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Precision medicine and beyond: Evolving roles of targeted therapy, immunotherapy, and artificial intelligence in oncology

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Abstract

Precision medicine in oncology is an evolving therapeutic approach that leverages genetic, clinical, and biomarker data to tailor treatments to individual patients. This review explores the three core pillars of modern precision oncology: targeted therapy, immunotherapy, and the integration of artificial intelligence (AI) into clinical practice. Targeted therapies, including monoclonal antibodies and antibody-drug conjugates, selectively inhibit molecular pathways involved in tumor growth. While conventional chemotherapy remains the backbone of treatment and has improved remission rates, its cytotoxic nature limits broader applicability and increases the risk of comorbidities. Immunotherapies, particularly immune checkpoint inhibitors and chimeric antigen receptor T-cell therapies, have transformed treatment for hematologic malignancies and are now being adapted for solid tumors such as colorectal, pancreatic, and hepatocellular carcinomas through novel combination regimens. This review also highlights the therapeutic potential of modulating the tumor microenvironment and introduces emerging modalities such as neoantigen vaccines and microRNA-based therapies. Furthermore, we outline the expanding role of AI in enhancing cancer diagnosis, drug development, and clinical decision-making. By integrating computational tools with molecular therapies, precision medicine rapidly advances toward individualized data-driven care. This review provides an overview of established therapies in the current clinical practice, novel regimens, and emerging AI technologies. Despite ongoing challenges, such as resistance and toxicity, precision medicine demonstrates significant promise in improving oncologic outcomes and transforming cancer care.

Keywords: Precision medicine; Targeted therapy; Immunotherapy; Artificial intelligence; Cancer treatment; Oncology

1. Introduction

Precision medicine is a medical approach focused on patient stratification using large-scale data, including clinical, lifestyle, genetic, and biomarker information, thus going beyond

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the classical "signs-and-symptoms" approach.[1] Targeted therapy, as defined by the National Cancer Institute, involves chemotherapy that blocks the action of specific molecules (enzymes, proteins, etc.) in pathways involved in neoplasm proliferation.[2] Cancer immunotherapy can be classified as active or passive. Active immunotherapies aim to induce specific immune responses against tumors and generate durable antitumor immune memory, whereas passive approaches involve the administration of immune components, such as monoclonal antibodies, without necessarily inducing immune memory.[3] The current chemotherapies have improved remarkably, with improved remission and cure rates. Traditional chemotherapy has undeniably established its importance regarding its precedence in treating cancer, its lower cost, and easier accessibility compared with targeted therapy. However, while there are abundant treatment options for chemotherapy, its cytotoxic nature limits the possibility of applying all potential options without inducing more comorbidities.[4] In addition, gaps remain in understanding the best approach to integrate novel targeted therapies and immunotherapies into routine clinical practice. As a result, this review summarizes both established targeted therapies currently approved for clinical use and those undergoing trials. Moreover, this review discusses the potential of incorporating artificial intelligence (AI) into discovering new targeted therapies and designing individualized treatment regimens, which can help tailor the most suitable treatment to achieve optimal outcomes.

This review explores current precision medicine practices in chemotherapy, focusing on targeted therapies and immunotherapy options, and potential AI applications. The review commences with a discussion on all established targeted therapies in standard care, specifically monoclonal antibodies or antibody-drug conjugates (ADCs) that target specific genes. The following section discusses monoclonal antibodies, including established therapies and combination regimens currently in clinical trials. It also covers preclinical trial models, exploring various strategies to enhance drug delivery and modulate the tumor microenvironment (TME), primarily focusing on hepatocellular carcinoma (HCC), pancreatic cancer, and colorectal cancer (CRC). Chimeric antigen receptor (CAR) T-cell therapy is featured in both sections due to its established success in hematological cancer and its expanding application to other advanced-stage solid tumors.[5] This is followed by a section exploring the potential of incorporating AI algorithms into precision medicine in various aspects, including diagnosis, drug development, and clinical practice.

2. Methodology

This review was first conceptualized by outlining the key topics to be discussed. It was then organized into subsections corresponding to each topic (established therapies, targeted therapies, and AI). To maintain a focused scope, the selection of publications prioritized studies addressing the pharmacological implications, treatment response, and adverse effects of targeted therapies. Commonly used treatments were identified, and a targeted, retrospective literature search was conducted to gather relevant information. Notably, this review does not follow a formal systematic review protocol.

This review also discusses the emerging targeted therapies currently in the pre-clinical or clinical trial phases for HCC, CRC, and pancreatic cancer. These cancers were selected due to their high resistance to treatment, poor response rates, and significant global prevalence. Tables were included to present summarized data from the reviewed publications more clearly.

3. Targeted therapies in clinical practice

Compared to traditional chemotherapy and radiation that indiscriminately damage both cancerous and healthy cells, targeted therapies concentrate on specific molecular pathways driving tumor growth, limiting systemic toxicity and adverse effects. These advancements have significantly improved clinical outcomes, with many targeted drugs achieving superior response rates and prolonged survival in patients with specific genetic mutations. Table 1 shows representative clinical trials highlighting the therapeutic application of targeted agents and immunotherapies across multiple cancer types.

3.1. Human epidermal growth factor receptor 2 (HER2)

HER2, a protein involved in normal cell growth, may be produced in excess by certain types of cancer cells, including those in breast, ovarian, bladder, pancreatic, stomach, and esophageal cancers. HER2 belongs to the epidermal growth factor receptor (EGFR) family, which comprises four types: ErbB1 (EGFR/HER1), ErbB2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). Overexpression of HER2 proteins leads to the formation of homodimers or heterodimers that promote cell growth and proliferation through the phosphatidylinositol 3-kinase/protein kinase B and rat sarcoma/mitogen-activated protein kinase (MEK) pathways, which ultimately contribute to oncogenesis, leading to cancer development. Targeted therapies that bind to the extracellular domain of HER2 prevent heterodimer formation and inhibit cancer growth.[16] Trastuzumab deruxtecan (T-DXd), an ADC consisting of a monoclonal antibody linked through a cleavable tetrapeptide to a membrane-permeable topoisomerase I inhibitor, ensures high drug delivery and cytotoxic effects within HER2-expressing cells, particularly targeting

Table 1. Drug list for established targeted therapies

Drug name	Target	Biomarker	Method of detection	Clinical use	Adverse effects	Sample size	Reference	Combinations
Trastuzumab-deruxtecan	HER2	HER2	Biopsy+IHC	Breast, bladder, ovarian, gastric cancers, NSCLC	Nausea, vomiting, constipation, diarrhea, anorexia, fatigue, alopecia, anemia	Synthesized in review[a]	Martín *et al.* [6]	Antibody - drug conjugate (trastuzumab + deruxtecan)
Pembrolizumab	PD-1	N/A	Biopsy+flow cytometry	NSCLC, HCC,	Diarrhea, autoimmune hepatitis, type 2 diabetes mellitus, and immune reactions	154	Reck *et al.* [7]	
Osimertinib	EGFR	N/A	Biopsy+flow cytometry and serum	NSCLC	Rash, acne, diarrhea, dry skin, interstitial lung disease, QT prolongation (0.33%), one patient each had fatal pneumonia, cerebral infarction, myocardial infarction, pulmonary embolism	279	Soria *et al.* [8]	Osimertinib platinum - based chemotherapies
Palbociclib	CDK4/6	N/A	Biopsy+flow cytometry	Hormone-positive breast cancer, HCC	Neutropenia, leukopenia, thrombocytopenia, fatigue, nausea, headache, upper respiratory infections	417	Turner *et al.* [9]	Palbociclib + fulvestrant
Letrozole	Aromatase	N/A	Biopsy+IHC	ER or PgR-positive breast cancer	Arthralgia, hot flashes, weight gain, insomnia, vaginitis, fatigue	164; 666	Ingle *et al.* [10]; Finn *et al.* [11]	Palbociclib; letrozole
Fulvestrant	ERa	HER2	Biopsy+flow cytometry	ER-positive breast cancer	Hot flashes, headache, nausea, vomiting, constipation, increased LFTs, UTIs, rashes, vaginitis	347 patients	Cristofanilli *et al.* [11]	Palbociclib + fulvestrant
Dabrafenib	BRAF V600E	N/A	Biopsy+flow cytometry	NSCLC	Fatigue, pyrexia, headache, arthralgia, hyperkeratosis, retinal vein occlusion, pneumonitis, interstitial lung disease, cutaneous SCC	36 patients	Planchard *et al.* [12]	Dabrafenib + trametinib
Trametinib	MEK1, MEK2, BRAF	Ki67	Biopsy+flow cytometry	Melanoma, NSCLC	Dermatitis acneiform, peripheral edema, fatigue, nausea	Synthesized in review[a]	Salama *et al.* [13]	Dabrafenib + trametinib
Sorafenib	Raf-1, BRAF, VEGFR1-3, PDGFR-β	ACSL4	Serum	HCC	Fatigue, weight loss, desquamation, hand-foot skin reaction, alopecia, diarrhea, anorexia, nausea, vomiting, voice change	227 patients	Llovet *et al.* [14] and Feng *et al.* [15]	

Note: N/A refers to not available. [a]Indicates data sourced from reviews Martín *et al.* [6] and Feng *et al.*,[15] which synthesize evidence rather than report original sample size.

