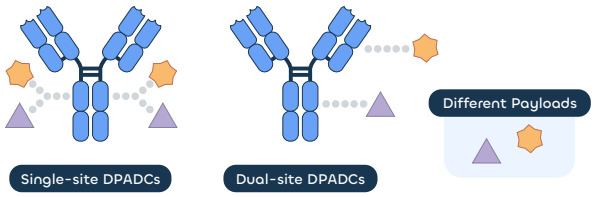
With current ADCs restricted to two payload classes, options for sequential use of ADCs in case of payload cross-resistance are limited. Accordingly, many sessions and discussions at ESMO 2025 highlighted the need for novel payload classes in addition to the expanded target portfolio.

Beyond ESMO 2025: What trends will be relevant in the future?

Dual-payload ADCs are developed to overcome resistance

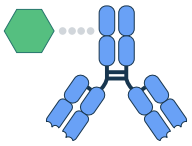
An increasing number of companies are addressing emerging ADC payload resistance by developing dual-payload antibody-drug conjugates (**Figure 3**).[14] This approach could boost therapeutic efficacy and potentially re-sensitize tumor cells to agents they have previously encountered through complementary and potentially synergistic mechanisms.[15] One of the most advanced dual-payload ADCs is KH815. KH815, developed by China-based Chengdu Kanghong, is composed of a humanized IgG1 antibody directed against the

Dual payload ADCs (DPADCs)



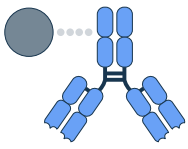
Dual payload ADCs are antibodies linked to two types of payload drugs—such as one TOP1 inhibitor and one ATR inhibitor. This approach could boost therapeutic efficacy and potentially re-sensitize tumor cells to agents they have previously encountered through complementary and potentially synergistic mechanisms

Cytotoxic payload beyond topoisomerase I or microtubule inhibitor



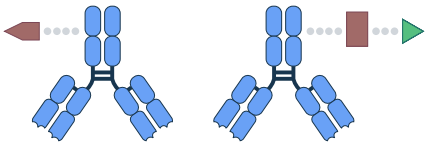
Multiple companies develop novel classes of cytotoxic payloads that have non-overlapping mechanisms of actions as compared to established payload classes. Most companies have not disclosed the exact mechanism.

Immunostimulatory antibody conjugates (ISACs)



Immunostimulatory antibody conjugates (ISACs) are antibodies linked with payloads that act as pattern recognition receptor (PRR) agonists (e.g. STING agonist). This approach might enhance the immune responses within the tumor microenvironment (TME) and further stimulate the adaptive immune system.

Degrader antibody conjugates (DACs)



Degrader antibody conjugates (DACs) are antibodies linked to targeted protein degraders—such as PROTACs or molecular glues. This approach might reduce toxicity associated with cytotoxic payloads.

Figure 3. Novel ADC payload classes in development.

clinically-established target TROP2 conjugated to a topoisomerase (TOPO1) inhibitor, as well as an RNA polymerase II inhibitor. This payload combination allows for the simultaneous inhibition of RNA synthesis and induction of DNA double-strand breaks. Preclinical data for KH815 indicate anti-tumor activity in a Triple-Negative Breast Cancer (TNBC) patient-derived xenograft model resistant to sacituzumab govitecan outperforming single payload TROP2-targeting ADCs such as datopotamab deruxtecan.[16] The program is now conducting its first-in-human trial, testing the approach in a clinical setting.

