Clinical Cancer Bulletin

REVIEW

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Innovative drugs promote precision cancer therapy

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Abstract

Targeted therapy has fundamentally altered the diagnosis and treatment of clinical cancers. By focusing on chromosomal abnormalities and various indications of cancer, these medications have paved the way for the precise treatment of malignant tumors. In addition to markedly reversing the status quo of reliance on radiotherapy, chemotherapy, and surgery, these drugs have radically transformed the clinical treatment of advanced malignant tumors and became the leading candidates in the fight against cancer. Significant advancements in new targeted medications, including small molecules (e.g., KRASG12C inhibitors), bispecific antibodies, antibody drug conjugates, and cellular immunotherapy, are due to the advent of new technology and treatments. Notably, numerous difficulties have been encountered, although each medicine class has its own unique benefits and drawbacks. To serve as a key summary for the development of new treatment options for precision cancer medicine recently, this review aimed to summarize the most recent anti-tumor revolutionary medications with significant prospective therapeutic advantages.

Keywords Cancer precision medicine, Innovative drugs, Clinical strategy, KRAS, Immunotherapy, Cellular immunotherapy

An important goal of precision cancer therapy is to discover the genetic changes that cause cancer development and treat them with targeted medicines. Since the launch of the first targeted drug, imatinib, 20 years ago, significant progress has been made in precision cancer medicine and innovative anticancer drug areas [1]. In fact, more than 100 anti-tumor targeted medications, immunotherapy medications, and cell therapy medications have been launched and have had enormous benefits in various cancer patients. For example, owing to significant progress in the targeted therapy era, EGFR inhibitors have developed to the fourth generation [2]. Notably, the concept of precision cancer treatment is becoming clearer with the introduction of new drugs and therapies [3].

Following this rationale, numerous innovative anti-tumor drugs, which precisely target tumor growth, proliferation, evolution and immune microenvironment, are introduced in clinics with the rapid promotion of early clinical research results and innovation progress [4, 5]. Various new conceptual anti-tumor drugs, including targeted small molecule drugs (e.g., KRAS G12C inhibitors), bispecific antibodies, innovative antibody drug conjugates (ADCs), cellular immunotherapies, etc., have recently opened a new chapter in precision medicine

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[6–8]. In the context of precision medicine, this review aimed to summarize the latest research hotspots of innovative anti-tumor therapy and related research frontiers of precision cancer medicine to provide useful reference for clinical cancer treatment.

KRAS targeted therapy conquers the undruggable cancer target

KRAS, a member of the RAS proto-oncogenes, is mainly associated with lethal malignancies, encoding protein GTPases and acting as a molecular switch in pathways regulating cell proliferation and survival [9, 10]. Among human cancers, KRAS mutations are found in approximately 90% of pancreatic, 30%-40% of colon, and 15%–20% of lung cancers (mostly NSCLC) [11]. KRAS mutations mainly occur in codons 12, 13, and 61, with codon 12 accounting for more than 80% of these mutations, including G12C, G12D, G12S, and G12V.

Previously, KRAS was labeled as "undruggable." In fact, no effective RAS inhibitor has been approved for nearly 40 years due to its extremely high affinity for GTP, lack of a suitable binding pocket on its surface, and high GTP concentration in the cytoplasm [12]. The medical community has been anticipating a breakthrough in KRAS target for a long time. Notably, there have been exciting breakthroughs in KRAS targeting in the past few years. New medications target KRAS and the related pathway proteins (Fig. 1).

KRAS-G12C targeted drugs

Sotorasib (AMG510) and adagrasib (MRTX849) are direct KRAS-G12C inhibitors developed by Amgen and Mirati Therapeutics. The covalent bond created by inhibitors of this target with cysteine 12 maintains KRAS in an inactive state and prevents cell division [9, 12].

In May 2021, the FDA approved sotorasib, making it the first KRAS-G12C inhibitor to enter clinical trials. Patients with locally advanced or metastatic NSCLC who have received at least one prior systemic therapy and carry the KRAS-G12C mutation were eligible for the trials. Data from a phase I trial, which included 13 patients with NSCLC, revealed an overall response rate (ORR) of 54% and a disease control rate (DCR) of 100%. The CodeBreaK 100 trial obtained impressive data, with an ORR of 37.1% and median overall survival (OS) of 12.5 months among patients enrolled in the sotorasib group, highlighting the long-term survival benefit of the treatment. Sotorasib, which has led to excellent clinical results, provides new therapeutic options for patients with advanced solid tumors [13].

A specific oral formulation, adagrasib, is a second-generation KRAS-G12C mutation-targeting drug [14]. In the phase II trial (NCT03785249) with adagrasib, the overall response rate was 43% and the median duration of response was 16.4 months [15]. Of note, compared to the original sotorasib, adagrasib has been enhanced in the following areas: adagrasib is more stable in terms of pharmacokinetics based on its longer half-life ($T_{1/2}$=23 h) than sotorasib ($T_{1/2}$=5 h); and adagrasib has a wider tissue distribution and may cross the blood–brain barrier. Based on the data, 42 patients with CNS metastases had a median follow-up time of 15.4 months, and the median intracranial progression-free survival was 5.4 months [15]. However, as the trial was not a prospective study, further research is required to substantiate this conclusion.

In February 2022, the FDA accepted a new drug application for adagrasib for the treatment of patients with NSCLC harboring the KRAS G12C mutation. The second KRAS-G12C inhibitor was administered to patients.

In addition, small molecule inhibitors have shown successful cases in cancer treatment. For example, inhibitors of nuclear export protein XPO1 are used to inhibit its function in cells. XPO1 is a crucial nucleocytoplasmic transport protein involved in regulating the transportation of proteins and RNA within the cell nucleus [16]. By inhibiting XPO1 activity, these inhibitors disrupt the normal transport processes, affecting cell survival and proliferation. Some XPO1 inhibitors, such as Selinexor, have received clinical approval and are utilized in treating various cancer types, including lymphoma, leukemia, and solid tumors. It has been reported that KRAS G12C inhibitors are used in combination with selinexor to synergically inhibit the proliferation of KRAS G12C mutant cancer cell lines [17]. However, the efficacy and safety of XPO1 inhibitors are still undergoing further research and evaluation due to individual patient tolerability and the variability of different tumor types.