Abbreviations: ACSL4: Acyl-CoA synthetase long chain family member 4; BRAF: V-Raf murine sarcoma viral oncogene homolog B1; CDK4/6: Cyclin-dependent kinase 4/6; EGFR: Epidermal growth factor receptor; ER: Estrogen receptor; HCC: Hepatocellular carcinoma; HER2: Human epidermal growth factor receptor 2; IHC: Immunohistochemistry; LFTs: Liver function tests; MEK: Mitogen-activated protein kinase; NSCLC: Non-small cell lung cancer; PD-1: Programmed cell death protein 1; PDGFR-β: Platelet-derived growth factor receptor beta; PgR: Progesterone receptor; Raf-1: Rapidly accelerated fibrosarcoma 1; SCC; Squamous cell carcinoma; UTIs: Urinary tract infections; VEGFR: Vascular endothelial growth factor receptor.

extracellular region IV. This combination therapy may reduce platelet count, fatigue, and anemia.[6] While earlier HER2-directed agents targeted tumors with high HER2 expression, T-DXd has demonstrated activity beyond these, including HER2-positive (immunohistochemistry [IHC] 3+ or IHC 2+/*in situ* hybridization [ISH]+) and HER2 low diseases (IHC 1+ or IHC 2=/ISH-). In HER2-low breast cancer patients (IHC 1+ or IHC 2+/ISH-negative), T-DXd received the Food and Drug Administration's (FDA) approval based on the DESTINY-Breast04 trial, which showed a median progression-free survival (PFS) of 9.9 months compared to only 5.1 months with physician's choice of chemotherapy, corresponding to a hazard ratio (HR) of 0.05.[17] Furthermore, in the DENSITY-Breast06 trial, T-DXd showed efficacy in HER2 ultra-low breast tumors (IHC 0 with membrane staining of ≤10%), with a median PFS of 13.2 months compared to 8.1 months in the physician's choice group (HR: 0.72).[18] In HER-mutated non-small cell lung cancer (NSCLC) with activated ErbB2 exon 20 insertions, T-DXd achieved an objective response rate (ORR) of 49% and a median duration of response of 16.8 months in the DESTINY-Lung02 trial.[19] In addition, compared to trastuzumab emtansine, another ADC, T-DXd features lysable linkers with an increased drug-to-antibody ratio, enhancing its antitumor effects.[20,21] With leading success rates in multiple trials and studies, HER2-targeting drugs have demonstrated remarkable efficacy in treating breast, bladder, NSCLC, ovarian, gastric, colon, cervical, and endometrial cancers.[16]

3.2. Programmed cell death protein 1 (PD-1)/ programmed death ligand 1 (PDL1)

PD-1 and PDL1 are transmembrane proteins belonging to the immunoglobulin superfamily. PD-1 can be found on activated T-cell membranes, while PDL1 typically acts as the ligand.[22] The interaction between PD-1 and PDL1 inhibits lymphocyte proliferation through the T-cell receptor, supporting immunosurveillance. However, many tumors exhibit elevated expression of PDL1, allowing uncontrolled proliferation.[23] Pembrolizumab, a monoclonal antibody, binds to these PD-1 receptors on T cells, prevents further conjugation with PDL1 ligands, and restores the immune response against tumor cells. The KEYNOTE-024 trial demonstrated significant overall survival (OS) benefits of pembrolizumab as monotherapy in NSCLC patients with a tumor total proportion score (TPS) of PDL1 ≥50%.[7] KEYNOTE-042 revealed a significant OS benefit in tumors with PD-L1 TPS ≥1% (median OS 16.7 versus 12.1 months; HR: 0.81) and in the 1–49% subgroup (HR 0.88).24 In addition, large-scale clinical trials such as KEYNOTE-189[25] and 407[26] have shown that pembrolizumab, when combined with platinum-based chemotherapy, improves survival in patients with advanced NSCLC regardless of PDL1 expression level. Similarly, the KEYNOTE-189 trial demonstrated improved OS across all PDL1 strata, including the <1% (HR: 0.59), the 1–49% (HR: 0.55), and the ≥50% (HR: 0.36) groups, by adding pembrolizumab to pemetrexed-platinum chemotherapy.25 KEYNOTE-407 reported similar results.26 Despite the common use of general platinum-based chemotherapies, targeted therapies like pembrolizumab have resulted in an increase in OS irrespective of *EGFR* or *ALK* sensitizing mutations, regardless of administering it in combination or as a monotherapy.

Atezolizumab is an immunoglobulin G1 (IgG1) antibody derived from phage display technology. It binds and blocks PDL1 on tumor cell surfaces and has shown significant curative results in kidney, bladder transitional cell carcinoma, and breast cancer.[27] In a study of 3,336 patients who had previously received platinum-based chemotherapies, those receiving atezolizumab were associated with a significantly improved OS compared to other treatments, including docetaxel and nivolumab.[28]

3.3. Tyrosine kinase inhibitor (TKI)-EGFR

TKIs target enzymes that are critical in various cellular processes, including signaling, growth, and proliferation. In several cancer types, these kinases are dysregulated due to mutations or overexpression, leading to unchecked cell growth. Targeting these kinases can inhibit tumor progression. Osimertinib is a third-generation EGFR-TKI that selectively targets both *EGFR*-sensitizing mutations and the T790M resistance mutation in patients with advanced NSCLC. In the FLAURA trial, osimertinib, used as first-line treatment in advanced *EGFR*-mutated NSCLC, demonstrated a median PFS of 18.9 months.[8] It also showed a favorable safety profile with lower incidences of grade ≥3 adverse events, such as rash, diarrhea, and interstitial lung disease. Current clinical guidelines recommend molecular testing for *EGFR* mutations in patients with advanced NSCLC to determine eligibility for EGFR-TKI targeted therapy.[29] Osimertinib is currently the preferred first-line treatment for patients harboring these *EGFR* mutations due to its strong efficacy, central nervous system penetration, and safety profile.[30] In addition, for patients who develop resistance to first- or second-generation EGFR-TKIs – particularly those with the T790M resistance mutation – osimertinib remains the recommended treatment option. In February 2024, the FDA approved osimertinib in combination with platinum-based chemotherapy for patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 19 deletions or exon 21 L858R mutations.[31,32] Furthermore, the FDA approved osimertinib for adults with locally

advanced, unresectable stage III NSCLC whose disease has not progressed during or following platinum-based chemoradiation therapy, provided their tumors have specific *EGFR* mutations.[33] These advancements highlight the crucial role of osimertinib in the management of EGFR mutant NSCLC, offering improved survival outcomes and enhanced quality of life through personalized therapeutic strategies.

