White Paper

Breaking New Ground: Advancing Cancer Care with Novel Therapeutic Modalities

Deep dive: Antibody drug conjugates, bi-/multi-specifics and radioligand therapies

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Introduction

Oncology continues to be a hotbed of innovation, with over 100 new cancer treatments expected to launch in the next five years alone. This frantic activity makes oncology one of the key growth engines of the biopharmaceutical industry and underpins its status as the dominant therapy area, generating $223 billion of global sales in 2023, at ex-manufacturer prices.[1]

Beyond the sheer scale of the innovation effort, oncology also finds itself at the forefront of transformational, therapeutic breakthroughs where different trends and technologies intersect, for example:

- Harnessing the power of the immune system, e.g., via next-generation checkpoint inhibition, T- and NK-cell therapies or therapeutic cancer vaccines
- Genome-targeted therapies and biomarker-based stratification to enable ever greater molecular precision and personalisation
- New modalities that combine different mechanisms of action to enable novel, targeted approaches offering superior efficacy/safety profiles with broader therapeutic windows, e.g., antibody drug conjugates to deliver toxic payloads with precision, radioligand therapies making radiotherapy more precise, or molecular glues, ligand-directed degraders and degrader antibody conjugates to utilise cells' protein homeostasis in the fight against cancer[2]

In this white paper, we will provide a latest outlook on the dynamic innovation landscape in oncology and take a deep dive into antibody drug conjugates, bi-/multi-specific antibodies and radioligand therapies as highlights of cutting-edge innovation.

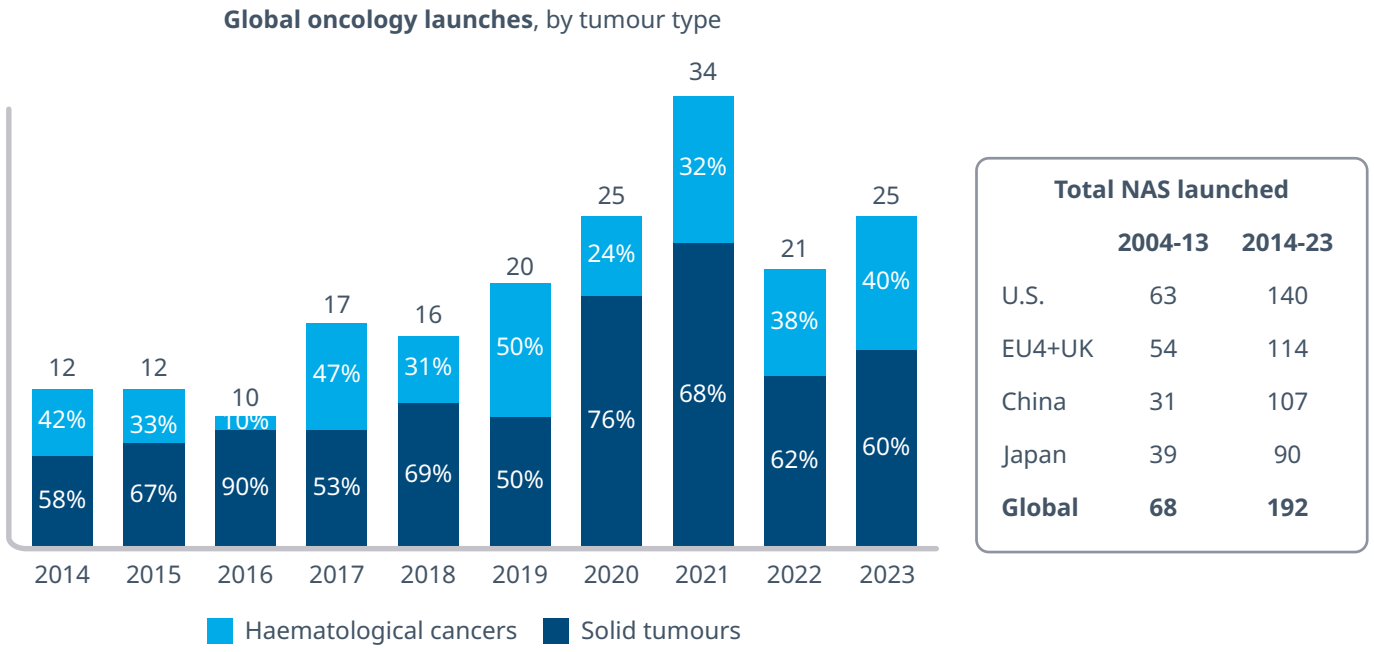
Innovation momentum in oncology accelerates

Over the past two decades, innovation momentum in oncology has accelerated dramatically, driven by a deeper understanding of the underlying disease aetiology, the expansion of genomics and biomarkers, and the emergence of novel modalities.

At the same time, regulators have become more flexible in their requirements to accelerate patient access to innovative therapies, given the high unmet need in oncology, for example accepting a higher degree of uncertainty at the time of regulatory approval, e.g., based on less mature data from single-arm trials, or surrogate endpoints.

Regulatory approaches continue to evolve to speed up innovation reaching patients, e.g., Project Endpoint and Project Frontrunner, initiated by the FDA's Oncology Center of Excellence, to advance the development and use of novel oncology endpoints, and to facilitate the approval of new therapies for advanced or metastatic disease in an earlier clinical setting, respectively.[3,4]

Figure 1: Global oncology launches of novel active substances (NAS)



Total NAS launched

	2004-13	2014-23
U.S.	63	140
EU4+UK	54	114
China	31	107
Japan	39	90
Global	**68**	**192**

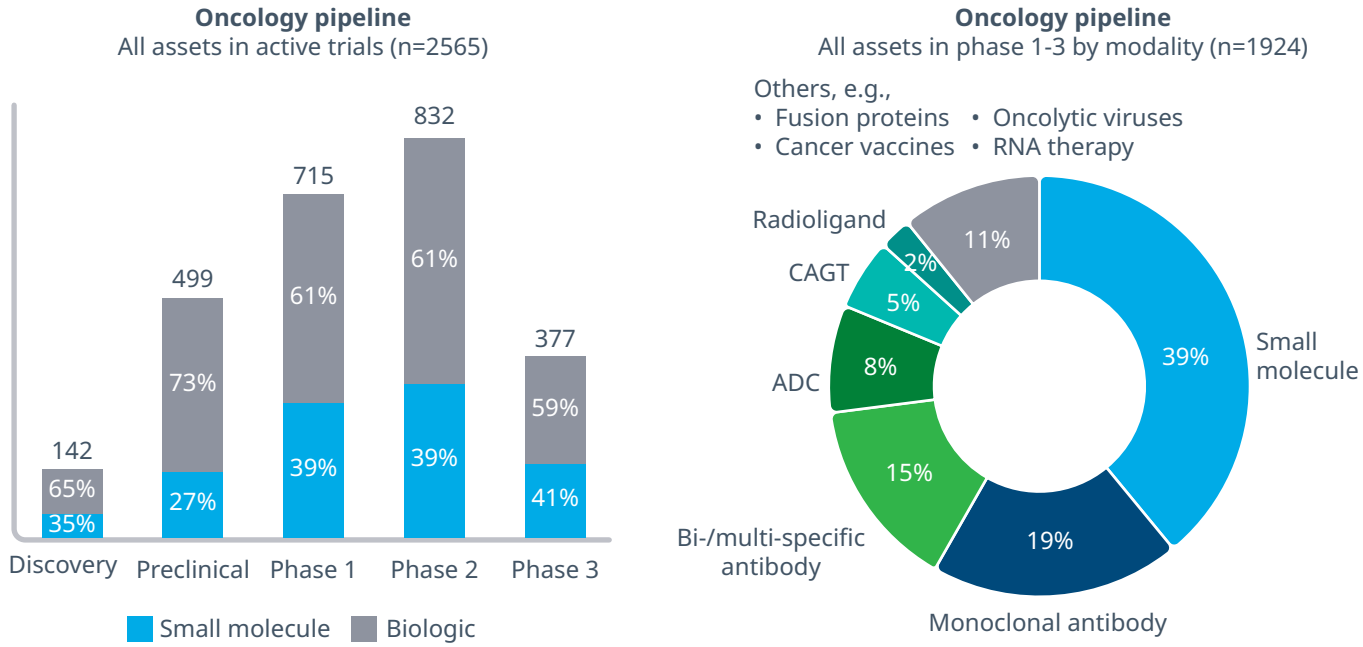
Source: Citeline Trialtrove, IQVIA Institute report Global Oncology Trends, Jan 2024

Between 2004 and 2013, a total of 68 novel active substances (NAS) were launched globally in oncology. That number increased nearly threefold for the time period of 2014-2023, which saw a total of 192 global oncology NAS launches. Within that decade, the annual number of global oncology NAS launches doubled from 12 in 2014 to 25 in 2023, with NAS launches targeting solid tumours accounting for the majority in all but one year (see Figure 1). Looking ahead to the next five years, we expect over 100 new cancer treatments to enter the market.

