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Antibody-drug conjugates: where are we now, where is it heading, and how can you get ahead of the opportunities and challenges with key stakeholders?

Since the first FDA approval of an antibody-drug conjugate (ADC) in 2011, the number of approvals within the drug class has increased dramatically, with 12 FDA-approved ADCs (see Figure 1, below) and at least 100 more in clinical trials [1]. ADCs hold great promise for the targeted treatment of cancer and the market for ADCs is expected to grow significantly in the coming years driven by the increasing incidence of cancer [2] and continued breakthroughs in ADC technologies opening doors to new tumor types. According to an analysis by GlobalData in March 2024, the global market for ADCs is expected to reach $15.3 billion USD this year, rising to exceed $40 billion USD by 2029 [3]. Even though considerable variability exists in 2030 projections across analysts' reports, it is clear that the ADC market is reaching an inflection point in sales [4,5].

Figure 1: Current FDA and/or EMA-approved antibody-drug conjugates (as of August 2024)

Product	Manufacturer	Target	Linker	Payload MOA	DAR	First Approved Indication	FDA Approval Date	EMA Approval Date
Adcetris	Seagen (Pfizer)	CD30	Protease-cleavable	Microtubule inhibitor	4	Hodgkin's lymphoma	2011	2012
Kadcyla	Roche	HER2	Non-cleavable	Microtubule inhibitor	3-4	Breast cancer	2013	2013
Besponsa	Pfizer	CD22	Acid-labile hydrazone	DNA damaging	5-7	ALL	2017	2017
Mylotarg	Pfizer	CD33	Acid-labile hydrazone	DNA damaging	2-3	AML	2017	2018
Enhertu	AstraZeneca / Daiichi Sankyo	HER2	Cleavable	DNA damaging	7-8	Breast cancer	2019	2021
Padcev	Astellas / Seagen (Pfizer)	Nectin-4	Protease-cleavable	Microtubule inhibitor	3.8	Urothelial cancer	2019	2022
Polivy	Roche	CD79b	Protease-cleavable	Microtubule inhibitor	3.5	DLBCL	2019	2020
Trodelvy	Immunomedics	TROP-2	pH-sensitive cleavable	DNA damaging	7.6	Breast cancer	2020	2021
Blenrep	GlaxoSmithKline	BCMA	Non-cleavable	Microtubule inhibitor	4	Multiple myeloma	2020	2020
Zynlonta	ADC Therapeutics	CD19	Protease-cleavable	DNA damaging	2.3	DLBCL	2021	2022
Tivdak	Seagen (Pfizer)	Tissue factor	Protease-cleavable	Microtubule inhibitor	4	Cervical cancer	2021	2024 (est)
Elahere	ImmunoGen	FRα	Cleavable	Microtubule inhibitor	3.5	Ovarian cancer	2022	2024 (est)

Source: CRA analysis

Below we highlight some of the key challenges faced by ADCs from the manufacturing, reimbursement, and clinical perspective.

What is the current R&D and clinical status of ADCs?

ADCs are formed of three core components: 1) the target: the binding site, 2) the payload: the effector agent that drives outcomes, and 3) the linker: the protein attaching the payload to the antibody. Each part is crucial in determining an ADC's clinical characteristics and much emphasis has been placed on these three dimensions by manufacturers in their communication strategies. However, several additional factors are showing increasing relevance in improving potency and reducing off-target effects (toxicity) as our knowledge of ADC science increases:

Antibody

- The choice of antibody in the design of ADCs dictates their specificity to the target, circulation half-life, immune function, and immunogenicity.
- Current ADCs are based predominantly on IgG1 due to its long serum half-life and strong Fc-mediated immune functions. Alternative IgG sub-classes, such as IgG3 may have greater immunogenicity but a shorter half-life.
- Where Fc-mediated binding is a concern and presents unwanted side-effects, IgG2 and IgG4 sub-classes can be employed. These sub-classes have a comparable half-life to IgG1 but a limited capacity for Fc-mediated effector functions and may be used in cases where potential for Fc-binding may lead to unwanted side-effects.

Drug-to-Antibody ratio (DAR)

- The number of payload molecules per antibody is crucial in determining ADC pharmacokinetics.
- Although a high DAR increases potency, it also increases off-target toxicity as well as risk of aggregation and rate of drug clearance, thus reducing circulatory half-life of the ADC.
- Currently, a DAR of 2-4 has been set as the clinical gold standard; however, newer ADCs have successfully employed novel linker chemistries to achieve DARs of 8, increasing the potency of ADCs while mitigating payload aggregation due to increased hydrophobicity. The result is a reduced potential for unwanted side effects that have historically been typical of such high DARs.