KRAS-G12D targeted therapeutic strategy

The most frequent oncogenic KRAS mutation, KRAS-G12D, is found in 34% of pancreatic cancers, 11% of cholangiocarcinomas, and 10%–12% of colorectal cancers. Unlike KRAS-G12C, the benefits of KRAS-G12D inhibitors are mainly directed at pancreatic cancer treatment.

Based on experiences with the KRAS-G12C inhibitor, adagrasib, Mirati Therapeutics developed MRTX1133 (AGS IC_{50}=6 nM), a potent, selective, and reversible KRAS G12D inhibitor, through extensive structure-based modification of activity [18]. In cellular assays, MRTX1133 displayed a 700-fold higher affinity and specificity than wild-type KRAS. Further, MRTX1133 was found to have a half-life of more than 24 h and no potential hERG (cardiotoxic) activity [19]. MRTX1133 displayed dose-dependent inhibition of KRAS signaling in vitro, and exhibited remarkable anticancer activity in

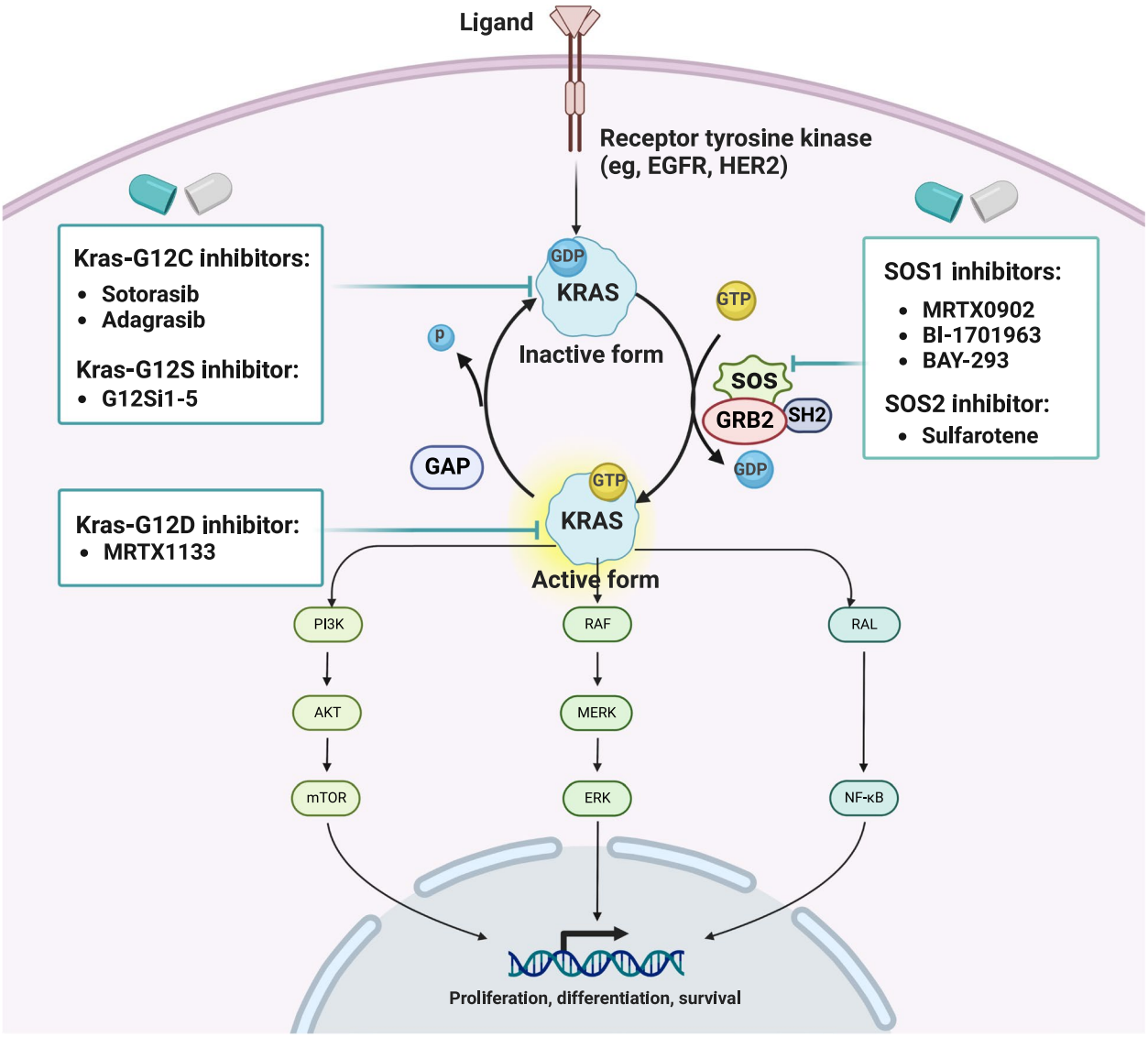

Fig. 1 KRAS-related drug targets and approved innovative drugs. Schematic diagram of the targets of direct KRAS inhibitors and KRAS-related pathway drugs

pancreatic cancer models, with eight of the 11 models showing tumor shrinkage of more than 30% [18].

KRAS-G12S targeted therapeutic strategy

KRAS-G12S is present in 1.84% of colorectal adenocarcinoma and 0.5% of NSCLC patients, which is one of the popular study sites of G12 [20]. Ziyang Zhang et al. proposed the G12Si series of drugs, a small molecule that binds irreversibly to KRAS (G12S), among which G12Si-5 exhibited the best inhibitory effect (Ki = 26 μM) [21]. G12Si series compounds have been demonstrated to covalently modify the KRAS protein to a certain extent, reduce the content of KRAS-GTP, and significantly inhibit the level of phosphorylated ERK in cells. KRAS-G12S inhibitors provide a new option for the development of other serine-targeted covalent inhibitors. However, the underlying mechanisms remain unclear.

KRAS pathway synergistic drugs: SOS inhibitors

The switch between inactivated and activated KRAS is regulated by guanine nucleotide exchange factors (GEFs) [12]. One of these GEFs is the SOS protein, a promising target for the treatment of solid tumors [22].