This extraordinary stream of launches is fuelled by a rich global oncology pipeline which comprises 2,565 assets, from discovery through phase 3. Clinical-stage oncology assets in industry-sponsored trials are split roughly 60/40 between biologics and small molecules. Among biologic therapies in clinical development, monoclonal antibodies, bi-/multi-specific antibodies, and antibody drug conjugates (ADCs) are the top 3 modalities, representing 19%, 15% and 8%, respectively, followed by cell and gene therapies in fourth place, at 5% (see Figure 2).

Looking ahead to the next five years, we expect over 100 new cancer treatments to enter the market.

Figure 2: Oncology R&D pipeline



Abbreviations: CAGT = Cell and Gene Therapies; ADC = Antibody-Drug Conjugate; Source: IQVIA Analytics Link July 2024

Health policy and cost containment measures can direct the future focus of innovation efforts. For example, under provisions of the Inflation Reduction Act for Medicare drug price negotiations, biologics are currently treated differently vs. small molecule drugs, with the former being protected from negotiations for 13 years from approval, while small molecule drugs are exempt for 9 years. This disparity was cited by Pfizer as a key consideration for decisively shifting the focus of its oncology pipeline away from small molecule assets towards biologics, including ADCs and bi-specifics.[5]

For the past decade, oncology has been the dominant therapy area in focus of clinical trials, with a share of 44% of all trial starts in 2023, up from 33% in 2014.[6]

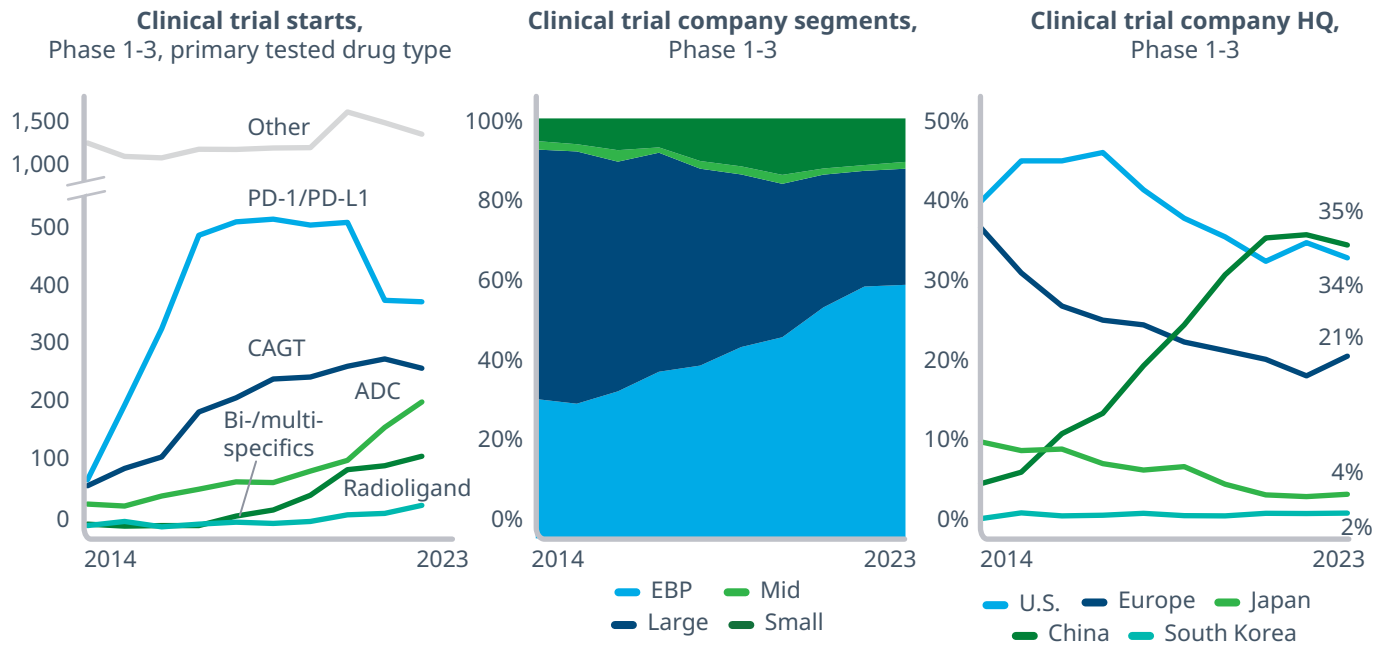
The emergence of novel modalities, including cell and gene therapies, ADCs, bi-/multi-specific antibodies and radioligand therapies, is reflected in recent trends in clinical trial activity, which has seen a steep increase in the number of oncology trial starts in those areas. Collectively, those four modalities have risen to 27% of oncology trial starts in 2023.

While PD-1/PD-L1 checkpoint inhibitors still accounted for over 300 industry-sponsored trials initiated in 2023, or 15% of all oncology trial starts, they have been on a downward trajectory in recent years. This is a reflection of an increasingly crowded and maturing checkpoint inhibitor market, prompting innovators to focus elsewhere, e.g., next-generation immuno-oncology targets, such as LAG-3, TIGIT or TIM-3.

Achieving long-term survival requires combination approaches to overcome resistance and deliver a deep and durable response, e.g., via a multi-modal attack on different cancer pathways to target multiple vulnerabilities, while optimising a regimen's tolerability and safety profile. The rise of combination therapies has led to a dramatic increase in the complexity of the oncology innovation landscape.

Emerging biopharma companies have become the dominant company segment among industry sponsors of oncology trials, nearly doubling their share of trial starts in ten years, from 33% in 2014 to 60% in 2023, at the expense of big pharma sponsors who saw their share of trial starts halving, from 59% to 28%, over the same time period (see Figure 3).

Figure 3: Oncology clinical trial activity



Abbreviations: CAGT = Cell and Gene Therapies; ADC = Antibody-Drug Conjugate; EBP = Emerging Biopharma
Source: Citeline Trialtrove, IQVIA Institute report Global Oncology Trends, Jan 2024; IQVIA EMEA Thought Leadership analysis

Meanwhile, China-headquartered companies have emerged as a major source of oncology innovation, with a share of 35% of oncology trial starts in 2023, up from just 5% a decade ago and now surpassing companies based in both the US and EU4/UK on this metric.

In our deep dive section further below, we will elaborate in more detail on key trends in three areas – ADCs, bi-/multi-specific antibodies, radioligand therapies – which are at the forefront of oncology innovation.

The competitive landscape in oncology and deal activity

High, persistent unmet patient need and the prospect of participating in an exceptional growth opportunity has attracted almost all of the top 20 pharma companies to oncology, as well as numerous small, mid-size and emerging biopharma companies, with many seeking a presence in novel modalities (see Figure 4).

AstraZeneca is an interesting case in point illustrating the critical role oncology innovation plays in many companies' future strategies. In its recently announced 'Ambition 2030 and beyond', AstraZeneca sets out a bold vision for delivering $80 billion in total revenue by 2030, and sustained growth thereafter.[7]

Achieving this bold ambition relies on delivering significant revenue growth from its existing portfolio, including several flagship oncology brands with Calquence, Enhertu, Imfinzi and Tagrisso, combined with launching 20 new molecular entities by 2030, again comprising several oncology assets, e.g., Dato-DXd, camizestrant, saruparib, volrustomig, rilvegostomig, among others. Sustained growth beyond 2030 will be supported by investment in transformative new technologies and platforms. Among those disruptive technologies AstraZeneca calls out several novel modalities in oncology, including ADCs, radio-conjugates, next-generation immuno-oncology bispecifics, cell therapies and T-cell engagers.

Oncology also provides fertile ground for emerging biopharma companies (EBPs). Reflective of their increasing share of oncology trial starts, EBPs originated 63% of new oncology drugs that were launched in the US over the past 5 years.