EGFR-inhibiting monoclonal antibodies such as cetuximab[34] and panitumumab[35] are also standard-of-care for *RAS* wild-type metastatic CRC. Cetuximab, a chimeric IgG1 monoclonal antibody, and panitumumab, a fully human IgG2 monoclonal antibody, both target the extracellular domain of EGFR to inhibit downstream signaling. However, their efficacy is restricted to patients with *RAS* wild-type tumors, as activating mutations in *KRAS* or *NRAS* result in constitutive downstream signaling that renders EGFR inhibition ineffective. Thus, *KRAS* mutation serves as a predictive biomarker of resistance to anti-EGFR therapy. Molecular profiling to assess *RAS* mutation status is essential before initiating treatment with cetuximab or panitumumab. Multiple clinical trials and meta-analyses have demonstrated that these therapies significantly improve PFS and OS in eligible patients.[36,37]

3.4. Cyclin-dependent kinase (CDK) 4/6

CDK4 and CDK6 regulate cell cycle progression by operating within the G1 to S phase transition; their enzymatic performance is based on D-type cyclins that are expressed in response to signals, including mitogens, cytokines, and estrogen. Once activated, CDK4/6 holoenzymes phosphorylate retinoblastoma tumor suppressor proteins that repress early 2 transcription factors responsible for DNA replication and mitosis. CDK4 and 6 inhibiting therapies can avert retinoblastoma phosphorylation and block the transcription of early 2 factor target genes, thereby inhibiting both estrogen- and mitogen-mediated cell growth.[38] Palbociclib and ribociclib can selectively inhibit CDK4/6, while abemaciclib is a more distinct pyrimidine scaffold that further enhances selectivity and pharmacokinetic properties that are more effective at lower doses and suited for long-term administration.[39] Palbociclib (pyridopyrimidine) showed a prolonged PFS across PDL1 strata; however, no statistically significant OS was observed in the PALSOMA-2/3 trial.[40] Ribociclib demonstrated a superior OS as the first-line treatment in the MONALEESA-2 trial (63.9 versus 51.4 months; HR: 0.76) and as an adjuvant in the NATALEE trial (HR: 0.74 in stage II/III). It efficiently modulated tumor immunity and was successfully combined in CDK4/6 plus immunotherapy regimens.[41] In addition, abemaciclib exhibited a higher selectivity for CDK4 over CDK6, enabling continuous dosing, brain penetration, and approval as a single agent for endocrine-refractory conditions. Consequently, studies investigating CDK4/6 inhibition in *ESR1*-mutant tumors have been conducted.[42,43]

While the PALOMA-2 and PALOMA-3 trials demonstrated a significant improvement in PFS with the addition of palbociclib to endocrine therapy – such as letrozole or fulvestrant – in hormone receptor-positive, HER2-negative advanced breast cancer, neither study showed a statistically significant OS benefit.[44-47] Nonetheless, the favorable PFS and manageable toxic profiles have led to the widespread use of palbociclib in clinical practice.

3.5. V-Raf murine sarcoma viral oncogene homolog B1

V-Raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitors block a specific protein called BRAF, a kinase enzyme that helps control cell growth and signaling. Dabrafenib is a BRAF inhibitor combined with trametinib, a MEK inhibitor. Together, they inhibit the BRAF V600E mutation and the downstream MEK pathway. Combination therapy has shown an overall response rate of approximately 64% in patients with *BRAF* V600E-mutant SCLC with minimal adverse effects such as pyrexia, hypertension, and vomiting.[12] Based on these findings, the FDA approved the combination of dabrafenib and trametinib for the treatment of metastatic NSCLC harboring the *BRAF* V600E mutation.[48] In clinical practice, identifying patients with *BRAF* V600E mutations is crucial for selecting appropriate targeted therapies. Comprehensive molecular profiling of tumors is recommended to detect actionable mutations, including *BRAF* V600E, to guide treatment decisions.[49] The combination of dabrafenib and trametinib offers a valuable treatment option for patients with this specific genetic mutation, providing significant clinical benefits with a tolerable safety profile.

3.6. Vascular endothelial growth factor receptor (VEGFR)

VEGFR inhibitors prevent the formation of new blood vessels required for tumor growth and may also induce cancer cell death. Sorafenib is an oral multi-kinase inhibitor of VEGFR, platelet-derived growth factor receptor, and rapidly accelerated fibrosarcoma. In patients with advanced HCC, it extends OS by about 3 months compared to placebo (median OS ~10.7 months).[14] Increasing levels of the enzyme DEAD box protein 5 (DDX5) in liver cancer cells improved the effectiveness of sorafenib. Higher DDX5 levels enhanced sorafenib's ability to reduce tumor growth, suggesting that therapies boosting DDX5 could potentiate sorafenib's anticancer effects.[50] Used as a second-line treatment for patients who have progressed

on sorafenib, regorafenib inhibits multiple kinases involved in tumor angiogenesis, oncogenesis, and the TME. The RESORCE trial reported a median OS of 10.6 months for regorafenib compared to 7.8 months for placebo.[51]

3.7. Anaplastic lymphoma kinases (ALK)

ALK belongs to the insulin receptor superfamily. These genes play crucial roles in alternative splicing, mutations, and amplifications linked to inflammatory myofibroblastoma and NSCLC. *ALK* rearrangements can also induce T cell activation, cytokine release, and immune surveillance in tumors. TKIs such as crizotinib, alectinib, and lorlatinib have gained approval for advanced ALK+ NSCLC due to their ability to significantly improve efficacy compared to standard chemotherapies. Second-generation ALK-TKIs, like alectinib, demonstrate greater clinical efficacy in terms of median PFS, ORR, duration, and higher central nervous system response rates compared to crizotinib, a first-generation ALK-TKI.[52] Alectinib functions as a selective inhibitor and substrate that easily penetrates through the blood–brain barrier and prevents downstream tumor survivability, avoiding the collateral damage of chemotherapy regimens.[53]

3.8. Rearranged during transfection gene fusions inhibitors

RET (rearranged during transfection) gene fusions are oncogenic drivers found in a small subset of solid tumors, including NSCLC and thyroid cancers. These gene rearrangements result in constitutive kinase activity that promotes tumorigenesis, making them actionable targets for precision therapies.

Selpercatinib and pralsetinib are highly selective RET inhibitors that have demonstrated significant clinical efficacy in RET fusion-positive NSCLC and thyroid cancers. The LIBRETTO-001 trial showed that selpercatinib achieved an ORR of 64% in previously treated NSCLC patients and 85% in treatment-naive patients.[54] In medullary thyroid cancer with RET mutations, selpercatinib also showed durable responses with manageable toxicity profiles, including hypertension and elevated liver enzymes.[55]

Given its clinical activity and favorable safety profile, RET inhibition represents a critical component of precision therapy in cancers harboring RET rearrangements. Genomic profiling for RET fusions or mutations is essential for patient selection, and ongoing trials are exploring combination strategies to enhance response and mitigate resistance.

3.9. Neurotrophic tyrosine receptor kinase (NTRK) inhibitors

NTRK gene fusions are rare but actionable alterations found across various adult and pediatric solid tumors, including salivary gland tumors, thyroid cancer, and some sarcomas. These fusions result in constitutive activation of TRK proteins, driving uncontrolled cell growth and survival.

Larotrectinib and entrectinib are first-generation TRK inhibitors approved for tumor-agnostic use in NTRK fusion-positive cancers. Larotrectinib demonstrated an ORR of 75% in a pooled analysis of adult and pediatric patients, with durable responses and minimal toxicity.[56] Entrectinib, which also targets c-ros oncogene 1 and ALK, has shown particularly strong efficacy in central nervous system-involved tumors due to its ability to penetrate the blood–brain barrier.[57]

Routine comprehensive genomic testing is critical for detecting NTRK fusions, and these therapies underscore the potential of histology-agnostic treatment strategies. Clinical trials continue to explore mechanisms of resistance and next-generation inhibitors.

3.10. CAR T-cell therapy

CAR T-cell therapy involves collecting a patient's T cells and genetically modifying them to express CARs that recognize specific antigens on cancer cells (Figure 1). Once infused back into the patient, these engineered T-cells can identify and destroy malignant cells expressing the target antigen. Tisagenlecleucel (Kymriah®), the first FDA-approved CAR T-cell therapy, is used for treating relapsed or refractory B-cell acute lymphoblastic leukemia in patients up to 25 years old.[58] Clinical trials have demonstrated high remission rates, offering hope to patients with limited treatment options. Axicabtagene ciloleucel (Yescarta®) and tisagenlecleucel have been approved for adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy, showing significant response rates.[59] CAR T-cell therapies targeting B-cell maturation antigen, such as idecabtagene vicleucel (Abecma®), have been approved for patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy.[60] Real-world data on idecabtagene vicleucel for relapsed/refractory multiple myeloma showed a 69% response rate with manageable toxicity,[61] though prolonged hematologic toxicity remains a challenge, highlighting the need for optimizing CAR T-cell expansion.