MRTX0902 is a new SOS1 inhibitor (MKN1 IC_{50} = 29 nM) developed by Mirati Therapeutics for the treatment of KRAS mutation-driven cancers [23]. This

inhibitor disrupts the interaction between SOS1 and KRAS, leaving GDP-bound KRAS in an inactivated state. MRTX0902 acts in different phases from the KRAS-G12C inhibitor, adagrasib, and the KRAS-G12D inhibitor, MRTX1133 [19]. Therefore, the combination of MRTX0902 with other drugs may further enhance the effect of the other drugs. MRTX0902 is currently undergoing preclinical studies to support IND applications. Compared to BI-1701963, developed by Boehringer Ingelheim, and BAY-293, developed by Bayer, this drug is expected to compensate for safety deficiencies [24].

SOS2 has the potential to be a potent target for RAS inhibition. Our group identified a cancer stem cell-targeting drug candidate, sulfarotene, which selectively targets SOS2-overexpressing HCC PDXs by suppressing the SOS2-RAS junction and its related signaling pathways in HCC stem-like cells [25].

New antibody drugs are highlighted in cancer immunotherapy

In the past five years, immune checkpoint inhibitors (ICIs) have revolutionized the clinical treatment of advanced malignant tumors and markedly reversed the dependence on radiotherapy, chemotherapy, and surgery [26, 27]. Recently, there have been more neoconceptual immune-antibody drugs that will bring more benefits to clinics [28].

PD-1/PD-L1 immune checkpoint inhibitors

Antibodies targeting the PD-1/PD-L1 checkpoint activate the immune system by disrupting the immunosuppressive state, thereby maintaining tumor control. This strategy has emerged as a novel cancer treatment approach and has rapidly become the standard treatment for more than one dozen tumors. Notably, this approach can significantly improve the clinical progression and poor prognosis of some tumor patients [29].

To date, at least 12 antibodies targeting PD-1 and five antibodies targeting PD-L1 have been approved by regulatory agencies worldwide. Numerous clinical trials are ongoing to evaluate the therapeutic potential of PD-1/PD-L1 antibodies in various combinations [30]. Opdivo and Keytruda remain as the leading treatments and are widely used in clinical practices, with 17 and 12 indications, respectively, including melanoma, non-small cell carcinoma, Hodgkin lymphoma, head and neck cancer, bladder cancer, and other cancers; these treatments are associated with prolonged progression-free survival and high safety [31, 32].

Unfortunately, some clinical patients cannot benefit from such treatment because its efficacy largely depends on the expression of PD-1/PD-L1, size of tumor mutation burden (TMB), low response rate of patients, and presence of immunosuppressive mechanisms in the tumor microenvironment, which limits the application of immune checkpoint inhibitors [33].

Furthermore, significant advancements have been made in the field of tumor treatment through the utilization of nanotechnology and nanocarriers. One approach involves the use of nanoparticles as carriers for delivering chemotherapy agents, radioactive isotopes, or other therapeutic substances. Nanobodies have emerged as particularly advantageous in oncology [34]. They benefit from the unique properties of nanomaterials, which enhance their bioactivity and stability, thereby increasing their effectiveness in disease diagnosis, drug delivery, and immunotherapy. Moreover, the small size and extensive surface area of nanobodies facilitate easier tissue and cell membrane penetration, resulting in improved targeting capabilities.

For instance, Alphamab Oncology has developed Envafolimab, the world's first subcutaneously injectable PD-L1 antibody. This innovative treatment has been granted orphan drug designation by the FDA and has received approval for the treatment of adult patients with advanced solid tumors exhibiting high microsatellite instability (MSI-H) or deficient DNA mismatch repair (dMMR) [35]. This includes individuals with advanced colorectal cancer who have experienced disease progression after initial or subsequent treatments, as well as patients with other advanced solid tumors who have not responded to prior systemic therapies and lack satisfactory alternative treatment options, particularly those with biliary tract cancer.

Based on data from a single-arm open-label Phase II pivotal clinical trial involving 103 Chinese patients with MSI-H/dMMR advanced solid tumors who had not responded to first-line or subsequent systemic treatments, Envafolimab demonstrated an objective response rate (ORR) of 42.7% in the overall population (n = 103) as evaluated by an independent review committee. However, the long-term clinical benefits and relative advantages of this drug require further investigation and validation [35]. It is anticipated that in the next 3–5 years, nanotechnology in the field of antibody drugs will likely receive additional clinical approvals and witness widespread applications.

A promising immunotherapy strategy: TIM3 blockade

T-cell immunoglobulin domain and mucin domain-3 (TIM-3), an immune checkpoint protein, works with other immune checkpoints, such as PD-1 and LAG3, to regulate CD8 + T cell exhaustion. TIM-3 is widely expressed on myeloid cells, natural killer cells, and dysfunctional T cells, and is often co-expressed with PD-1. However, the specific functional mechanism of TIM-3 is

not fully understood and should be further investigated [36, 37].

Globally, several TIM-3 antibodies are being clinically evaluated at various stages. Sabatolimab (MBG453), which was developed by Novartis and has been granted rapid review for MDS indications by the FDA, is in a phase III trial for acute myeloid leukemia (AML) and high-risk myelodysplastic syndromes (HR-MDS). When sabatolimab was combined with hypomethylating agents (HMAs) for AML and HR-MDS, the ORR was 41.2% for 34 AML patients, 50% for high-risk MDS patients, and 84.6% for extremely high-risk MDS patients; these patients had encouraging response rates [38].

Although there has been little progress in obtaining single-drug data in preclinical and clinical practice, There are combination drugs expected to become a viable treatment strategy. According to prior studies, adaptive resistance leads to the upregulation of TIM-3 and other immune checkpoints. T cells co-expressing TIM-3 and PD-1 exhibit severe exhaustion. Moreover, low response to anti-PD-1 treatment, drug resistance, and tumor immune escape are often highly associated with TIM-3 expression. In independent experiments, anti-TIM-3 antibodies reduced the development of drug resistance when combined with anti-PD-1 agents [39].

In addition to the mentioned targets, other tumor-targeting antibody drugs have been widely used in clinical practice. For example, HER2 is overexpressed or mutated in breast cancer and some other tumors. Drugs like Trastuzumab specifically target HER2 to inhibit tumor growth and spread. EGFR is another important target in various cancers. Drugs such as Cetuximab block EGFR signaling, inhibiting tumor cell proliferation. VEGF plays a critical role in angiogenesis and tumor blood vessel formation. Bevacizumab, for example, binds to VEGF, reducing tumor blood supply and inhibiting tumor growth and spread. Ongoing research and development focus on identifying additional targets for more precise and effective cancer treatment strategies.