Furthermore, the unique features of oncology, e.g., high unmet need, comparatively compact go-to-market infrastructure requirements, make self-commercialisation a real possibility for EBPs that maximises the value they can capture from their assets vs. partnering or licensing agreements. Indeed, over the past 5 years, EBPs launched 57% of their own products in the US market.[1]

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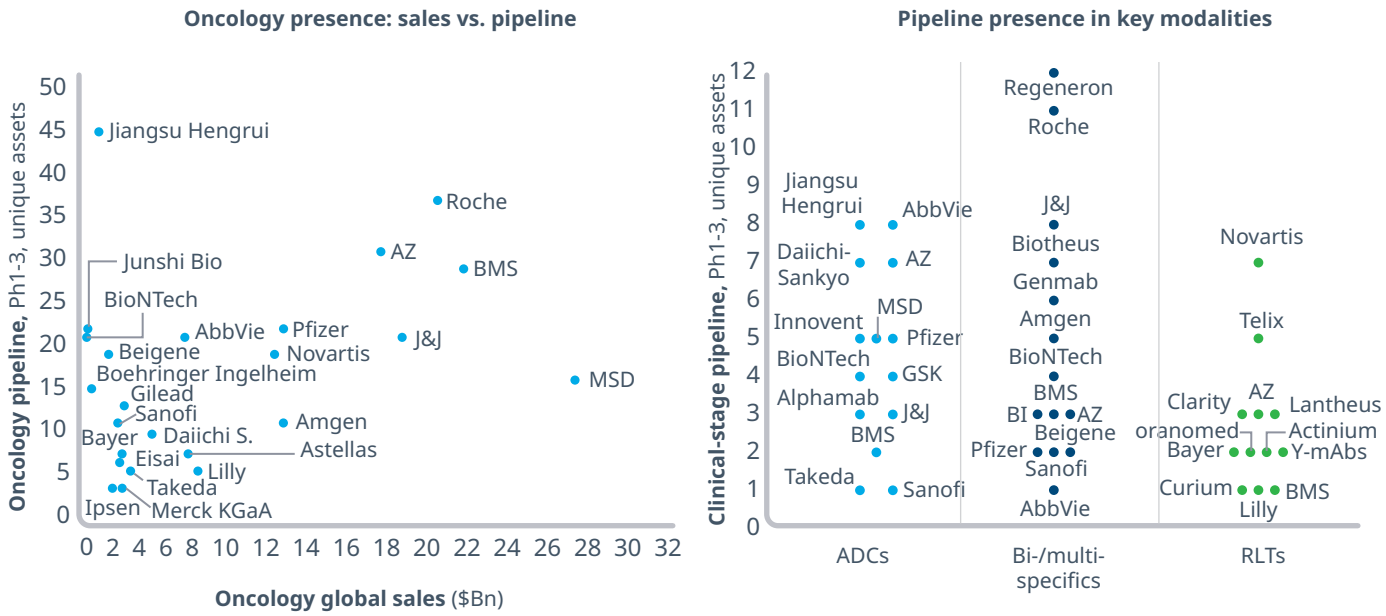
Figure 4: Competitive landscape — selected companies



Source: IQVIA MIDAS Q1 2024; IQVIA Analytics Link July 2024; desk research; IQVIA EMEA Thought Leadership

Deal activity

Despite the option of self-commercialisation, many EBPs choose the M&A route to crystallise value for their investors, especially following positive clinical trial results. As we discussed elsewhere, oncology offers the most favourable risk-reward profile among all therapy areas in how financial markets respond to positive vs. negative clinical news, while phase 2 readouts represent a pivotal value inflection point in the asset journey and a unique opportunity for EBPs to lock in substantial deal value.[8]

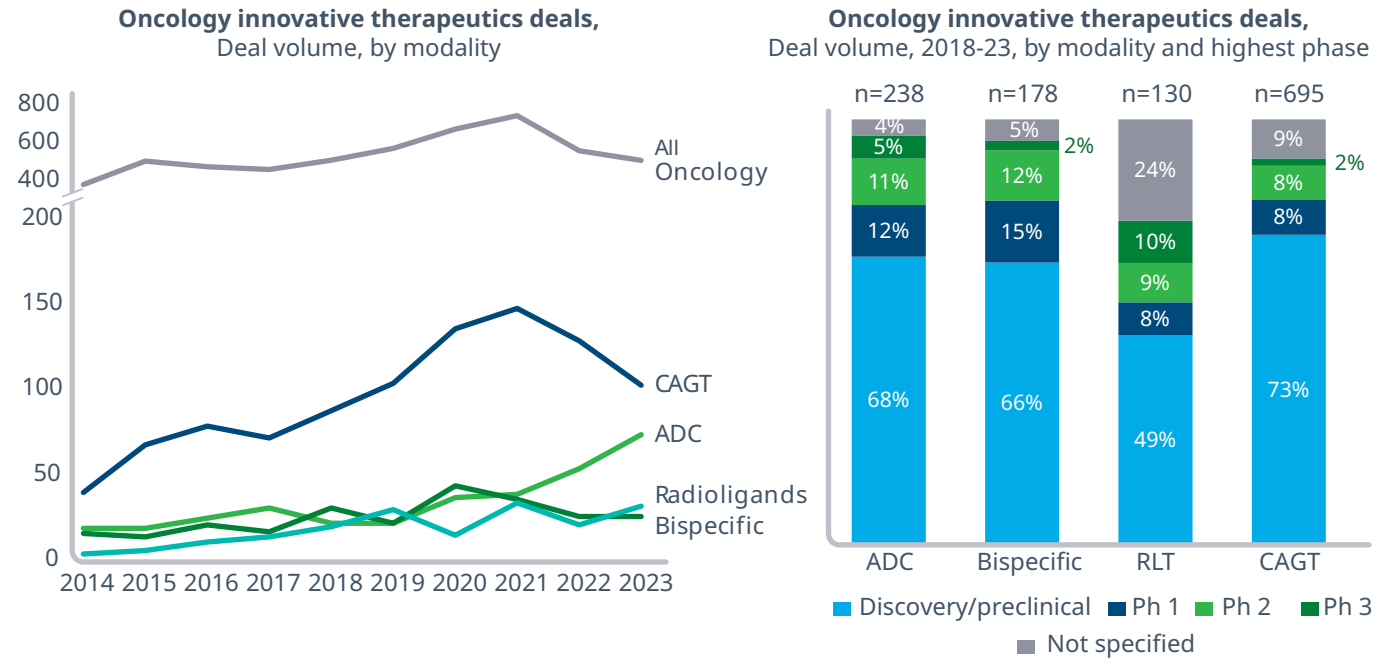
As many big pharma companies seek to expand their oncology presence and gain access to novel technology platforms, oncology unsurprisingly continues to be the leading therapy area for dealmaking, as it has been for the past 5 years, representing 40% of all asset-focused transactions in 2023.[9]

The number of oncology deals related to key novel modalities has grown in the past 5 years, with ADC deal volume surging more than threefold, while radioligand therapy focused deal volume increased by 60% over this time period. Cell and gene therapy deal volume reached a peak in 2021, up by 70% from 2018, but it has since declined by 31% (see Figure 5).

Interestingly, assets and technology platforms at discovery- and pre-clinical stage account for the largest share of transactions, ranging from 49% to 73% across the four novel modalities in focus. Arguably, this reflects the novelty of these modalities, with many nascent assets, but it also indicates dealmakers' appetite for risk to secure access to these transformative technologies. This contrasts with a broader trend of risk aversion that we observed among biopharma dealmakers in recent years, with a clear preference for de-risked, later-stage assets.[10]

Novel oncology modalities were the focus of several high-profile deals in recent years, e.g., the $43 billion acquisition of Seagen by Pfizer[11] centred on the former's ADC platform, while radiopharmaceutical platforms were the driver of the $4.1 billion acquisition of RayzeBio by BMS[12] and the $1.4 billion acquisition of Point Biopharma by Lilly.[13]

Figure 5: Oncology deal activity by modality



Note: Includes M&As, product deals and excluding generics
Source: IQVIA Pharmadeals July 2024; IQVIA EMEA Thought Leadership

Deep Dive: The promise of new modalities

In this section we will elaborate in more detail on three areas – ADCs, bi-/multi-specific antibodies and radioligand therapies – as examples of the promise of cutting-edge oncology innovation.

I. Antibody drug conjugates

Antibody-drug conjugates (ADCs) have emerged as a significant advancement in the realm of precision oncology by combining the specificity of monoclonal antibodies with the potency of cytotoxic drugs through specialised chemical linkers.[14] This maximises the anti-tumour effect while limiting the systemic exposure to the cytotoxic agent, thus reducing adverse side effects typically associated with chemotherapy.