Bystander functionality

- The free drug, when released from the ADC, can either directly induce target cell death or be taken up by neighbouring cells to cause cell death (bystander killing), depending on the type of drug used. These cells may not necessarily express the target antigen and can therefore allow cell death in tumours where there is low or heterogeneous expression of the target, thus overriding the requirement for high and homogeneous target expression on tumour cells.
- The properties of the linker, and specifically whether it is cleavable, dictate whether the ADC will display bystander functionality.
- Despite the utility of non-cleavable linkers in mitigation of ADC instability in circulation, these linkers generally hinder the potential for bystander killing. Such linkers are therefore mainly effective for the treatment of tumours with high and homogeneous antigen expression.

- Furthermore, the mechanism of payload release from the ADC, when using non-cleavable linkers, may drastically modify the payload and adversely impact its cytotoxicity, justifying the broad use of cleavable linkers in current randomized clinical trials (RCTs).

As the ADC space becomes more competitive, manufacturers will need to drive differentiation by highlighting more aspects of the ADC's design and mechanism of action beyond target and payload to support their drug's scientific narrative and differentiation against competition. However, the ease of convincing stakeholders may vary considerably, particularly given their differing priorities and decision-making criteria.

What are the key current and future Medical Affairs considerations?

Selecting the right ADC, for the right indication, used at the right time

- ADCs are hypothesized to have synergistic effects with other targeted agents and chemotherapies.
- Increasingly, trial programs are looking into the effects of ADC treatment regimens being added to current standard of care options, including targeted therapies, chemotherapies and immune checkpoint inhibitors (ICIs).
- As has been the case with ICIs of the PD-(L)1 class, not all products have the same efficacy across tumor types, with variable results shown in clinical practice; this is likely to also be the case with ADCs.
- The added layer of complexity for ADCs used in combination is knowing when patients should receive the ADC relative to the backbone therapy and optimizing this to ensure maximum efficacy.

Selecting the appropriate combination partner for ADCs

- Considerable effort is being focused on understanding the optimal combination partner, or approach, for the use of ADCs, given the need for internalization by tumor cells to be effective. Importantly, the optimal combination partner is likely to be at a tumor-specific and disease progression-specific level, adding an additional layer of complexity for physicians.
- Ongoing studies are looking at combinations and sequencing with chemotherapies, targeted therapies, ICIs, endocrine therapies and radiotherapy to understand their combined or sequential impact on efficacy, as well as potentially additive effects on safety.
- Fundamentally, we are still in the infancy of ADCs taking a central role in oncology, with a paucity of evidence regarding how they should most optimally be used.

Managing dosage level to minimize toxicity and off-target effects

- The current first generation of ADCs exhibits a pronounced toxicity and tolerability profile that differs from other targeted therapies and ICIs.
- One of the quickest growing topics in ADC use among physicians is identifying how dosage level can be varied outside of the RCT setting to maintain efficacy but reduce the overall toxicity profile.
- As with previously novel treatments, such as the tyrosine kinase inhibitors (TKIs), physicians learned the value of varying dosage level, timing and capacity for treatment holidays; ultimately, the same is likely to be true for ADCs.

- However, at present there is a lack of evidence on how to optimize the ADC class to result in strong efficacy, but at a lower level of toxicity.

Expanding the role of patients in treatment choice

- ADCs are entering the market when multiple treatment options could be under consideration for patients in each line of therapy.
- Each approach can be characterised by its opportunities and risks in terms of response rate, potential efficacy upsides, toxicity profiles and impact on quality of life.
- The role of patients in the selection of their treatment approach is expected to increase in the non-curative, advanced stages of disease, where their priorities may not solely be driven by potential efficacy upsides.
- As a result, although ADCs are being shown to extend patients' lives beyond the current standard of care, the broader role of patient choice may not always translate into preferential selection due to safety and tolerability.

What are the key current and future commercial considerations?