Bispecific Antibodies (BsAbs), an increasing precision oncology field

As an emerging class of antibodies, BsAbs are of great significance in cancer immunotherapy and are considered prospective candidates for tumor and cancer treatments. Compared to monoclonal antibodies, BsAbs add a specific antigen-binding site to target tumor cells more specifically and reduce off-target toxicity. Simultaneously, BsAbs are urgently needed to overcome many challenges, such as the inability to balance and coordinate the load, efficacy, and safety of the two targets in patients with different expression levels of the target [33, 40].

Many innovative bispecific antibody structures have emerged, such as the heterodimeric bispecific antibody, catumaxomab; the bispecific T-cell engbler (BiTE), blinatumomab; and the tetrovalent antibody, cadonilimab. In addition, new antibody-based therapies have emerged, such as moxetumomab pasudotox with antibody coupled toxin, Iodine 131 derlotuximab biotin with radiolabeled antibody, Iodine 131 Metuximab with radiolabeled Fab fragment, etc [41]. To date, seven bispecific antibodies have been approved (Table 1).

Table 1 Bispecific antibody products launched globally

Drugs	Company	Targets	Indications	Clinical trials	Reference
Teclistamab	*Johnson & Johnson*	BCMA × CD3	Multiple myeloma (MM)	NCT03145181[a] NCT04557098[a]	[42, 43]
Mosunetuzumab	*Roche*	CD20 × CD3	Follicular lymphoma (FL)	NCT02500407[a]	[44]
Cadonilimab	*Akeso,Inc*	PD1 × CTLA4	Cervical cancer	CTR20182027[b] CTR20210428[b]	-
Faricimab	*Roche*	VEGF × Ang-2	Macula edema, Macular degeneration	NCT03823287[a] NCT03823300[a] NCT03622580[a] NCT03622593[a]	[45, 46]
Amivantamab	*Johnson & Johnson*	c-MET × EGFR	NSCLC	NCT02609776[a]	[47]
Emicizumab	*chugai pharmaceutical, Roche*	Factor X × Factor IXa	Hemophilia A	NCT02622321[a] NCT02795767[a]	[48, 49]
Blinatumomab	*Amgen*	CD19 × CD3	Precursor B-cell lymphoblastic leukemia	NCT01466179[a] NCT00198991[a] NCT00198978[a]	[50, 51]
Catumaxomab (Delisted)	*Trion Pharrna*	EpCAM × CD3	Malignant ascites	NCT00836654[a]	[52]

[a] http://www.clinicaltrials.gov

[b] http://www.chinadrugtrials.org.cn

In early 2021, cadonilimab, developed by Akeso Inc., was approved by the NMPA for the treatment of metastatic cervical cancer. Cadonilimab was the first bis-specific antibody with dual immune checkpoint inhibition approved in the world. A total of 111 patients with advanced cervical cancer were enrolled based on previously published phase II clinical trial data. Among the 100 evaluated patients, the 6-month and 12-month ORRs were 33.0% and 12.0%, respectively. The 6-month and 12-month response (DOR) rates were 77.6% and 52.9%, respectively, and the median survival time (mOS) was 17.51 months. The approval of cadunilizumab may lead to more effective treatment options for patients with advanced cervical cancer.

Cadonilimab targets both PD-1 and CTLA-4 by optimizing the antibody structure, which can quadrivalently bind to co-expressed TIL, thereby preferentially enriching the tumor microenvironment (Fig. 2). Preliminary research data on cervical cancer, gastric cancer, and other tumors revealed that cadonilimab has significantly reduced toxicity compared with the combination therapy of PD-1 and CTLA-4 and has obvious safety and efficacy advantages [53].

When 10 mg/kg cadonilimab was administered, regardless of PD-L1 expression, the ORR was 79.3% for combination therapy with cadonilimab, 82.4% for those with CPS ≥ 1, and 75.0% for those with CPS < 1. These data highlight the potential for the comprehensive coverage of recurrent and metastatic cervical cancer populations with cadonilimab.

ADC drugs show great potential in precision cancer therapy

Antibody–drug conjugates (ADCs) are a class of targeted biological agents consisting of antibodies with high specificity and affinity, highly stable linker heads, and highly potent small-molecule cytotoxic drugs (Fig. 3) [54, 55].

Compared with other traditional tumor-targeted drugs, ADCs have the following advantages. First, the curative effect of ADCs is remarkable and they can achieve complementary advantages. Monoclonal antibodies targeting tumor cell surface proteins on ADCs have tumor specificity and potency that cannot be achieved by traditional drugs. Combined with the high efficiency of small-molecule toxic drugs, the comprehensive effect of ADCs leads to remarkable curative effect [56]. Secondly, ADCs are highly safe. The linker