ADCs themselves are not a novel concept. The first pioneering ADC, Mylotarg, was approved already in 2000. Today, fifteen ADCs are approved globally and have demonstrated superior clinical profiles in both solid and haematological cancers.[1]

ADCs and their success, both clinically and commercially, make them a very attractive investment case for pharmaceutical companies. In 2023, ADCs alone accounted for 80% of oncology deal value according to IQVIA Pharma Deals. As discussed earlier, the total number of deals involving ADCs increased sharply over the past ten years (see Figure 5).

Moreover, 857 ADC clinical trials were started in the past decade, making ADCs the fastest growing area among oncology trials.[1] As of July 2024, there are 204 industry-sponsored ADC drug development programs underway, from discovery through phase 3 (see Figure 6). Most assets target solid tumour indications, with 80% of ADC trials focused on solid cancers.[1]

HER2 is the leading target in the clinical-stage ADC pipeline, followed by TROP2 and B7-H3. Typically, ADC targets are highly expressed tumour antigens like HER2 or TROP2 that are found in many solid cancers and can promote tumour growth. However, this dogma was challenged by the pivotal clinical data for Enhertu (trastuzumab-deruxtecan) which demonstrated impressive efficacy in patients with low and, most recently, ultra-low expression of HER2.[15,16]

While established targets remain a key focus, the ADC pipeline indicates considerable interest from innovators in exploring novel targets, with over 30 distinct targets currently in development.

Payloads of approved and currently developed ADCs can be broadly categorised in microtubule inhibitors, topoisomerase I (Topo-1) inhibitors and DNA damaging agents, which account for 41%, 38% and 9% of the clinical-stage ADC pipeline, respectively.

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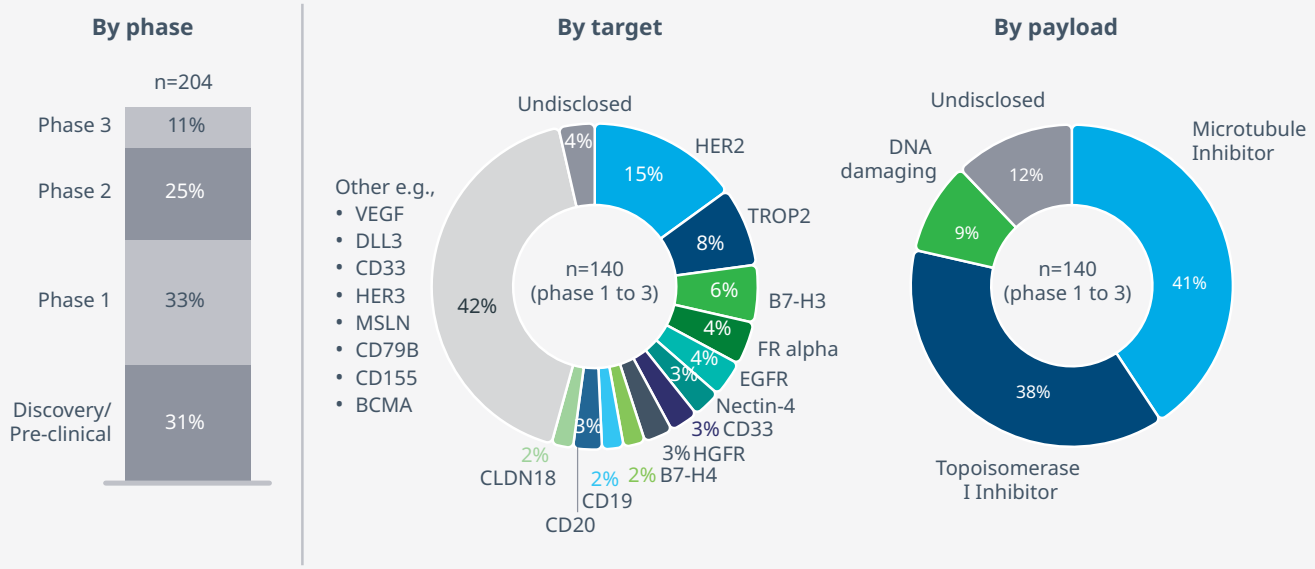
Figure 6: ADC development pipeline



Source: IQVIA Analytics Link July 2024; industry-sponsored R&D pipeline

AstraZeneca's and Daiichi-Sankyo's Enhertu (trastuzumab-deruxtecan) and Gilead's Trodelvy (sacituzumab-givotecan) pivoted away from established payloads used in earlier ADCs, which primarily relied on payloads based on microtubule inhibitors or DNA damaging agents. Instead, they utilised Topo-1 inhibitors that interfere with DNA replication and ultimately lead to cell death. This was a bold move, because Topo-I inhibitors were thought to be far less potent and had seen a string of failures among earlier ADC programmes.[17]

Topo-I inhibitor deruxtecan (DXd) is a derivative of exatecan which, unlike its original form, can be conjugated to an antibody while retaining its efficacy. The DXd platform is now tested in several ADC programmes spanning a range of targets, e.g., TROP2, HER3 or B7-H3.

The future direction for ADCs

Next-generation ADCs will evolve around innovation in the antibody target, its payload and linker chemistry aiming to balance potency with a manageable side effects profile. In addition to changing target, payload, or linker on its own, innovators are testing both novel target/payload combinations or improve established ones:

- **Targets:** Advances in our understanding of cancer biology has led to the identification of many underexplored targets expressed by tumours. For example, Immunome chose to partner with Nectin to gain access to antibodies directed against a potentially first-in-class target. Nectin's most advanced asset is currently undergoing a phase 1 trial in solid tumours and is targeted against the immune checkpoint CD155.[18] Targets not associated with the cancer but with the tumour microenvironment (TME) provide another potential avenue for ADCs. Pyxis Oncology PYX-210, for example, targets fibronectin extra-domain B (ED-B), a protein associated with the TME of many solid cancers.[19]

  Bispecific ADCs (bsADCs) are an exciting approach amalgamating the merits of both modalities. This approach could overcome challenges around off-target toxicity but comes with a trade-off around target selection. Development is currently focusing on HER2, cMET and EGFR.[20] Zymeworks' HER2xHER2 dual targeting bsADC lead asset zanidatamab zovodotin showed very encouraging results in a phase 1 study.[21] A bsADC including a binding site of an immune checkpoint inhibitor might be a promising target combination to explore.

- **Payload:** The cytotoxic agent landscape of ADCs is constantly evolving. The combination of ADCs with targeted protein degraders could achieve target specificity and efficacy not seen before. In this approach, the payload triggers degradation of cancer-related proteins using the cell's own machinery. Large pharma has already moved into this field and pursued deals with biotechs to gain access to degrader ADC (DAC) platforms. Although preclinical, Orum Therapeutics DAC ORM-5029 demonstrated similar anti-tumour activity as Enhertu with a first-in-human phase 1 study ongoing.[22]

  Dual payloads can improve potency and overcome issues around tumour heterogeneity and drug resistance. Such a two-pronged approach may include two different cytotoxic agents or, more ambitiously, payloads with completely different MoAs. Hummingbird Bioscience recently presented encouraging preclinical data on their dual-payload ADC technology.[23]

- **Linker** chemistry is crucial as it physically attaches the toxic payload to the antibody until its release when binding to cancer cells. Therefore, an ADC's therapeutic profile is largely determined by its linker.[24] Unsurprisingly, innovators carefully guard their linker technology, with limited details shared publicly. Cleavable linkers dominate among approved ADCs and exploit the TME to ensure selective delivery of the payload at the tumour site only. Next-generation linkers will focus on improving ADC stability during blood circulation, maintaining payload capacity whilst keeping manufacturing complexity manageable.

Antibody-drug conjugates have established themselves as valuable, targeted therapeutic options with the potential to supplant traditional, non-specific chemotherapy. Having taken centre-stage in oncology R&D efforts, future advances in ADCs will likely see their utility expand into earlier lines of therapy and earlier stages of disease.

Next-generation ADCs will evolve around innovation in the antibody target, its payload and linker chemistry aiming to balance potency with a manageable side effects profile.