4. Therapies in preclinical/clinical trials

After the success of targeted therapies and immunotherapies in lung cancer, breast cancer, and hematological cancer, the use of targeted therapies has been expanded to other types of advanced-stage cancer with high metastatic potential, such as HCC, CRC, and pancreatic ductal adenocarcinoma (PDAC). For HCC, the primary tumor generated from

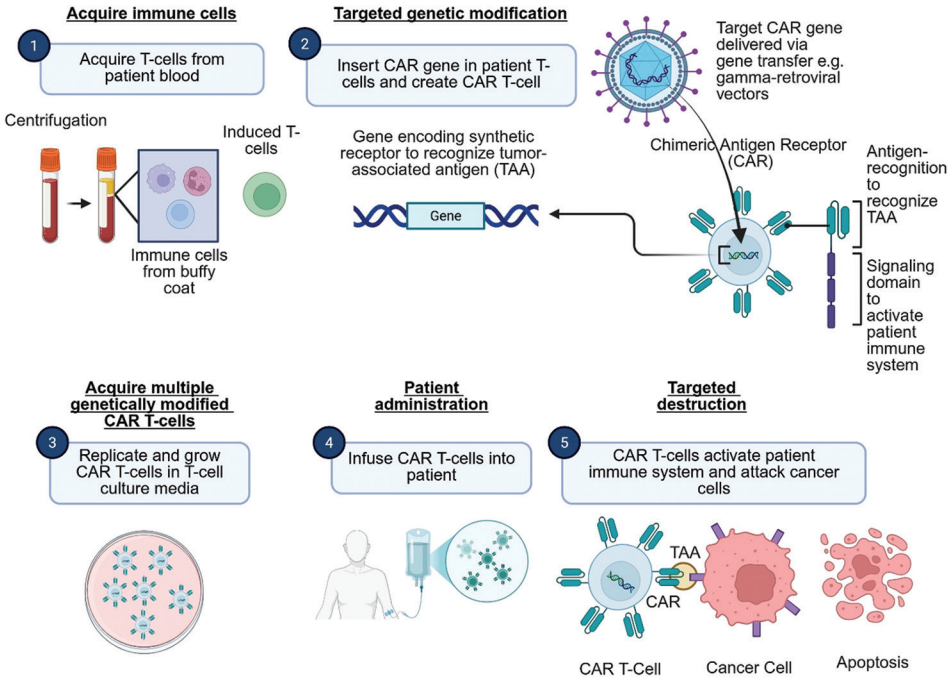

Figure 1. General mechanism of action for chimeric antigen receptor (CAR) T-cell therapy. Created in BioRender. Mito, S. (2025) https://BioRender.com/gqcdtct.

hepatocytes accounts for 90% of liver cancers. Although early-stage detection and subsequent surgical resection can increase the 5-year survival rate (50–75%), the recurrence rate can reach 50%. As a result, targeted therapy is one of the established therapies to suppress the rate of recurrence and enhance the 5-year survival rate.[62]

Comparably, CRC is the third most common cancer diagnosis and is ultimately the second leading cause of cancer-related death in the United States. The 5-year survival rate for early-stage CRC is 90%; however, the declining survival rate in metastatic CRC is heavily associated with minimal advancements in colorectal screening and therapeutics.[63] PDAC is acknowledged as one of the most challenging cancers to approach with management, as it is often diagnosed in its advanced stage due to difficulty in screening and detection. With precision medicine growing and newer targeted therapies taking the lead in promising clinical trials and research studies, PDAC has become one focus of such investigations.[64]

The major approaches in clinical trials have two directions: (i) to test the efficacy of a combined regimen between monoclonal antibodies targeting different genes and (ii) to explore options that can potentiate targeted therapies and reduce chemotherapy resistance in tumor cells. This section primarily discusses clinical trials testing combination regimens in HCC, CRC, and PDAC and their efficacies, along with their toxicity profiles. It also includes other candidates in Phase I/II clinical trials or in preclinical settings that show significant potential in enhancing the drug regimen. The drug list is summarized in Table 2.

4.1. PD-1/PDL1 combination therapy

In patients with CRC, characterized by DNA mismatch repair deficiencies and high microsatellite instability, immune checkpoint inhibitors (ICIs) have been effectively researched as therapies against solid tumors and other cancers as monotherapies. However, these patients are only a fraction of the total number of individuals with cancers that cannot be effectively treated in the same way and require combination therapies instead.[81] Therefore, PD-1/PDL1 has been tested in future clinical trials in combination with other therapies and slowly integrated into clinical practice.[82]

The treatment of HCC has slowly transitioned from molecular therapies, such as sorafenib and lenvatinib, toward immunotherapy as the first-line approach.[83] For example, nivolumab and pembrolizumab have been approved for late-stage HCC.[84] Pembrolizumab (Keytruda®) has demonstrated moderate efficacy as monotherapy in patients with higher PD-1/PDL1-expressing tumors but poor efficacy in other cancer types. However, when combined with gemcitabine (Gemzar®) and nab-paclitaxel in intermittently-scheduled doses, results have been shown to improve significantly with longer median PFS

Table 2. Drug list for preclinical/clinical therapies

Drug name	Target	Biomarker	Clinical use	Method of detection	Adverse effects	Sample size	Reference	Combination
Sotorasib	KRAS	N/A	CRC, PDAC, endometrial cancer, NSCLC, melanoma	Biopsy+flow cytometry (mainly serum for CRC progression)	Diarrhea, fatigue, nausea, anemia, elevated LFTs, hepatitis, hyponatremia	129 patients	Hong *et al.* [65]	Sotorasib + panitumumab
Adagrasib	KRAS	N/A	NSCLC, CRC, PDAC	Biopsy+flow cytometry	Fatigue, nausea, vomiting, diarrhea	25 patients	Ou *et al.* [66]	Adagrasib + docetaxel + cetuximab
CAR T-cell	CD19, GCC	N/A	Metastatic CRC, B-cell ALL, DLBCL, multiple myeloma	Serum	Cytokine release syndrome, diarrhea	15 patients	Chen *et al.* [67]	
Regorafenib	VEGFR	N/A	CRC, liver metastasis,	Serum	Hand-foot syndrome, rash, fever, hoarseness, diarrhea, hypertension, hepatotoxicity, chest distress, myalgia, headache, thrombocytopenia, fatigue	42 patients	Wang *et al.* [68]	Regorafenib + toripalimab
Toripalimab	PD-1	N/A	CRC, liver metastasis, nasopharyngeal carcinoma	Serum	Leukopenia, hypothyroidism, pruritus, pneumonia, and immune myocarditis	289 patients	Mai *et al.* [69]	Regorafenib + Toripalimab
Cabozantinib	VEGFR, c-MET	N/A	CRC	Serum	Acneiform rash, fatigue, diarrhea	25 patients	Strickler *et al.* [70]	Cabozantinib + panitumumab
Panitumumab	EGFR	N/A	CRC	Serum	Nausea, neutropenia, dermatitis acneiform, hypomagnesemia, diarrhea, hepatotoxicity	160 patients	Fakih *et al.* [71]	Cabozantinib + panitumumab and sotorasib + panitumumab
Nivolumab	PD-1	N/A	Melanoma, squamous cell lung cancer, NSCLC, HCC	Serum	Maculopapular rash, erythema, hepatitis, infusion reactions		Abedi Kiasari *et al.* [72]	
Camrelizumab	PD-1	N/A	Esophageal squamous cell carcinoma, HCC	Biopsy+flow cytometry	Neutropenia, hepatitis, reactive cutaneous capillary endothelial proliferation	596 patients	Xu *et al.* [73]	Camrelizumab + apatinib
Apatinib	VEGFR2	N/A	HCC	Serum	Hypertension, hand-foot syndrome, and thrombocytopenia	400 patients	Qin *et al.* [74]	Camrelizumab + apatinib
Cadonilimab	PD-1, CTLA-4	N/A	Cervical cancer	Serum	Neutropenia, lymphopenia, and anemia	445 patients	Wu *et al.* [75]	

(Cont'd...)

Table 2. ***(Continued)***

Drug name	Target	Biomarker	Clinical use	Method of detection	Adverse effects	Sample size	Reference	Combination
Tisotumab	Transcription factor	N/A	Cervical cancer	Biopsy+flow cytometry	Anemia, diarrhea, nausea, and thrombocytopenia	142 patients	Vergote *et al.*[76]	
Atezolizumab	PDL1	N/A	Kidney, bladder, transitional epithelial, breast, and cervical cancer, HCC	Biopsy+flow cytometry	Diarrhea, arthralgia, pyrexia, rash, hypothyroidism, hyperthyroidism, constipation, myalgia, infusion reaction	410 patients	Oaknin *et al.*[77]	
Sintilimab	PD-1	TMB, circulating tumor DNA	Hodgkin lymphoma, HCC	Serum	Pneumonia, diarrhea, colitis, hepatitis, nephritis, endocrine disease, infection reactions, rashes	146 patients	Zhang *et al.*[78]	Sintilimab+ bevacizumab
Durvalumab	PDL1	N/A	SCLC, HCC,	Serum	Febrile neutropenia, anemia, leukopenia, thrombocytopenia,	805 patients	Al-Salama *et al.*[79]	
Tremelimumab	CTLA-4	$CD4^+$, $CD8^+$	Melanoma, HCC, PDAC	Biopsy+flow cytometry	Increased LFTs, diarrhea, increased lipase, and amylase	332 patients	Kelley *et al.*[80]	Tremelimumab+ gemcitabine