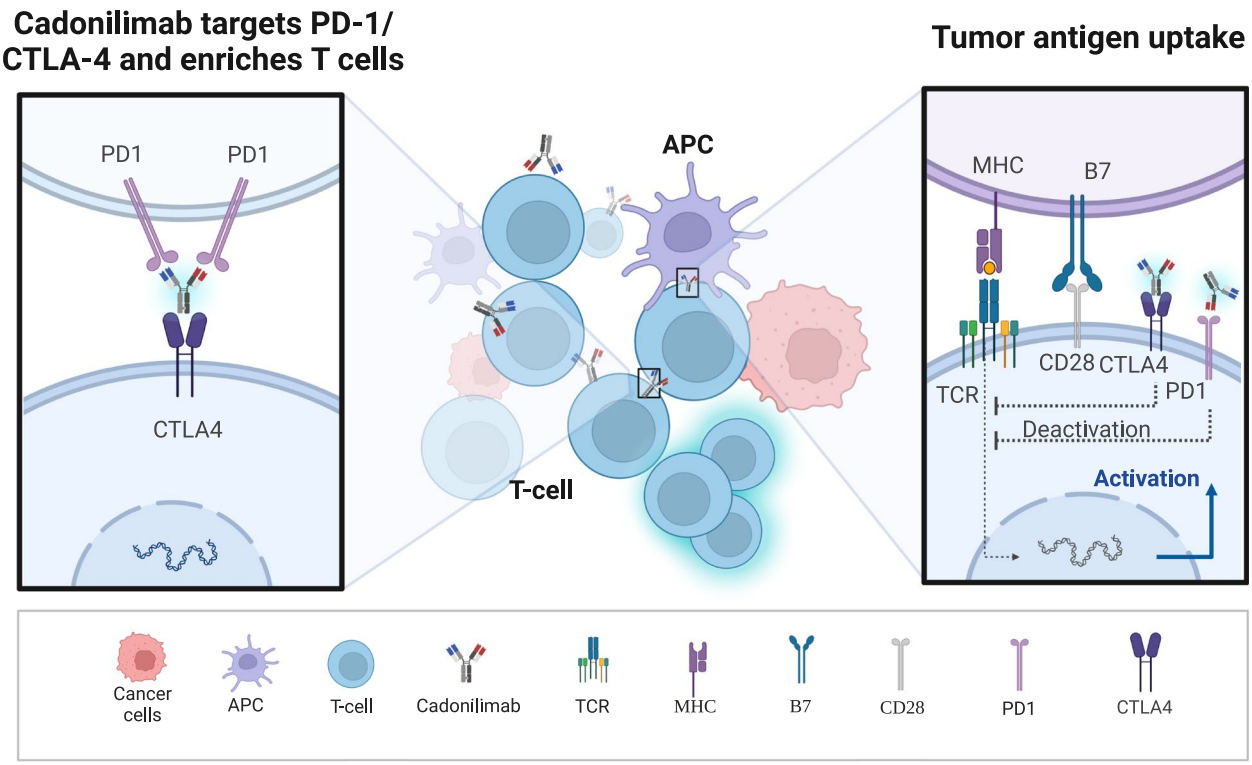

Fig. 2 Schematic diagram of the mechanism of action of Cadonilimab. Cadonilimab targets PD-1/CTLA-4 and can bind TILs quadrivalent, resulting in preferential enrichment in the tumor microenvironment. Peripherally, Cadonilimab reduces the risk of activated T cells attacking healthy tissue, thereby mitigating toxicity concerns outside the tumor

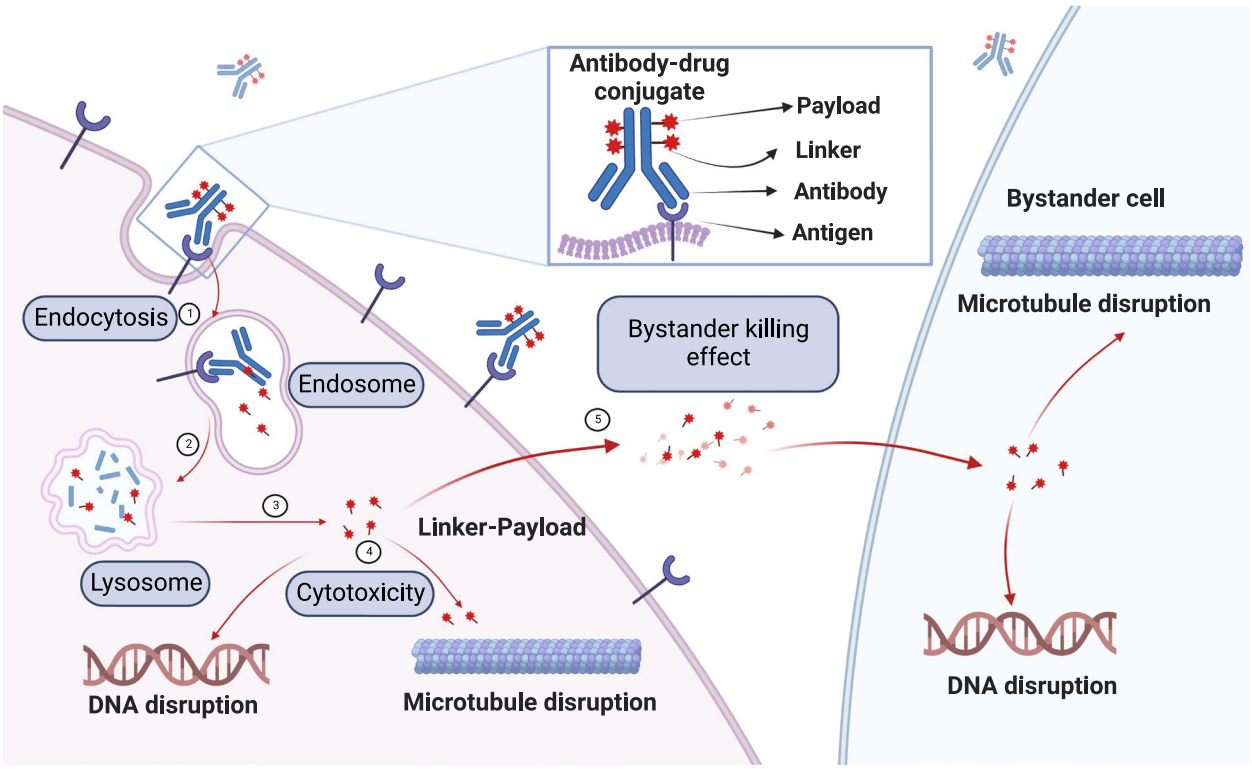

Fig. 3 Schematic diagram of the action of ADCs. 1) ADCs bind to tumor cell target antigen; 2) ADCs enter into tumor cells through internalization; 3) Lysosomal degradation; 4) ADCs release cytotoxic loads that lead to DNA damage and microtubule disruption, affecting tumor cell proliferation; 5) Bystander killing effect. Cytotoxic loads that are lipid-soluble can exit tumor cells and enter surrounding cells, affecting their proliferation, regardless of whether the cells express the target antigen

connects the cytotoxic payload to the monoclonal antibody and maintains the antibody–drug conjugate in a stable state in circulation. Intracellular lysis releases small-molecule drugs, which can minimize the exposure of normal tissues and reduce damage to surrounding healthy tissues [57]. ADCs have been developed for decades. These drugs were initially used to treat hematological malignancies and gradually covered solid tumors, mainly breast cancer.

Owing to the advantages of clear targets, mature technology, and high specificity, the rapid development of coupling technology has promoted the development of ADCs, and updated iterations are very rapid. Drugs comprising a variety of new antibodies, such as peptide drug conjugates (PDCs), antibody-fragment conjugated, small-molecule drug conjugates (SMDCs), nanoparticle-conjugated, and bicyclopeptide-conjugated drugs, are emerging. The payloads include Toxins, TLR agonists, STING agonists, nuclides, and double-warhead couplings. To date, 14 ADC drugs have been approved for clinical use worldwide, and more than 100 candidate drugs are in different stages of clinical trial [58, 59].