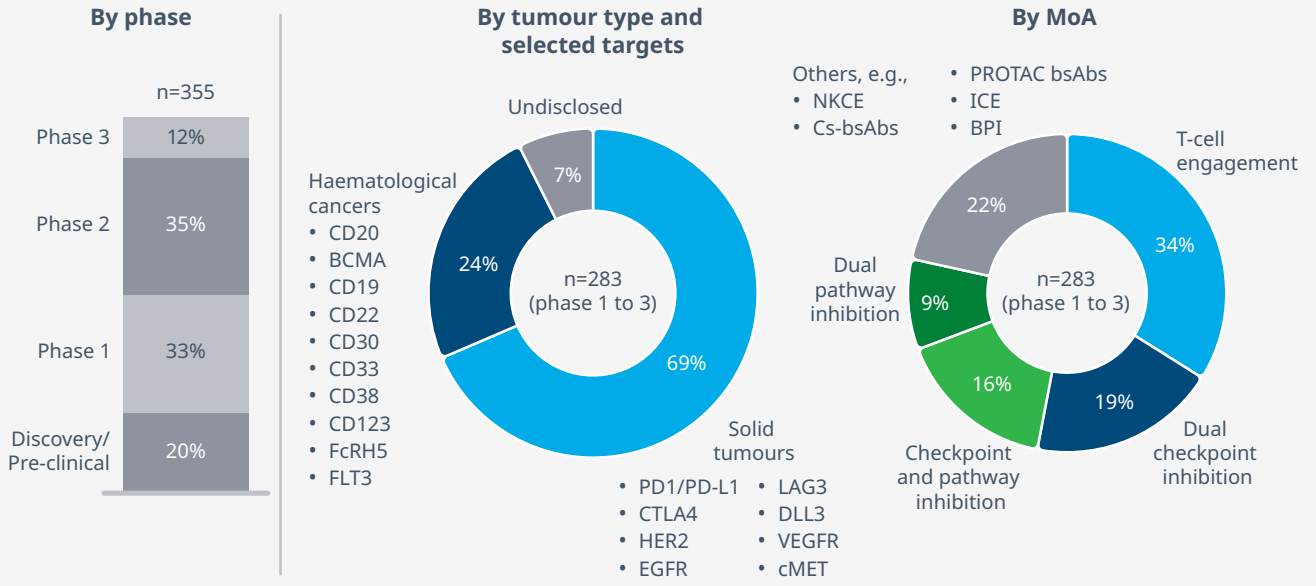
II. Bi-/multi-specific antibodies

Bispecific antibodies (bsAbs) with their versatile modes of action (MoA) rapidly expanded the oncology toolkit to help patients with hard-to-treat cancers. The world's first bsAb catumaxomab was already approved in 2009 but was later withdrawn from the market for commercial reasons. Today, ten bsAbs are approved for cancer immunotherapy across the U.S., EU, and China, with nine approvals happening in the last three years (2020-2023) alone, illustrating their growing importance as a class of novel biologic therapeutics.[25]

Bispecific antibodies come in many flavours and can be broadly categorised into combinatorial and obligate. Combinatorial bsAbs inhibit two targets at once, for example, two receptor tyrosine kinasases (RTKs) or two immune checkpoint inhibitors (ICIs), in the case of Rybrevant (amivantamab) and Kai Tan Ni (cadonilimab), respectively. In contrast to combinatorial bsAbs, where each binding activity can function independently, obligate bsAbs depend on the sequential action of both target-antigen binding. T cell-engaging antibodies like Blincyto (blinatumomab) enhance tumour killing by redirecting T-cells to tumour cells.[26] T cell engagement (TCE) is the pre-dominant MoA in cancer immunotherapy today, accounting for eight of the ten approved bsAbs.

The ten bsAbs on the market today signify just the beginning, as interest in developing a new wave of bsAbs is growing strongly. The current R&D pipeline for bi-/multi-specific antibodies comprises 355 assets from discovery through phase 3, which explore over 50 different target combinations and multiple MoAs across both solid and haematological tumours (see Figure 7).

Figure 7: Bi-/multi-specific development pipeline



Abbreviations: NKCE – Natural Killer Cell Engagers; ICE – Immune Cell Engagers; Cs-bsAbs – Co-stimulatory bispecific antibodies; BPI – biparatopic pathway inhibition; PROTAC - proteolysis targeting chimeras;
Source: IQVIA Analytics Link July 2024; industry-sponsored R&D pipeline

Solid tumours are the focus of clinical development, at 69%, despite in the past having proven to be more difficult to treat with bispecifics compared to blood cancers, which represent 24% of the pipeline. Leading targets being investigated for solid tumours include immune checkpoint inhibitors, such as PD1/PD-L1, CTLA4 or LAG3, RTKs and factors involved in angiogenesis.

In bsAbs directed at haematological malignancies one arm binds to tumour-associated antigens (TAAs) while the other arm typically binds to CD3 on the surface of T-cells. Some of the most common TAAs include CD20, BCMA or CD19.[27]

Most bsAbs in clinical development act via T cell-mediated cytotoxicity, overcoming checkpoint inhibition, tumour pathway inhibition or a combination of checkpoint/pathway inhibition. T cell engagement (TCE) has already proven successful and remains a major area of interest in the field. Unsurprisingly, TCEs are the leading MoA in the clinical-stage pipeline for bi-/multi-specifics, with a share of 34%.

Blincyto was approved in 2014 for the treatment of B cell precursor acute lymphoblastic leukaemia (B-ALL). However, its use was hampered by requiring continuous infusions because of the antibodies' short half-life. Several TCEs faced similar issues and consequently failed in early clinical development.[28] Today, most recently developed TCEs have half-lives and pharmacokinetics comparable to monoclonal antibodies. TCEs are available off-the-shelf, combine good clinical efficacy with a favourable safety profile and are being investigated in earlier lines of therapy. Therefore, they are expected to become an increasingly promising alternative to CAR-T-cell-therapies.[29]

Immune checkpoint inhibitors have transformed cancer treatment across a broad range of tumour indications. Targeting two checkpoint proteins simultaneously can further enhance efficacy and reduce the likelihood of resistance. Moreover, such dual checkpoint inhibitors (DCPIs) offer a superior safety profile with fewer adverse events. The PD1 and CTLA4 targeting DCPI cadonilimab is approved in China while many more bsAbs with the same approach are currently being investigated in phase 3 studies.

The combination of overcoming checkpoint inhibition with blocking another pathway is emerging as an attractive strategy. A notable example is dual-targeted PD1 and VEGF bsAb ivonescimab from Akeso, which received marketing authorisation in China for the treatment of non-small cell lung cancer (NSCLC) in combination with chemotherapy in May 2024. The approval was based on a phase 3 study demonstrating that progression free survival was significantly improved compared to placebo and chemotherapy.[30]

Many tumour surface antigens are validated targets for well-established antibody-based therapies, such as EGFR, VEGF or HER2. However, cancer cells can activate redundant pathways to mitigate the impact of these efficacious therapies. Simultaneously blocking two tumour-associated pathways offers the potential to improve efficacy while blocking resistance mechanisms. For example, EGFRxMET targeting antibody amivantamab is approved for a subtype of NSCLC, while several other EGFR-targeting bsAbs are in development. Various bsAb combinations targeting HER2 or HER3 are being investigated in solid tumours.

The future direction for bi-/multi-specific antibodies

As novel, bispecific antibody MoAs continue to enter clinical practice, several themes are emerging that will shape their future role in cancer therapy:

- **New modalities:** Adding binding sites can embed additional functionality in an antibody. For example, tri-specific TCEs are currently in clinical trials which add a co-stimulatory receptor to orchestrate an effective on-target immune response. Moreover, the development of engagers of different immune cells, such as NK cells, will further expand therapeutic options. To improve specificity and safety, the concept of pro-drugs is being explored, which harnesses selective, local activation in response to specific triggers, e.g., in the tumour microenvironment.
- **Bridging/combination therapies:** As has been proven in other areas of cancer care, combination therapies deliver superior patient outcomes vs. monotherapies. Therefore, future regimens will see bsAbs used in combination with other approaches including chemotherapy, targeted therapy, or other monoclonal antibodies. For example, at ASH 2023, Roche showed potentially best-in-class progression-free survival with a novel bispecifc-ADC combo (Columvi + Polivy).[31] Furthermore, in haematological malignancies, bsAbs will continue to play an important role as bridging therapies before patients are treated with a CAR-T therapy.
- **Efficacy and safety:** While bsAbs offer a favourable safety profile compared to CAR-Ts, specifically in terms of cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity (ICANS), they must still establish their long-term effectiveness. This applies particularly in B-cell malignancies where CAR-Ts currently offer superior durability. Therefore, eliciting a strong and durable immune response, which also involves the innate immune system, will be critical for bsAbs to achieve broad success in clinical practice.