Note: N/A refers to not available.
Abbreviations: ALL: Acute lymphoblastic leukemia; c-MET: Cellular-mesenchymal epithelial transition factor; CRC: Colorectal cancer; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; DLBCL: Diffuse large B-cell lymphoma; EGFR: Epidermal growth factor receptor; GCC: Guanylyl cyclase C; HCC: Hepatocellular carcinoma; KRAS: Kirsten rat sarcoma virus; LFTs: Liver function tests; NSCLC: Non-small cell lung cancer; PD-1: Programmed cell death protein 1; PDAC: Pancreatic ductal adenocarcinoma; SCLC: Small-cell lung cancer; TMB: Tumor mutational burden; VEGFR: Vascular endothelial growth factor receptor.

time (median of 9.1 months) for PDAC, suggesting that chemotherapy and immunotherapy combinations are a promising direction for further investigation, rather than relying on immunotherapy alone.[85]

Adjunct therapy combining VEGFR2 inhibitors and PD-1/PDL1 inhibitors has become an important strategy to treat HCC. For example, atezolizumab-bevacizumab has recently been approved by the FDA to treat HCC.[86] However, resistance to atezolizumab-bevacizumab, such as high *HES1* (transcriptional target of NOTCH pathway) expression, has been observed in clinical settings, highlighting the need for alternative therapeutic strategies.[87] First-line camrelizumab plus apatinib (VEGFR2 inhibitor) has shown remarkable efficacy and has since been used as a first-line therapy for unresectable HCC in a Phase 3 trial.[74] In addition, camrelizumab and apatinib are employed in a Phase I trial for advanced gastric cancer, and they showed favorable clinical outcomes with an overall response rate of 76.5%.[88] Sintilimab has shown superior clinical benefits compared to sorafenib when combined with bevacizumab.[89]

In addition, ADCs, the novel agents designed to deliver cytotoxic drugs into tumors, can further increase the efficacy of targeted therapies (Figure 2). The structure of ADC includes monoclonal antibodies that recognize specific markers expressed by tumor cells, linked to monoclonal antibodies with cytotoxic drugs that induce tumor cell death upon binding. Among several biomarkers, tumor mutational burden is currently the most widely accepted.[90,91] While efficacy is remarkably stronger, combination regimens generally induce stronger Grade 3 adverse events than single monoclonal antibody therapy; the most common side effects include hypertension and palmar-plantar erythrodysesthesia syndrome.

Numerous molecular targets have been identified in HCC, and targeting them may enhance the efficacy of ADCs. For instance, in an HCC mouse model, diacylglycerol kinase gamma was found to promote tumor

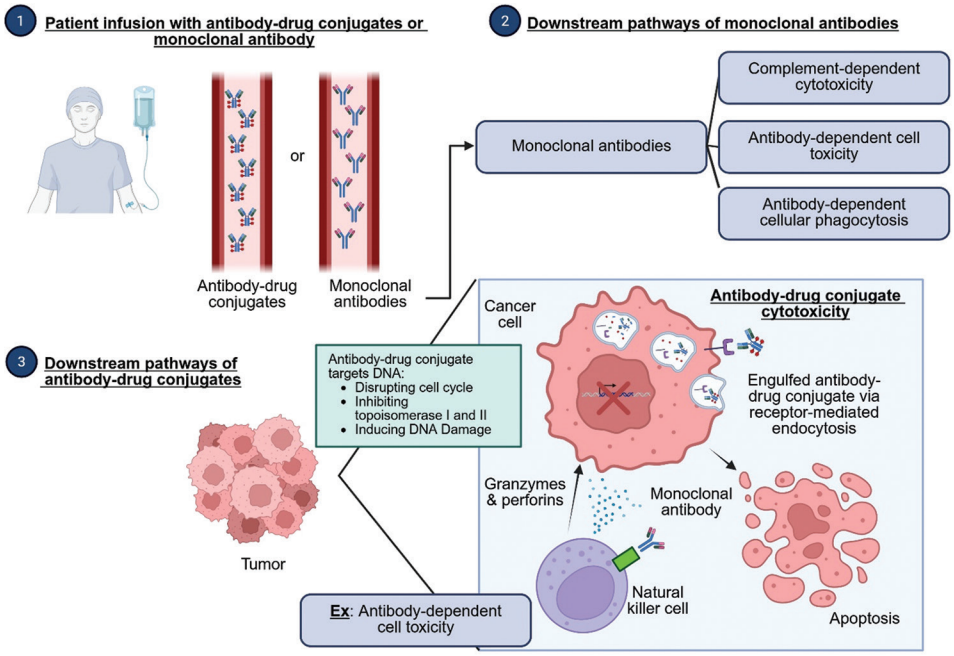

Figure 2. General mechanism of action of antibody-drug conjugate to potentiate the effects of monoclonal antibodies. Created in BioRender. Mito, S. (2025) https://BioRender.com/gqcdtct.

angiogenesis and immunosuppressive regulatory T-cell differentiation in HCC treated with camrelizumab and apatinib.[92] As more pathways and clinical data continue to emerge, genomic and transcriptomic sequencing have been employed to personalize treatment for HCC patients based on specific genetic mutations. For example, patients with *TSC2* inactivation have been treated with everolimus, while patients with *CDK4* amplification were treated with palbociclib.[82]

Another example of this chemo-immunotherapy combination effectiveness is explored in a Phase I trial combining tremelimumab (Imjudo®), a cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody, and gemcitabine. The trial suggested that increasing the dosage of the immunotherapy will result in a prolonged OS. However, the severity of Grade 3 toxicities also increased with increasing drug dose, including thrombocytopenia, nausea, diarrhea, anemia, neutropenia, and general weakness; nonetheless, the regimen was generally well-tolerated under close management.[93] However, a Phase II trial investigating tremelimumab combined with durvalumab (Imfinzi®), a PD-1/PDL1 inhibitor, reported minimal efficacy in PDAC patients, with a median PFS and OS of 1.5 months and 3.1 months, respectively, and an ORR of only 3.1%. It was speculated that the active T-cell suppression and nitric oxide synthase overexpression created by the dysregulated immune signaling cells produced a resistance to the antitumor response of the combined therapy. Thus, although this combination therapy was found to be well-tolerated, the results did not meet the efficacy threshold and highlighted the need for further investigation on both tremelimumab and durvalumab as plausible ICI choices when treating cancers like PDAC.[94]

A similar area of ongoing research for drug therapy combinations is the use of ipilimumab (Yervoy®), a cytotoxic T-lymphocyte-associated protein 4 monoclonal antibody, combined with GVAX (a granulocyte-macrophage colony-stimulating factor-secreting vaccine cancer therapy) to achieve a greater tumor response and survival rate. Although the study revealed no improved OS in patients with metastatic PDAC, it demonstrated promising biological effects, including increased T-cell differentiation and M1 macrophage infiltration.[95] Another Phase I study of metastatic castration-resistant prostate cancer patients treated with the same combination of ipilimumab and GVAX found a notable decline in prostate-specific antigen levels along with adequate clinical activity and tolerability.[96]

While anti-PD-1 therapy is especially helpful in targeting tumors with high microsatellite instability and DNA mismatch[97] – which are significantly associated with immunogenic subtypes of CRC, such as Lynch syndrome – combination therapy is crucial in treating microsatellite stable CRC with low immune cell infiltration

and is resistant to therapies targeting PD-1/PD-L1.[68] The use of multi-kinase inhibitor regorafenib with anti-PD-1 monoclonal antibody toripalimab has recently progressed to early phases of clinical trials to treat metastatic CRC. A Phase I/IIb trial analyzing the ORR and disease control rate in CRC patients treated with this therapy reported a 15.2% response rate of the 42 patients who were treated with the combination therapy; however, lower ORRs were seen in patients with liver metastases (8.7%). This reduction in response in CRC patients with liver metastases is likely due to resistance to checkpoint blockade, as the liver harbors a significant proportion of immunosuppressive cells that mediate this resistance.[68] High levels of the anaerobic species *Fusobacterium* are also associated with decreased response to the combination of regorafenib and toripalimab, and its presence can be used as a marker in monitoring treatment resistance.[68] In addition, the disease-control rate was 36.4% in patients who were specifically treated with the recommended dose of 80 mg of regorafenib plus toripalimab.[68] The study also noted that while 94.9% of patients in the trial experienced an adverse event due to the treatment, only 38.5% experienced a significant Grade 3 or higher event.[68] This response suggests that the combination treatment has a safety profile comparable to that of the individual drugs, while providing the added benefit of improved efficacy.