The FDA recently approved a new ADC drug, T-DXd (trastuzumab deruxtecan), jointly developed by Daiichi Sankyo and AstraZeneca for the treatment of HER2-positive breast cancer [60]. Structurally, T-DXd is composed of a trastuzumab-like anti-HER2 antibody, a triggered tetrapeptide linker, and a novel topoisomerase I inhibitor exatecan derivative (DXd) [61]. According to DESTINY-Breast03 Phase III, compared with the first-generation ADC drug, T-DM1, T-DXd significantly prolongs the PFS of patients (6.8 months), reduces the risk of disease progression or death by 72%, and resulted in an ORR of 79.7% [62]. This agent improves the survival of patients with HER2-positive breast cancer as an adjuvant and neoadjuvant therapy and of those with metastatic disease.

T-DXd has been included in the NCCN guidelines as a class I-preferred second-line treatment for recurrent unresectable (local or regional) or stage IV HER2-positive breast cancer [63].

The cytotoxic bystander effect of T-DXd causes the release of the payload to be membrane-permeable, inducing cytotoxicity in nearby tumor cells. This characteristic suggests that T-DXd may be used to treat heterogeneous tumors with high HER2 expression, including NSCLC

and colorectal cancer [64]. T-DXd has been tentatively confirmed for the treatment of NSCLC and gastric cancer [65].

Significant achievements have been made in the active exploration of ADC drugs. Currently, there are approved or under development drugs, such as Ado-trastuzumab emtansine, used for the treatment of HER2-positive breast cancer and gastric/esophageal adenocarcinoma [66]. Brentuximab vedotin, used for the treatment of Hodgkin lymphoma and systemic anaplastic large cell lymphoma [67]. And Polatuzumab vedotin, used for the treatment of relapsed or refractory diffuse large B-cell lymphoma [68].

In addition to these drugs, numerous other ADC compounds are currently undergoing clinical trials and research to explore their potential in different types of cancer treatment. These ADC drugs have demonstrated significant therapeutic effects in clinical trials and hold potential benefits for certain types of cancer patients. With further research and development, ADC drugs are expected to broaden their application in the field of oncology, expanding their potential in tumor treatment.

Cellular immunotherapy as a cancer treatment

CAR-T cell therapy

At least seven CAR-T cell therapy products have been approved in the US, China, and EU, and numerous clinical trials and studies have promoted the rapid development of CAR-T cell therapy (Table 2).

Currently, CAR-T therapy is mainly used to treat hematological tumors, which can be roughly divided into three categories: lymphoma, acute lymphoblastic leukemia (ALL), and multiple myeloma (MM), and involve two major targets, CD19 and BCMA (Fig. 4) [76–78]. For

Table 2 CAR-T cell therapy products launched globally

No	Generic name	Company	Year & Country[#]	Target	Indications	Efficacy	Reference
1	Tisagenlecleucel	*Novartis*	2017, US	CD19	B-cell Acute Lymphoblastic Leukemia (B-ALL),	Tisagenlecleucel has shown a complete remission rate of 81% in pediatric and young adult patients with relapsed or refractory B-ALL	[69]
2	Axicabtagene ciloleucel	*Kite-Gilead* *Fosun Kite*	2017, US 2021, China	CD19 CD19	Diffuse Large B-cell Lymphoma (DLBCL)	Axicabtagene ciloleucel has demonstrated an overall response rate of approximately 60% in patients with relapsed or refractory DLBCL	[70]
3	Brexucabtagene autoleucel	*Kite-Gilead*	2020, US	CD19	Relapsed or refractory mantle cell Lymphoma (r/r MCL)	Brexucabtagene autoleucel has shown an overall response rate of 87% in patients with relapsed or refractory MCL	[71]
4	Lisocabtagene maraleucel	*Juno-BMS*	2021, US	CD19	Diffuse Large B-cell Lymphoma (DLBCL)	Lisocabtagene maraleucel has demonstrated a complete response rate of 54% in patients with relapsed or refractory DLBCL	[72]
5	Idecabtagene vicleucel	*BMS*	2021, US	BCMA	Multiple myeloma (MM)	Idecabtagene vicleucel has shown an overall response rate of 72% in heavily pretreated patients with relapsed or refractory multiple myeloma	[73]
6	Relmacabtagene autoleucel	*JW Therap*	2021, China	CD19	relapsed or refractory large B-cell lymphoma (r/r LBCL)	Approximately 40% of patients achieved a complete response, and around 50% of patients achieved a partial response (PR)	[74]
7	Ciltacabtagene Autoleucel	Legend	2022,US	BCMA	Multiple myeloma (MM)	Ciltacabtagene autoleucel has shown an overall response rate of 95% in heavily pretreated patients with relapsed or refractory multiple myeloma	[75]