Bispecific and future multi-specific antibodies hold the promise of a true Swiss army knife in cancer immunotherapy, with their utility poised to expand in years to come as pivotal clinical data continues to accumulate.

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III. Radioligand therapies

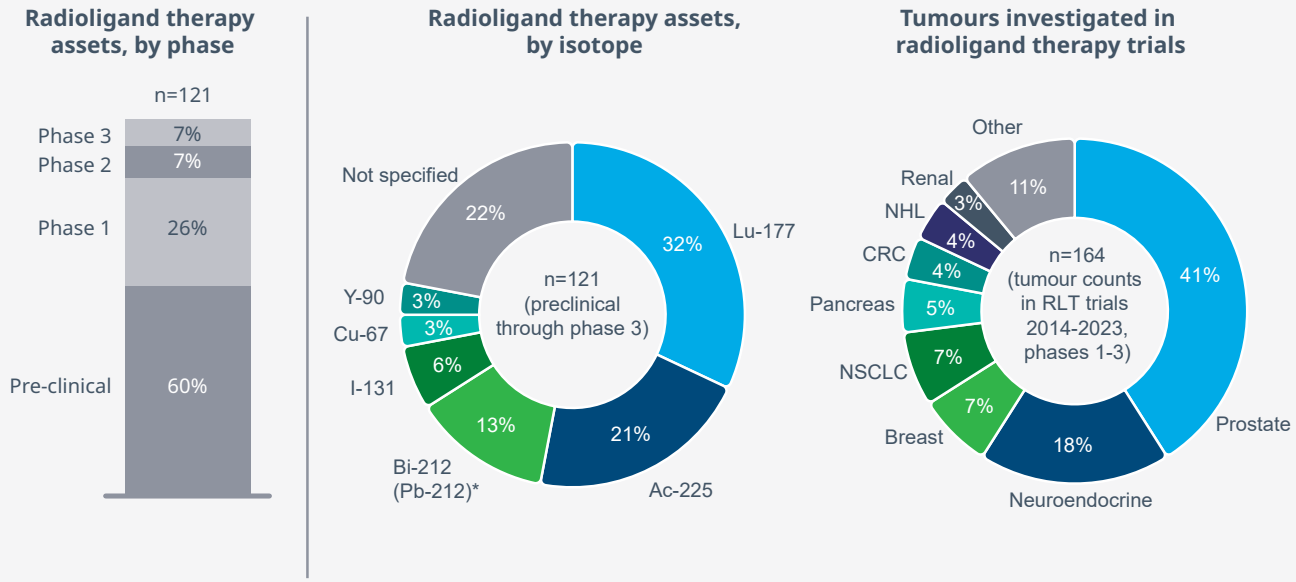
The emergence of radioligand therapies (RLTs) in many ways mirrors the rise of ADCs. Radioligand therapies, like ADCs, deliver a lethal payload, in this case a radioactive isotope, which is precisely steered by the ligand towards markers on tumour cells or their microenvironment. This highly targeted approach brings precision to the blunt instrument of traditional radiotherapy, with the promise of combining high anti-tumour potency with selectivity, thus minimising damage to healthy surrounding tissues.[32]

To date, two Luthetium-177 (Lu-177) based radioligand therapies have been approved which are commercialised by Novartis: Lutathera, for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (SSTR+ GEP-NETs); and Pluvicto, for treating prostate-specific membrane antigen-positive metastatic castration-resistant prostate cancer (PSMA+ mCRPC).[33,34]

The growing interest in radioligand therapies has led to significant funding inflows and is fuelling an expanding pipeline now comprising 121 RLT assets that are being developed by over 40 companies. Forty percent of those RLT assets are in clinical development, while a pipeline share of 60% for pre-clinical RLT assets reflects the nascent nature of this modality (see Figure 8).

The choice of radioisotope plays a key role in shaping the next generation of RLTs and future competitive dynamics. The intrinsic properties of different isotopes, such as radiation type (alpha vs beta), potency and half-life, translate into distinct clinical profiles and have implications for the ease of manufacturing and the supply chain.

Figure 8: Radioligand therapy development pipeline



Note: Includes industry-sponsored trials only; multiple indication counts per trial possible; RLT: Radioligand therapy
* Beta-emitting Pb-212 is used as RLT payload for in vivo generation of short-lived alpha-emitting Bi-212
Source: IQVIA Analytics Link, July 2024; Citeline Trialtrove; clinicaltrials.gov; desk research; IQVIA EMEA Thought Leadership

For example, beta particles are able to irradiate large volumes of multicellular dimensions, due to their long range in tissue. This positions them well for treating large tumours, but with the risk of exposing healthy neighbouring cells. Conversely, alpha particles combine high energy with shorter paths of tissue penetration. This allows them to cause double-stranded DNA breaks which are more damaging to cancer cells compared to mostly single-stranded DNA breaks caused by beta-emitters, while their limited tissue penetration minimises off-target damage to healthy cells.[35]

Beta-emitting Lu-177 is the leading isotope for radioligand therapies in development, with a share of 32% of RLT pipeline assets, as many innovators try to build on the momentum and learnings from the two approved, trailblazing therapies. Examples include PSMA-targeting phase 3 assets for mCRPC from Telix (TLX591),[36] Curium (Lu-177-PSMA-I&T)[37] and Lantheus (PNT2002).[38]

However, focus is shifting towards alpha emitters, which offer several advantages over beta-emitting isotopes, as explained earlier.

- Actinium-225 (Ac-225) is the leading alpha emitter among RLT development assets, accounting for 21% of the pipeline. However, clinical research using Ac-225 has been hampered by supply shortages, forcing some innovators to temporarily pause patient enrolment for planned trials.[39] Notable Ac-225-based RLT examples include BMS/RayzeBio's SSTR-targeting, phase 3 asset RYZ101 for GEP-NETs,[40] and Fusion's PSMA-targeting, phase 2 candidate FPI-2265 for mCRPC.[41]
- Lead isotope Pb-212 has been at the centre of growing interest and represents 13% of the RLT pipeline.[42,43] Pb-212 itself is a beta emitter but acts as an in vivo generator of potent, short-lived alpha-emitting Bismuth-212 (Bi-212). The half-life of Pb-212 of 10.6 hours makes it a convenient source of fast-decaying Bi-212, with a half-life of just 60.6 minutes, and better matches the pharmacokinetic profiles of RLTs. Furthermore, the shorter half-life of Pb-212 vs. Ac-225 and Lu-177 (10 days and 6.5 days, respectively) allows simplifying waste management for hospitals, e.g., reducing storage time to 4-5 days compared to several months for Ac-225 and Lu-177 until radioactive waste becomes safe to handle.
- Finally, while the shorter half-life of Pb-212 presents some challenges, e.g., the need for a distributed manufacturing model with nodes very close to where Pb-212 will be used, the raw material for lead radioisotopes, thorium-228, occurs naturally, is available from multiple sites and allows readily scalable production of Pb-212.
- Prominent Pb-212-based RLT examples include Orano Med and RadioMedix's SSTR-targeting, phase 2 asset AlphaMedix for GEP-NETs,[44] and Perspective Therapeutics' MC1R-targeting, phase 1/2 candidate VMT-01 for metastatic melanoma.[45]

Other notable radioisotopes being investigated in RLTs include iodine-131 (I-131), copper-67 (Cu-67) and yttrium-90 (Y-90), all beta emitters, which represent 6%, 4% and 2% of the RLT pipeline, respectively. A limited number of pre-clinical and early clinical studies are exploring alpha emitter astatine-211 and beta emitter terbium-161 as potential payload in RLTs.[46,47]

Focus is shifting towards alpha emitters, which offer several advantages over beta-emitting isotopes.

Radioligand therapy is already helping patients with hard-to-treat tumours who have limited treatment options, in the case of mCR-prostate cancer and neuroendocrine tumours. While these two tumours have been the main focus of RLT clinical trial activity over the past decade, development efforts are expanding RLTs into other cancers, mostly solid tumours, e.g., breast, lung, gastrointestinal and renal.