Another clinical trial also investigated the efficacy and safety of combination treatment with regorafenib and toripalimab in 33 patients with microsatellite instability subsets of CRC, a malignancy typically considered non-immune-responsive due to resistance to ICIs, which is often attributed to poor infiltration of immune cells into the TME.[98] A response to the treatment was seen in 16 patients, with 12 patients experiencing stability in their disease, with further analysis using a Kaplan–Meier survival curve displaying a median PFS of 113 days and a Cox regression model demonstrating a 12.12% objective remission rate.[98] Safety assessment of the therapy showed an incidence rate of Grade 3/4 adverse reactions of 9.09%, with the majority of adverse events (33.3%) being hand-foot syndrome. Altogether, the current studies are exploring PFS, OS, and safety outcomes associated with different combination therapies, with the goal of optimizing the use of ICIs as targeted cancer therapies in specific patient populations.

4.2. CAR T-cell therapy in colorectal cancer

CAR T-cell therapy is showing promise in the treatment of hematological malignancies but has scarce clinical data for solid tumors. However, there have been recent pre-clinical studies investigating the effect of CAR T-cell therapy in the treatment of CRC. One investigational approach involving engineered T-cells incorporated modifications that promote the targeted expression of interleukin 6, interferon gamma, and interleukin 2 toward guanylate cyclase-c (GCC19), a target expressed in 70% to 80% of CRC.[67] A study analyzing the adverse effects of GCC19 CAR T-cell in patients with metastatic CRC revealed that 93% of participants experienced a Grade 3 or higher adverse event, primarily related to cytokine release syndrome (CRS). However, these adverse events were transient. The median PFS was significantly longer in patients who received higher doses (2×10^6 cells) of GCC19 CAR T-cell compared to those receiving a lower dose (1×10^6 cells), with a PFS of 6 months versus 1.9 months, respectively. Although the sample size was small, the results suggest potential clinical activity of GCC19 CAR T-cell therapy in patients with advanced-stage CRC.

Another antigen under investigation is carcinoembryonic antigen, commonly overexpressed in CRC. A Phase I trial evaluating carcinoembryonic antigen-specific CAR T-cell therapy in 10 patients with metastatic CRC revealed that seven achieved stable disease, with two showing a reduction in liver metastases.[99] Moreover, CRS was reported in only three patients, with one experiencing a severe adverse event.[99] While overall safety appeared manageable, CRS remains the most common adverse event and requires vigilant monitoring during trials to prevent systemic complications.

CAR T-cell therapy has also been used to target mesothelin (MSLN), a differentiation antigen normally expressed in the mesothelium but also highly expressed in solid cancers, including in 48–61% of CRC cases.[100] In a pre-clinical study using MSLN-targeted CAR T-cells with irinotecan in patient-derived xenograft mouse models, significant antitumor activity was observed in MSLN-positive cells – particularly with the CAR_R47 construct, which targets the Region 1 epitope of MSLN – while no effects were observed in MSLN-negative cells.[101] Complete tumor regression was noted in two of the five mice receiving the combination treatment. Although these results are encouraging, further validation should be considered in future clinical trials.

Despite early promise, CAR T-cell therapy in CRC faces multiple significant external factors that impact the potency and overall safety profile of CAR T-cell therapy, including inherent immunosuppressive barriers; secretion of immunosuppressive cytokines; heterogeneity of CRC tumors; and on-target, off-tumor effects that can lead to severe toxicity and unintended damage in normal tissue.[100] These limitations have hindered clinical translation. Future directions in overcoming these challenges include optimizing T-cell persistence, identifying new CRC-specific antigens, and designing combinatorial or

checkpoint-modified CAR constructs to improve efficacy and safety. For now, CAR T-cell therapy in CRC should be regarded as a promising but investigational modality under active clinical evaluation.

4.3. Novel therapies targeting Kirsten rat sarcoma viral oncogene homolog mutations

Kirsten rat sarcoma viral oncogene homolog (KRAS) is a guanosine triphosphatase (GTPase) molecular switch that is active when bound to guanosine triphosphate and inactive when bound to guanosine diphosphate; this cycling is controlled by guanine nucleotide exchange factors and GTPase-activating proteins. In its active form, KRAS controls a signaling cascade of over 80 effector proteins and kinases, including nuclear transcription factors involved in cell growth, proliferation, survival, migration, and cell differentiation. When mutated at codon 12, the KRAS GTPase is unable to convert guanosine triphosphate to guanosine diphosphate, causing it to remain in the activated state and continuously stimulating the downstream cancerous cellular process.[102] Hypomethylation of CpG islands in the promoter sequence of the *KRAS* gene can lead to overexpression of *KRAS* and ignite the cascade of p53 mutations and associated overexpression of cyclooxygenase-2.[103] Consequently, *KRAS* mutations are strongly associated with CRC and PDAC.

The current standard-of-care therapy for metastatic CRC associated with wild-type *KRAS* typically involves the use of EGFR inhibitors, such as panitumumab and cabozantinib. Nevertheless, resistance to monotherapy still arises, particularly due to amplification of the *MET* oncogene.[70] To combat EGFR treatment resistance, combination therapy with the TKI cabozantinib has been investigated in early clinical trials to assess for any changes in clinical activity or safety profile compared to monotherapy. A Phase Ib trial treating 25 patients with a combination therapy of cabozantinib and panitumumab reported an ORR of 16% with a median PFS of 3.7 months. In regard to the safety profile, 20% of the patients discontinued treatment due to experiencing adverse events relating to toxicity; however, these adverse events were reduced with lower doses of cabozantinib.[70] With a PFS that is higher than that of monotherapy, early clinical outcomes of cabozantinib and panitumumab prove to be a promising regimen in the management of KRAS-mediated metastatic CRC. Further research is needed to determine the appropriate dosing to improve the safety profile and overall tolerability of this combination therapy.

The oncogenic *KRAS* mutation at codon 12 results in different subtype allele frequencies, which have been found to play a significant role in the aggressive advancement and worsening prognosis of PDAC. Sotorasib (Lumakras®), a drug targeting *KRAS* G12C mutations in solid tumors, is recognized as a useful therapy for PDAC. At present, in Phase I/II trials, this drug restrains the activation of the KRAS signaling cascade in cancer development and cell differentiation by keeping the molecule in a guanosine diphosphate-bound inactive state.[65] Low-grade toxic effects of diarrhea and fatigue were frequently observed in trials evaluating safety, making it a plausible option for PDAC compared to other existing therapies. Out of 38 patients, between both Phase I and Phase II trials, diarrhea and nausea were reported in nine patients, and eight patients experienced vomiting. The most common Grade 3 adverse events observed were diarrhea and fatigue in two patients, with no reported Grade 4 or 5 adverse events.[104] Moreover, sotorasib demonstrated an increased success rate when combined with panitumumab, an EGFR inhibitor, as a chemorefractory cancer therapy in patients without previous treatment. The treatment resulted in a median PFS of 5.6 months with a 96 mg dose and 3.9 months with a 240 mg dose. The standard care group in this trial demonstrated a median PFS of only 2.0 months and was used as the reference.[71] Further trials with larger patient cohorts and investigations into combination therapies as second-line therapy in previously treated patients are underway, reflecting growing confidence in the efficacy of sotorasib as a solid tumor cancer therapy.

Adagrasib (Krazati®) has been identified as a selective, covalent inhibitor of the *KRAS* G12C mutation, with known favorable pharmacokinetic properties and efficient bioavailability. With a similar mechanism of action to sotorasib, sustained levels of adagrasib above a determined threshold have been shown to suppress the synthesis and rebound of KRAS-dependent signaling in solid tumors, especially in NSCLC. The study resulted in a median PFS of 11.1 months for eight out of the 15 patients who were determined to have a confirmed partial response to the drug.[66] Nausea, diarrhea, vomiting, and fatigue are some of the classically presenting adverse effects with the use of adagrasib, similarly seen with other chemotherapies. Moreover, adagrasib acts as an inhibitor of cytochrome P450 3A4, the enzyme responsible for its metabolism along with other drugs, causing concern for drug–drug interactions when co-administering other therapies.[105] After promising Phase I/Ib trials, Phase III trials observing adagrasib in combination with drugs such as docetaxel and cetuximab to treat *KRAS* G12C-mutated solid tumors in NSCLCs and CRCs are underway.[66]