[#] The first approval year and country of the CAR-T product

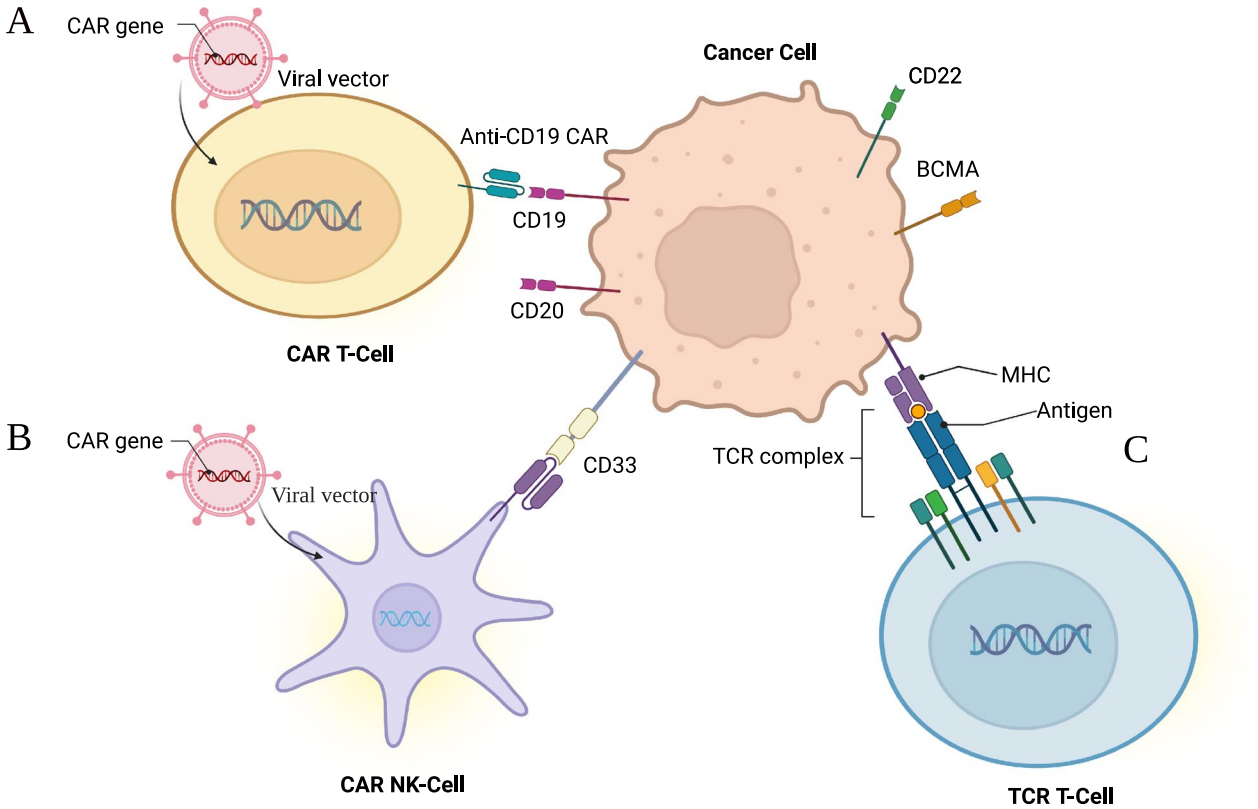

Fig. 4 Schematic representation of CAR-T, CAR-NK, and TCR-T. A, B) Scientists use genetic engineering techniques, such as viral vector transduction, to transform T cells and NK cells into CAR-T cells and CAR-NK cells. After expansion of the cells, these cells will target antigens on tumor cells to kill tumor cells. C) Scientists use genetic engineering methods to transfer TCR sequences into T cells. The modified T cells are then infused back to the patient's body to specifically recognize and kill antigen-expressing tumor cells for tumor treatment

example, Relmacabtagene autoleucel, a CD19-targeting CAR-T product from Minstracycline with a strong safety profile, was approved by the FDA for the treatment of relapsed or refractory large B-cell lymphoma (r/r LBCL) in adults after second-line or more systemic therapy. The efficacy of Relmacabtagene autoleucel was demonstrated in the ZUMA-1 clinical trial, where it achieved a high overall response rate and durable responses in patients with r/r LBCL. In the trial, approximately 40% of patients achieved a complete response, meaning no evidence of cancer, and around 50% of patients achieved a partial response (PR), indicating a significant reduction in tumor burden [74]. The median duration of response was over a year, indicating long-lasting remissions in responders.

The effectiveness of CAR-T cells in the treatment of solid tumors is poor. A description of the three areas that present the biggest difficulties is given below [79]. First, there are concerns about safety and specificity. Patient benefits must be weighed against potential risks because TAA-targeting CAR-T cells can have serious side effects, such as neurotoxicity and cytokine release syndrome (CRS). The effector-target ratio should also be considered for a solid tumor with a diameter of 1 cm; a solid tumor has approximately 10 [9] cells. Finally, two main barriers to solid tumors must be considered: the physical barrier and the immunosuppressive microenvironment [80].

From the perspective of technological development, the CAR technology has undergone rapid amendments. Recently, fifth-generation CAR-T cells were introduced and designed to simultaneously activate TCR, costimulatory domain CD28, and cytokine triple signaling. Fifth-generation CAR-T cells can destroy the TCR and HLA class I genes of T cells through gene editing technology (ZFN, TALEN, and CRISPR/Cas9) in vitro to avoid graft-versus-host disease (GVHD). As a result, individual limitations can be overcome and widespread applications in both large-scale production and treatment are enabled. Investigators have demonstrated that fifth-generation CAR-T cells are genetically modified to enhance T-cell proliferation, survival, and anti-tumor efficacy compared to second-generation CAR in both hematologic and solid tumor models [81].

To reduce side effects and improve safety, CAR-T cells are expected to create CAR architectures that can

recognize new targets and modify CAR-T cells to release substances that can alter the tumor-suppressive microenvironment [77, 78].

CAR-NK cell therapeutic strategy

The advantages of CAR NK cells over CAR T cells are presented below. To the best of our knowledge, this is the first report of a significant safety benefit of these cells. Notably, allogeneic NK cell infusion does not result in CRS or significant neurotoxicity because it is well tolerated. Second, a wide range of anticancer drugs is available as the inhibitory activity of MHC on the cell surface is not necessary for tumor-specific recognition and does not prevent this recognition [82].

In terms of targets, CAR-NK as similar to CAR-T targets, such as CD19, CD22, BCMA, and CD33 (Fig. 4). NK92-CD19-CD3ζ for B-cell malignancies and CD138-CAR-NK-92 for multiple myeloma have been recently developed. Some drugs that target TAA, such as PSMA, ROBO1, and NKG2D, are also being evaluated [83, 84]. In 2021, the NMPA approved a clinical trial application for targeted mesothelial chimeric antigen receptor NK cell injection (CAR-NK injection) developed by Guojian Chengnuo Biotechnology for the treatment of advanced epithelial ovarian cancer. In recent years, CAR-NK cell therapy has been widely applied in studies on glioblastoma, breast cancer, ovarian cancer, and pancreatic cancer, and its therapeutic effects on solid tumors have been confirmed [85].

TCR-T cell therapeutic strategy

TCR-T cell therapy not only acts on common tumor-associated peptide targets, but also targets neoantigens derived from somatic mutations in tumors, which represents a highly personalized approach to therapy (Fig. 4) [86, 87]. Common targets of TCR-T include NY-ESO-1, PRAME protein, MAGE protein, melanoma differentiation antigen MART-1, and cancer drivers, such as WT1, KRAS, and TP53, which are highly expressed in myeloma and melanoma. On January 25, 2022, the first TCR-T therapy, tebentafusp-Tebn, received FDA approval for HLA-A* 02:01-positive adults with unresectable or metastatic uveal melanoma.