Another strategy, pursued by companies such as Crossbridge Bio and Callio Therapeutics, is the combination of a TOPO1 inhibitor with an ATR inhibitor. The scientific rationale for this approach is provided by preclinical data indicating that ATR inhibition could sensitize tumor cells to TOPO1 inhibitors.[17] Indeed, Callio's ADC CLIO-8221, directed against HER2, showed tumor regression in T-DXd insensitive and refractory preclinical models, demonstrating the potential of this approach.[18]

A potential limitation of dual payload ADCs is that many programs still rely on a TOPO1 inhibitor as their "anchor agent."[15] Depending on the specific mechanisms resulting in payload resistance, some tumors might not be re-sensitized and benefit from TOPO1 inhibitor-based dual payloads.[19] Moreover, adding two warheads to an ADC instead of one is not trivial and additional toxicities may arise from combining multiple payloads.

Novel payload classes are explored to expand the ADC arsenal

Several companies are now investigating entirely different classes of cytotoxic agents with non-overlapping mechanisms of action to address tumors that are resistant to existing ADC payloads while avoiding the added complexity of dual-payload designs. While some companies are turning to well-known cytotoxic drug classes that have not yet been deployed as ADC payloads, others are pursuing entirely novel mechanisms to expand the therapeutic possibilities of ADCs.

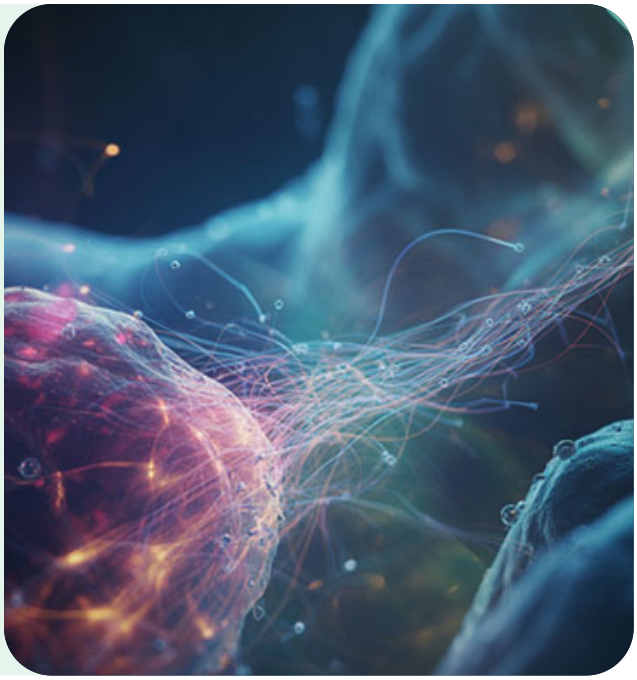
Byondis, for example, is developing antifolate-based ADCs.[20] Antifolates are a well-established class of chemotherapy agents that block key enzymes involved in folate metabolism, which in turn disrupts the production of the building blocks required for DNA and RNA synthesis, resulting in cell death.

Another strategy, leveraged by Hexagon Bio, involves protein translation inhibitor payloads. Preclinical data indicate that this approach may be able to overcome DXd payload resistance.[21]
An example of a completely novel approach includes N-myristoyltransferase inhibitors (NMTi) developed by Myricx Bio to target clinically validated cancer associated antigens B7-H3 and HER2.

Other new payload classes in development include immunomodulators, such as STING agonists and degraders, but many companies have not disclosed the exact payload mechanism they are planning to use (**Figure 3**). For any new payload class, safety profiles, therapeutic index, and the ability to overcome emerging ADC resistance will be key determinants of success in the evolving ADC landscape.

Conclusions

The data presented at ESMO 2025 reinforce that ADCs are cementing their role across earlier and potentially curative settings while continuing to expand into new biological space. As optimal ADC sequencing becomes increasingly complex, innovation in payload design will be essential to sustain clinical impact. The next wave of ADCs will be defined not only by what they target but by how effectively they overcome emerging payload resistance to deliver durable benefit.



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Janna Leiz, PhD, is an experienced consultant with a background in biochemistry, single cell transcriptomics, and genetic models of human disease. She conducted her doctoral research at the Max Delbrück Center for Molecular Medicine and Charité university hospital in Berlin.

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