Studies comparing the efficacy and toxicity of sotorasib and adagrasib have been synthesized in meta-analyses to

analyze differences in their drug profiles and how these relate to patient characteristics and medical history.[106] For example, sotorasib was observed to be associated with significantly lower rates of gastrointestinal adverse effects such as diarrhea and nausea (around 40% and 55% lower prevalence of each, respectively), when compared to adagrasib. Hepatotoxicity with increased alanine aminotransferase levels was also found to be associated more with adagrasib use than sotorasib, suggesting that sotorasib is a better option in patients with prior gastrointestinal or liver-related health issues. For example, the prevalence of diarrhea and nausea associated with adagrasib (70.7% and 69.8%, respectively) was higher than in sotorasib (34% and 14%). Moreover, the overall Grade 3 adverse effects were 89.1% with adagrasib and 20% with sotorasib. In addition, although adagrasib was found to have a slightly higher therapeutic efficacy in sustaining cancer control, most studies suggested similar efficacies between the two drugs. The choice between them often hinges on patient group-specific considerations regarding adverse effects profiles. Importantly, the efficacy of both drugs overall was partially dependent on wild-type *RAS* feedback reactivation induced by Src homology-2 domain-containing protein tyrosine phosphatase-2, known to be the primary resistance mechanism of KRAS inhibitors.[106]

4.4. Poly(ADP-ribose) polymerase inhibitors in PDAC

In cancers with *BRCA* mutations, including some pancreatic adenocarcinomas, poly-ADP-ribose polymerase (PARP) inhibitors such as olaparib and talazoparib are being investigated as potentially effective therapies. Olaparib (Lynparza®) was studied in Phase II trials with results suggesting a well-tolerated response in patients with long-standing ovarian, breast, pancreatic, and prostate cancers, with a significant efficacy (about a 26.2% tumor response rate overall) in genetically targeting PARP enzymes in *BRCA* 1/2-mutated circumstances.[107] Upon further investigation of DNA damage repair genes in trials with olaparib, cross-resistance with platinum analogues was identified. However, after modifying the study accordingly, the drug was ultimately determined to be consistent in its efficacy, supported by parallel studies in Israel and the United States, with only minor expected toxic effects such as anemia, fatigue, anorexia, and nausea.[108]

Another PARP inhibitor of newfound importance in cancers with *BRCA* 1/2 mutations is talazoparib (Talzenna®), with a significant improvement in PFS and efficacy compared to other chemotherapies. The results of the recent controlled Phase 3 EMBRACA trial demonstrated a double response rate and 46% risk reduction for cancer progression or death with talazoparib. Minor myelotoxicity and hematological complications, such as anemia, are conveniently managed with dose modifications.[109]

In contrast, olaparib carries a higher risk than talazoparib in terms of drug–drug interactions, as it is primarily metabolized by cytochrome P450; thus, it is less preferred as an option in patients taking multiple medications. In addition, the recommended oral dosage of talazoparib (1 mg) is lower than olaparib (300 mg) and is taken only once daily, whereas olaparib is often prescribed to be taken twice a day.[110] In different trials observing drug efficacy, the EMBRACA trial (for talazoparib) determined a slightly longer median PFS than the OlympiAD trial (for olaparib) in similar patient populations.[111] However, in terms of safety profiles, olaparib has less severe adverse effects, but with more gastrointestinal changes like vomiting, whereas talazoparib is associated with hematological toxicity, including more severe forms of anemia and neutropenia.[112] Overall, both olaparib and talazoparib are being studied and have so far been determined to be effective PARP inhibitor therapies for *BRCA* 1/2-mutated cancers, with carefully monitored dose management and symptom monitoring.

4.5. TME

TME plays a pivotal role in tumor progression, therapeutic resistance, and immune evasion. Composed of immune cells, stromal components, vasculature, signaling molecules, and extracellular matrix, the TME interacts dynamically with tumor cells to influence treatment outcomes. As a result, strategies aimed at remodeling the TME have emerged as a critical complement to conventional and targeted therapies.

4.5.1. Modulating the TME through immunogenic vaccines

One of the primary approaches to overcoming TME-associated immunosuppression is the use of cancer vaccines in combination with ICIs.

Vaccines can also be combined with ICI to potentiate their efficacy. For instance, combining the alpha-fetoprotein vaccine with ICIs has been shown to elicit strong $CD8^+$ cytotoxic T-cell responses and hinder HCC progression in pre-clinical models.[113] Interestingly, engineered oncolytic viruses capable of inducing hyperacute rejection were administered in 20 patients with refractory cancer and reached a 90% response without any Grade 4 adverse event.[114] Neoantigen-based vaccines, personalized formulations derived from somatic mutations identified through whole-exome or RNA sequencing, have demonstrated the ability to provoke highly specific antitumor immunity when combined with ICI therapy.[115]

4.5.2. Epigenetic and microRNA-mediated reprogramming of the TME

MicroRNAs (miRNAs) also influence the immunological and angiogenic features of the TME. In HCC, certain miRNAs, such as miR-139-5p, directly target *WTAP* to suppress epithelial-mesenchymal transition, thereby reducing metastasis and altering the TME toward a less invasive phenotype.[116,117] In addition, miR-126, another critical regulator, is stabilized and processed to interact with METTL14 in a N^6-methyladenosine-dependent manner, ultimately, to exert anti-angiogenic effects and inhibit the metastatic potential of HCC.[118] As they modulate tumorigenesis, metastasis, or suppression, they can be valuable biomarkers predicting prognosis or treatments. Regarding treatments, inhibitors targeting genes modulating N^6-methyladenosine regulators such as *METTL3*, *FTO*, and *ALKBH5* have been developed.[119] Notably, STM2457, a potent methyltransferase-like 3 inhibitor, has been shown to reduce N^6-methyladenosine modification levels, disrupt leukemogenic gene expression programs, and recondition the immune TME in multiple malignancies, including acute myeloid leukemia, intrahepatic cholangiocarcinoma, prostate cancer, and Sonic Hedgehog medulloblastoma.[120-123] In HCC, STM2457 enhances the efficacy of lenvatinib by modulating both tumor-intrinsic signaling and the microenvironment,[124] representing a bridge between miRNA regulations, epigenetic remodeling, and TME reprogramming. However, research in this area remains in its early stages and is currently limited to pre-clinical settings. Other newer therapeutic approaches include gene therapy, proteolysis-targeting chimera, and the targeting of upstream regulators in cancer.[119] So far, several proteolysis-targeting chimeras have entered Phase I and Phase II trials, marking a promising new chapter in targeted cancer treatment.

4.5.3. Targeted delivery and localized modulation of the TME

Additional strategies to overcome physical and metabolic barriers in the TME include localized chemotherapy and nanotechnology. Hepatic arterial infusion chemotherapy, which allows high-dose drug delivery to the liver, reduces systemic toxicity and has shown efficacy in advanced infiltrative HCC when used alongside targeted agents.[125] Nanoparticles offer another promising platform to directly deliver small interfering RNA, clustered regularly interspaced short palindromic repeats-associated protein-9 nuclease-synthetic guide RNA, or immunostimulatory agents to tumor or immune cells. By silencing the oncogenes through the delivery system, the efficacy of anti-PD-1 therapy against CRC has markedly improved.[126,127] Nanoparticles can also help deliver substances to tumor cells or immune cells to induce tumor cell death or boost antitumor immunity, such as fat mass and obesity-associated protein inhibitors and tumor-associated antigens, into HCC.[128] Despite their strong potential, nanoparticles are still under consideration due to concerns regarding long-term safety and biodegradability.[129]

Interestingly, treatment targeting TME can significantly reduce the relapse rate. For pediatric patients with high-risk acute lymphoblastic leukemia, blinatumomab (bispecific antibodies) showed a significantly higher event-free survival than consolidation chemotherapy (31% versus 57%, $p<0.001$), with an HR of 0.33 (95% confidence interval: 0.18–0.61).[130] Given the significant role of TME in relapse and metastasis, therapies targeting the TME are expected to yield superior clinical outcomes.

5. Precision medicine and AI

Precision medicine is heavily reliant on big data sets, yet biomedical knowledge is often fragmented across manuscripts and non-standardized data repositories, making the effort of parsing through the existing literature a time-consuming and intensive task.[131] While the implementation of AI in biomedical research and clinical practice is not without its challenges, AI shows promise as a powerful investigative and diagnostic tool in cancer research. AI-based summary tools can be used by clinicians to stay updated on the most recent developments in cancer diagnosis and treatment. Specifically, this section will focus on three key areas where AI is being applied: cancer diagnosis, drug development, and clinical practice, and its various applications, as summarized in Figure 3.