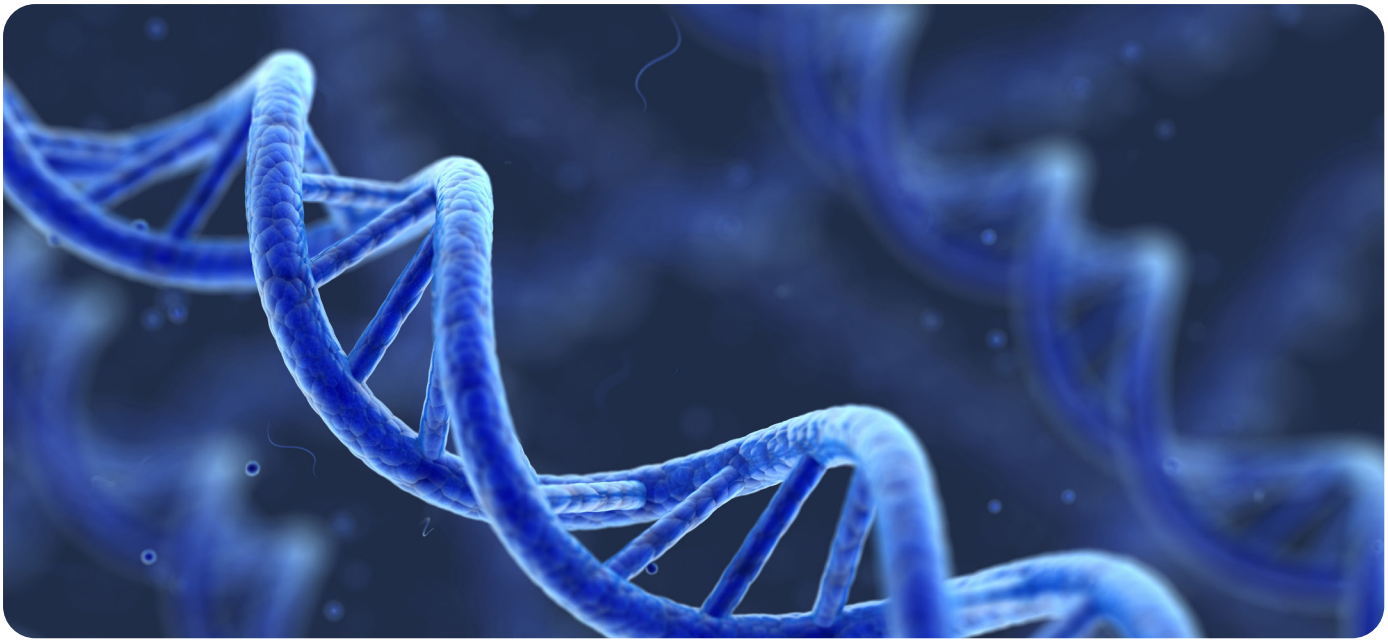
Radioligand therapy is already helping patients with hard-to-treat tumours who have limited treatment options.

The future direction for RLTs

Looking ahead, innovation efforts will focus on enhancing the clinical value of RLTs and broadening their utility within the armamentarium of cancer treatments:

- **Reduced toxicity** through novel ligands with enhanced specificity and target site affinity; incorporating stimulus-responsive release systems, e.g., pH- or redox-sensitive nanoparticle carriers that respond to the unique tumour microenvironment.[35]
- **Novel targets:** Exploring novel receptors for directing RLTs and expanding their application to new tumours, e.g., neurokinin receptor NK1, proven to be overexpressed in primary malignant gliomas, gastrin-releasing peptide receptors (GRPR), chemokine receptor type 4 (CXCR-4) or fibroblast-activation protein (FAP), expressed by 90% of epithelial cancers' stroma, to enable pan-cancer approaches.[48]
- **Combination therapies**, harnessing synergies of multiple MoAs, e.g., upregulating target receptors to increase cellular uptake of RLTs; amplifying RLTs' efficacy by inhibiting DNA repair, e.g., with PARP or topoisomerase inhibitors; radio-sensitisation by inhibiting other essential processes, e.g., mTOR pathway, Hedgehog signalling pathway, or blocking immune checkpoints, e.g., with PD-(L)1 inhibitors.[49]
- **Theranostics:** Pairing radionuclide-based diagnostic imaging and therapeutic agents to accurately identify patients who benefit the most, locate cancers, personalise RLT therapy and monitor response.[50]

Radioligand therapies, as cutting-edge precision medicines, hold tremendous potential as a critical, and eventually mainstream, pillar in cancer care.



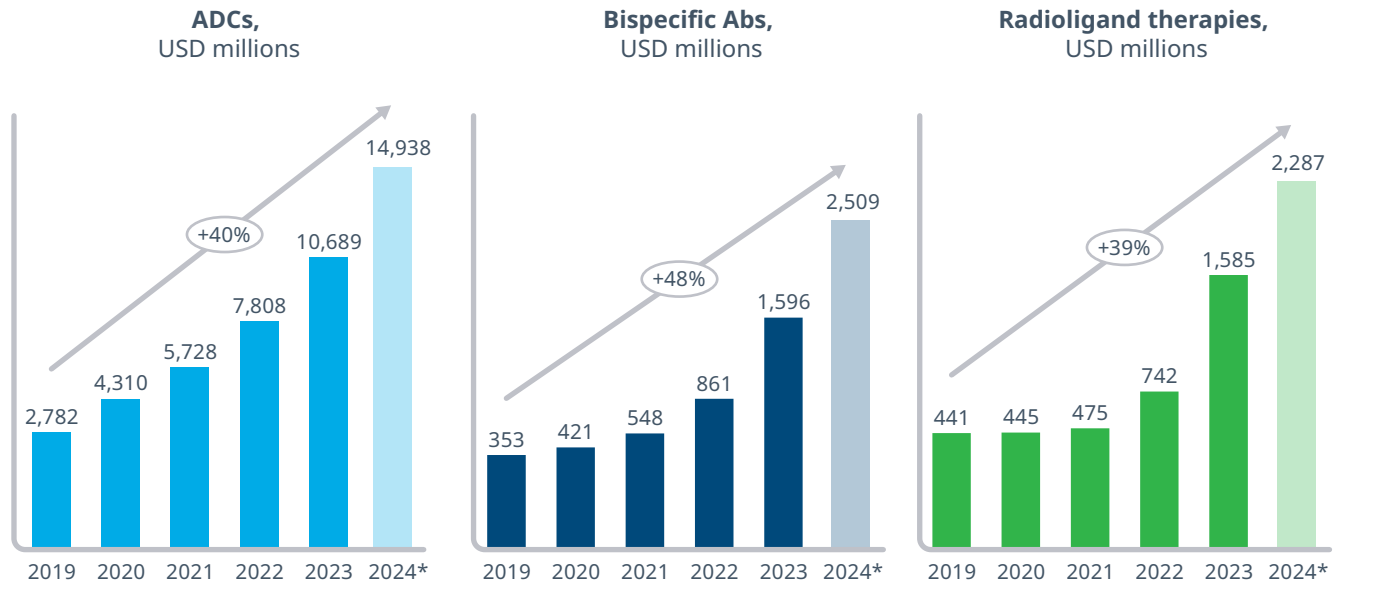
Market outlook for new modalities

Antibody drug conjugates, bi-/multi-specific antibodies and radioligand therapies are emerging as sizeable market segments which are expected to generate annual global sales in 2024 of $14.9 billion, $2.5 billion and $2.3 billion, respectively. Over the past five years, these three modalities have been growing considerably faster than the overall oncology market, with 5-year CAGRs (2019-2024) of 40%, 48% and 39% for ADCs, bi-/multi-specific antibodies and RLTs, respectively, compared to 11.5% for oncology overall, at ex-manufacturer prices (see Figure 9).

Looking ahead, we expect these three modalities to continue to out-perform the overall oncology market, with a collective 5-year CAGR of around 20% to reach combined sales of $37 billion by 2028, at ex-manufacturer prices, in a base case scenario (see Figure 10).

However, the outlook for these modalities includes high degrees of clinical and commercial uncertainty, such as potential trial failures; competitive dynamics vs. other modalities, e.g., cell, gene and RNA therapeutics, or immuno-oncology therapies, impacting their relative positioning in treatment algorithms and adoption in earlier lines of therapy; market access and reimbursement constraints; and bottlenecks in treatment infrastructure, e.g., specialist facilities for administering RLTs, or feasibility of moving treatments into an outpatient setting.