A total of 378 HLA-A*02:01 positive patients with metastatic uveal melanoma were enrolled in the IMCgp100-202 trial [88]. Compared with the investigator's selected regimen, the median overall survival (21.7 months vs 16 months) and median progression-free survival (PFS) (3.3 months vs 2.9 months) were significantly prolonged, and the 1-year overall survival rate (73.2% vs 58.5%) was significantly improved. Tebentafusp-tebn monotherapy reduced the risk of death by 49%, and significantly reduced the risk of disease progression or death by 27%.

With the updated iteration of the technology, more innovations have been applied to TCR-T [87, 89]. For example, the Xiangxue Precision Company took the lead in applying phage display technology to T-cell receptor research worldwide, invented the directed evolution technology of TCR, and developed the world's first human-derived high-affinity soluble TCR.

Conclusion and perspective

The rapid advancement of the gene sequencing technology and integration of bioinformatics and big data science have led to the development of precision medicine, a novel medical concept and paradigm focused on personalized medicine. Fortunately, more novel therapies and new targeted medications have made considerable advancements in recent years, and the utilization of cutting-edge technology to address specific problems associated with cancer has offered many patients fresh hope.

The path of "precision targeting" treatment is continuously being extended by the significant advancement of "undruggable" KRAS targets, antibody immune drugs to break the impasse dependent on chemotherapy and radiotherapy, the extension of ADC drugs from hematological malignancies to solid tumors, and the emergence of new therapies, including cellular immunotherapy.

Compared to traditional cancer treatment strategies, they show more advantages as followed. Firstly, small molecule targeted therapy, antibody drugs, CAR-T cell therapy, and ADC act more precisely on cancer cells or their associated molecules, reducing damage to normal cells. These treatment strategies provide more effective treatment strategies by specifically targeting cancer cells. Secondly, the new generation of cancer treatment strategies emphasizes personalized treatment based on factors such as patients' genetic variations, tumor characteristics, and immune status. This individualized approach helps improve treatment outcomes, reduce unnecessary treatments, and minimize side effects. Thirdly, antibody drugs and CAR-T cell therapy activate patients' own immune systems to attack cancer cells. They enhance patients' immune response, helping the body recognize and eliminate cancer cells while providing long-term immune protection. Fourthly, the new generation of cancer treatment methods has demonstrated higher efficacy in certain types of tumors. For example, small molecule targeted therapy and ADC can target specific cancer driver genes or surface molecules, inhibiting tumor growth and metastasis. CAR-T cell therapy shows excellent results in treating refractory or relapsed hematologic malignancies. Lastly, nanobody drugs and ADC utilize nanotechnology and drug carriers to enhance drug delivery and stability, increasing local drug concentration and reducing adverse reactions.

However, these new generation cancer treatment methods also face challenges, including high treatment costs, complexity, individual patient resistance, and treatment-related adverse reactions. The KRAS mutation types, G12S, G12V, and G12D, and other targeted drugs must be conquered. Overall, BiAbs should improve stability and reduce immune escape, ADC is expected to widen the therapeutic window and increase efficiency, and improved safety and application of CAR-T in the field of solid tumors are needed, all of which require further research.

Further therapeutic innovations are anticipated as we continue to remove technical obstacles, address drug resistance, identify molecules linked to cancer recurrence and metastasis, and enhance the accuracy, safety, and controllability of targeted drugs. Recently, advancements have been made in the use of KRAS inhibitors. BiAbs are expected to replace monoclonal antibodies as a mainstream therapy. By 2025, CAR-T therapy is expected to be approved for solid tumors.

The long-standing treatment model will gradually be fundamentally altered, clinical outcomes will be significantly improved, a significant pattern of individualized diagnosis and treatment will be established, and future generations of patients will benefit from precision medicine.

Abbreviations

KRAS	Kirsten rat sarcoma viral oncogene
EGFR	Epidermal growth factor receptor
ADCs	Antibody drug conjugates
ORR	Overall response rate
DCR	Disease control rate
mOS	Median overall survival
NSCLC	Non-small cell lung cancer
CNS	Central nervous system
GEFs	Guanine nucleotide exchange factors
SOS	Son of sevenless homolog
HCC	Hepatocellular carcinoma
ICI	Immune checkpoint inhibitors
TMB	Tumor mutation burden
TIM-3	T cell immunoglobulin domain and mucin domain-3
IC_{50}	Half maximal inhibitory concentration
AML	Acute myeloid leukemia
HR-MDS	High-risk myelodysplastic syndromes
LAG3	Lymphocyte-activation gene 3
BsAbs	Bispecific Antibodies
BiTE	Bispecific T-cell engager
NMPA	The National medical products administration
FDA	Food and drug administration
PDCs	Peptide drug conjugates
SMDCs	Small molecule drug conjugates
T-DXd	Trastuzumab deruxtecan
ALL	Acute lymphoblastic leukemia
MM	Multiple myeloma
r/r LBCL	Relapsed or refractory large B-cell lymphoma
TAA	Tumor-associated antigen
CRS	Cytokine release syndrome
MHC	Major histocompatibility complex
HER2	Human Epidermal Growth Factor Receptor 2
EGFR	Epidermal Growth Factor Receptor
VEGF	Vascular Endothelial Growth Factor

Acknowledgements
This study was supported by the National Natural Science Foundation of China (82173662), Natural Science Foundation of Shanghai (20ZR1410400), State Key Basic Research Program of China (2018YFC0310905), Extraordinary 2025 Elite Project of Fudan University, and Open Funding of the Key Laboratory of Diagnosis and Treatment of Severe Hepato-Pancreatic Diseases of Zhejiang Province (2018E10008). All figures were created with biorender.com.

Authors' contributions
X. Cao, H. Jiao, and X. Lu conceived the review. X. Huang, R. Chen, J. Ni, W. Zhao, and S. Li performed the literature review, and organized and prepared the manuscript. X. Huang, X. Lu, and X. Cao revised the manuscript. All authors approved the submission of this manuscript.

Availability of data and materials
The data that support the findings of this study are available from the author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study complied strictly with national ethical guidelines and with the Helsinki Declaration (as revised in 2013).

Competing interests
The authors declare no competing interests of this manuscript.

Received: 18 May 2023 Revised: 5 July 2023 Accepted: 12 July 2023
Published online: 06 December 2023

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