5.1. AI applications in histopathology and radiology for cancer diagnosis

Histopathologic grading and radiologic imaging are often key elements of obtaining a cancer diagnosis. AI has shown promise in augmenting the detection and assessment of cancerous lesions found in these images. Conventionally, histological preparation and assessment of tumor samples can be labor-intensive and prone to observer variability.[132] Certain tumors, such as those derived from breast or prostate tissue, have diverse presentations and thus are more susceptible to observer variability than others.[133,134] While errors in pathological diagnosis are relatively low and do not pose clinically significant concerns at the population level, the movement toward precision medicine may make these faults increasingly decisive in the care of individual patients.[135,136] Recent advances in imaging and storage technology have allowed the routine digitization of conventional glass slides in pathology laboratories. Machine learning algorithms have been developed to

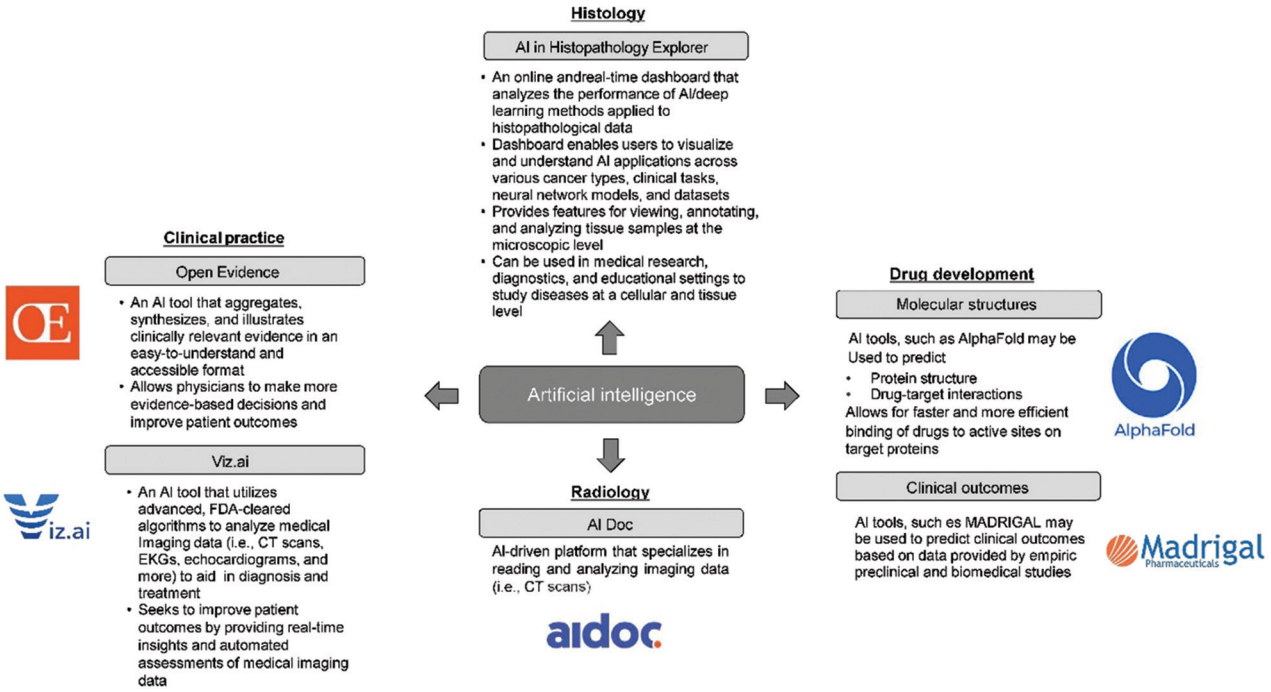

Figure 3. Current summary of diverse applications of artificial intelligence
Abbreviations: CT: Computed tomography; EKGs: Electrocardiograms; FDA: Food and Drug Administration.

automate the process of detecting and labeling tumor markers in cancers such as HCC and mesothelioma.[132] In addition, numerous studies have demonstrated the diagnostic power of deep learning in histopathology.[137-139] For example, Ko *et al.*'s[139] study revealed how AI can be used to increase efficiency and accuracy in diagnosing gastrointestinal cancers.[136] In the study, pathologists used an AI-based tool instead of human pathologists to double-check the screening of gastric and colorectal biopsy specimens. By incorporating AI into their quality control protocol, they were able to increase the number of slides reviewed in the same period by 7–10 times. The accuracy rates of the gastric and colorectal models were 93.08% and 95.03%, respectively. These findings align with broader trends in the field: a meta-analysis of 48 AI-assisted diagnostic pathology studies found a mean sensitivity of 96.3% (confidence interval: 94.1–97.7) and a mean specificity of 93.3% (confidence interval: 90.5–95.4) in disease detection across all studies.[140]

Similar principles driving AI innovations in pathology can be applied to developments in radiology. AI has demonstrated promise toward aiding the detection and diagnosis of cancerous lesions in radiological imaging. A 2025 study compared breast cancer detection rates between two groups of radiologists: those who used AI-supported double reading and a control group who used the conventional double reading method. Radiologists in the AI-supported group had a detection rate that was 17.6% (95% confidence interval: 5.7, 30.8) higher than those in the control group.[141] In the diagnosis of prostate cancer, AI can be used to identify clinically significant lesions to allow more targeted biopsy procedures.[142] This enables the clinician to focus on specific areas of the prostate, potentially reducing the risk of under- and overtreatment.

5.2. AI in drug development

AI-based tools can also be used to investigate the progression of carcinogenesis and predict the fitness of potential anticancer targets. For example, AlphaFold 2 uses AI to obtain a protein sequence, predict its backbone shape and side-chain conformations, and subsequently generate a model of the overall protein structure.[143] Increasing the accuracy of structure prediction can help researchers better understand factors, such as ligand binding and molecular function, that contribute to drug-target interactions. Other AI tools attempt to streamline the process of identifying the most promising treatments for specific cancers. PINNED is one such machine learning model that can be used to assess potential anticancer therapies and evaluate the druggability of potential target proteins by assigning scores based on the proteins' structure, sequence, localization, biological function, and network information.[144] In addition, Huang *et al.*'s[145] MADRIGAL is a multimodal AI

model that uses genomic profile and xenograft model data from pre-clinical and biomedical studies to predict clinical outcomes of drug combinations for cancer patients with comorbid conditions such as type II diabetes.[146] Although this particular tool is in its early stages of development, innovations such as PINNED, MADRIGAL, and AlphaFold are indicative of AI's potential in pharmaceutical research.

5.3. AI in clinical practice

Some studies have explored the idea of using AI to inform clinical decision-making. A recent study from China assessed the impact of an AI-based clinical decision support system on the treatment of breast cancer patients.[147] A group of physicians was asked to provide treatment recommendations for an average of 198 patients before and after viewing individualized AI-generated treatment plans. Researchers found that adherence to National Comprehensive Cancer Network guidelines increased slightly (0.5%; p=0.003) after the implementation of AI support for the treatment of patients with stages I–III breast cancer.[147]

Clinicians can also use AI-based knowledge graphing and summary tools to stay updated on the most recent developments in cancer treatment. Chandak *et al.*[148] presented an AI-based multimodal knowledge graph, PrimeKG, which synthesized data from 20 primary databases to map relationships between the proteins, genes, phenotypes, and risk factors associated with over 17,000 diseases, including cancers.[148] PrimeKG's integrative network also describes indications, contraindications, and off-label uses of drugs used to treat these diseases.[148]

Several large language model AI tools capable of generating human-like text are in development for clinical applications. However, this particular area of AI research is still in its infancy and requires further investigation before large language model tools can be integrated into clinical workflows.[145]

6. Conclusion

This review discussed the potential of precision medicine in the field of oncology. The review has explored first-line targeted therapies and immunotherapies that have been well-established in the current standard care. Furthermore, the review discussed current targeted therapies in HCC, CRC, and PDAC and various trials of different targeted therapies and immunotherapies to achieve a more efficacious regimen. Finally, this review has examined the emerging avenues in the field of precision medicine in cancer diagnosis, drug development, and clinical practice. We chose to discuss the possibility of including AI in our review, as we have seen the immense potential for AI as a tool to be more patient-specific with improved clinical outcomes. We also believe that AI will eventually be incorporated into medical practices. However, we would like to acknowledge significant challenges, such as logistical challenges to digital pathology, data quality concerns, risk of bias, ethical implications, and potential compromise to patient trust. The current advancement of AI in medicine accompanies a worrying lack of legislative framework, making it susceptible to breaches of patient rights. Therefore, rash adoption of powerful technology is like building a new story on a foundation of quicksand, which will lead to an ultimate collapse. We are optimistic that with careful planning and thoughtful implementation, AI can be incorporated in a way that truly benefits patients while minimizing unintentional harm.

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