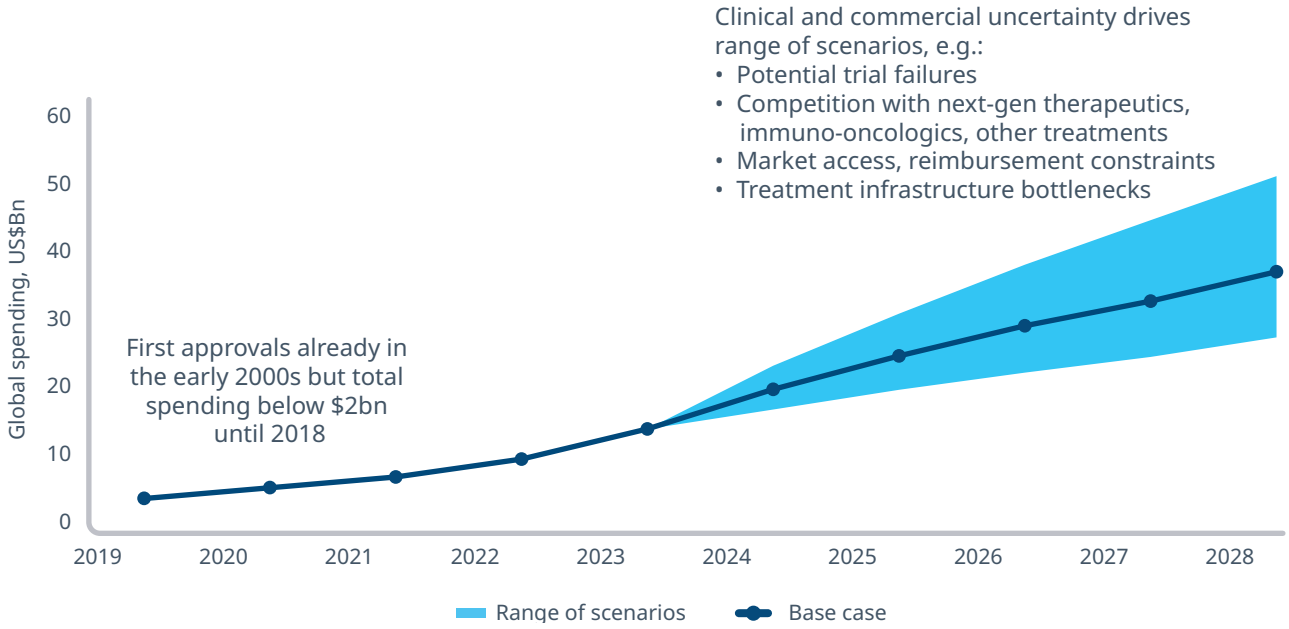
Figure 9: Global sales trends for novel modalities



Note: * forecast for full year 2024
Source: IQVIA Analytics Link July 2024

Looking ahead, we expect these three modalities to continue to outperform the overall oncology market, with a collective 5-year CAGR of around 20% to reach combined sales of $37 billion by 2028.

Figure 10: Market outlook for novel modalities — ADCs, bi-/multi-specific antibodies, radioligand therapies



Source: IQVIA Analytics Link July 2024, analyst consensus, company-reported sales; IQVIA EMEA Thought Leadership Analysis

Overcoming the innovator's curse: How to capture the opportunity

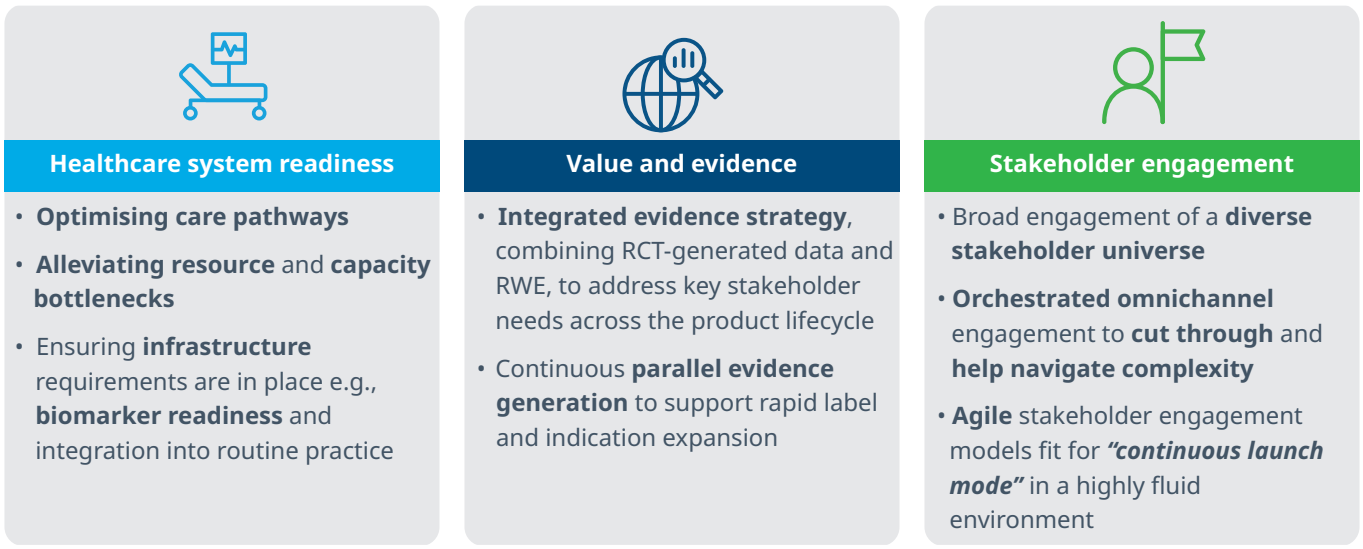
Prolific biopharmaceutical innovation is moving faster than healthcare systems' ability to adopt new therapies. This innovator's curse manifests itself particularly in oncology which is at the forefront of transformational medical advances.

The challenges innovators face extend beyond healthcare budget constraints and include operational and practical barriers to the effective adoption of novel therapies:

- Resource constraints, including skilled staff shortages following pandemic burnout.[51]
- Lack of infrastructure and capacity bottlenecks for delivering highly specialised therapies, e.g., CAR-T or radioligand therapies, the latter requiring accredited facilities with highly trained staff to handle radioactive materials, and shielded isolation rooms to protect healthcare workers and other patients from radiation exposure.[52]
- Mis-aligned or unprepared care pathways, leading to unwarranted pathway variations, including delayed diagnosis, referrals, and treatment, that result in sub-optimal patient outcomes and poor experiences, as well as the inefficient utilisation of healthcare resources for delivering cancer care.
- Overwhelmed oncologists struggling to keep abreast of rapidly evolving disease management and with navigating an increasingly complex cancer treatment landscape, e.g., matching the plethora of therapy options with sub-populations who benefit the most, optimally sequencing combination regimens or correctly handling novel, cutting-edge therapies in routine practice.

As we elaborated in our recent IQVIA white paper 'Achieving Oncology Launch Excellence',[53] addressing this innovation readiness gap is one of three strategic pillars for bringing new treatments to cancer patients which form the foundation for oncology launch success (see Figure 11):

Figure 11: The three pillars of oncology Launch Excellence



Source: IQVIA EMEA Thought Leadership

1. **Healthcare system readiness:** Partner with health systems to support adoption of innovation and accelerate change in clinical practice. This requires facilitating care pathway optimisation and improving decision support, alleviating resource and capacity bottlenecks, and ensuring specific infrastructure requirements are in place, including upgrading both physical and digital infrastructure

2. **Value and evidence:** Develop and execute an integrated evidence strategy, combining RCT-generated data and RWE, to support clear, differentiated product positioning and address the needs of all key stakeholders along the product lifecycle, ensuring approval, access and to facilitate the adoption of novel therapies.[54] Furthermore, maximising the potential of oncology assets requires continuous, parallel evidence generation to support rapid label and indication expansion

3. **Stakeholder engagement:** Engage a diverse stakeholder universe, spanning payers, HTA bodies, providers/local health systems, HCPs, nurses, patient advocacy groups and patients. Orchestrated omnichannel engagement is critical to efficiently deliver timely, relevant and succinct content, as well as value-add services.[55] Medical affairs plays an outsized role in early market shaping, building advocacy, facilitating health system readiness and helping HCPs navigate overwhelming complexity[56]

The unprecedented pace of scientific advances in oncology creates exceptional opportunities for innovators while bringing hope to patients. Novel modalities offer the potential of transforming cancer care by addressing high unmet need and setting new standards for delivering deeper, more durable patient benefits with ever greater precision.

Translating cutting-edge innovation into commercial success, however, is not a forgone conclusion, as innovators face formidable challenges in an unforgiving environment. Only those who master oncology Launch Excellence will seize the commercial opportunity and fulfill the promise of their transformational therapies.

The unprecedented pace of scientific advances in oncology creates exceptional opportunities for innovators while bringing hope to patients.

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