Driving familiarity and prescribing preference

- As with any new technology, physicians have shown heterogeneity in their willingness to prescribe ADCs to their patients, given the lack of familiarity with their use, particularly in solid tumors, which are a newer frontier for ADCs. Such a pattern of use is not unexpected, as it was also seen for ICIs on their first use in solid tumors.
- However, what is most striking is likely to be the geographic variability in physicians' comfort in prescribing ADCs; particularly in markets that currently do not have access to them.
- Although advances in understanding of the use of ADCs in the US will be of benefit to physicians in other countries, the lack of real-world exposure to these products could lead to prolonging headwinds in gaining traction and growing share in other markets. This problem is exacerbated in markets where combination therapeutic approaches are not possible, due to cost issues, adding an additional barrier to uptake.

Pivoting the value story

- While ADCs have demonstrated significant advantages in response rate, duration of response and prolongation of life over previous treatments, physicians are increasingly emphasizing preservation of patients' quality of survival. This places an emphasis on the tolerability of the product and the types of side effects experienced by patients.
- Typically, these interventions are in the non-curative, advanced stage of tumor progression; therefore, emphasis shifts to prolonging patients' comfort and Eastern Cooperative Oncology Group (ECOG) status, while managing the symptoms created by the tumor. This can result in adverse events such as peripheral neuropathy becoming a key consideration, due to its impact on a patient's day-to-day independence and quality of life.
- Manufacturers of current non-ADC therapeutic options are likely to tailor their value story to accentuate the toxicity shortcomings of ADCs, which could resonate with physician, patient and payer stakeholders. ADC manufacturers will need to ensure their value stories and objection handling materials have a significant focus on this element, given the likely targeting of the competition.

- Given the potential for increased patient empowerment in decision making, it may be necessary to develop patient value stories, focusing on demand pull-through from patients, and not just on physician prescribing preferences.

What are the key current and future reimbursement and access considerations?

Valuation of the benefits of ADCs relative to other options

- Payers largely remain driven by the magnitude of survival improvement demonstrated in RCTs in the advanced and metastatic stages of cancer, with other considerations such as quality of life and toxicity profiles largely being secondary drivers. However, this narrow view of what defines “efficacy” for payers presents challenges for novel ADCs, as well as favoring some of their advantages.
- Some ADCs benefit from this view, given their demonstrated improvements in overall survival in multiple RCTs.
- Overall response rate (ORR) is also a key positive differentiator for ADCs, which are broadly higher than ICI monotherapies; however, response rate is typically not accredited with value in the majority of health technology assessments (HTAs) and pricing processes in solid tumors.
- Currently, ADCs are benefitting from the “narrower” view of outcomes that place less emphasis on quality of life and the safety / tolerability profile of drugs, if they do not in themselves cause mortality. However, should this change, and safety and quality of survival are afforded a higher value in HTA processes and value demonstration, manufacturers will need to adjust their access strategies to account for such changes in viewpoint.

Further squeezes on combination costs

- In solid tumors, ADCs are more frequently under development alongside “backbone” therapies, including ICIs and targeted therapies, which are often higher-cost, branded products.
- Currently, combination reimbursement status shows considerable heterogeneity across developed and developing markets, given multiple concerns regarding pricing and cost.
- Therefore, many of the challenges that face non-ADC combination regimens remain in place for novel ADCs and are exacerbated when factoring in the higher prices that are sought for ADCs by manufacturers.

Tolerability and impact on discontinuation

- Owing to the use of potent cytotoxic agents in their design and their imperfect mechanisms of targeting tumour cells, most ADCs are associated with unique adverse event profiles, such as pneumonitis, interstitial lung disease, and neuropathies.
- Toxicity-related discontinuation has been an issue for several of the current ADCs, wherein patients do not receive the full course of therapy, resulting in sunk costs for payers without realizing the ADC’s potential efficacy outcomes.
- Current toxicity data for ADCs has sometimes led to payers viewing them as akin to “targeted chemotherapy”, with a similarly detrimental adverse event profile as the older, non-specific agents. These side effects may warrant additional monitoring and/or treatment, adding an additional level of complexity in understanding the total indirect costs associated with the use of an ADC, relative to other targeted options.

- The fact that this uncertainty exists for payers can lead to more cautious approaches to pricing or add significant time to reimbursement delays, particularly in budget impact-focused markets where value-for-money is a focus.
- Future ADCs will need to demonstrate improvements in this area if they are to overcome perceptions generated by the first generation of ADCs and will ideally show a reduction in the rate of treatment-related discontinuation.

ADCs are set to play a pivotal role in the evolving management of oncology, as shown by the scale of outcomes delivered by early launches. It will be important for manufacturers to take a broad, cross-functional view of how best to position ADCs for medical, commercial and pricing success, leveraging synergies where possible to address stakeholders' key concerns.

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