

REVIEW

RECALCITRANT CANCERS: WHERE ARE WE NOW?

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ABSTRACT: Recalcitrant tumors pose a significant clinical challenge because of their biological complexity and resistance to conventional therapies. These tumors develop mechanisms to evade drug toxicity, including alterations in drug metabolism, enhanced DNA repair capabilities, and changes in the tumor microenvironment that support their survival. The lack of identifiable molecular targets in many recalcitrant cancers limits precision medicine approaches, necessitating the development of novel therapeutic strategies. Early diagnosis remains difficult because these tumors present with nonspecific symptoms or are detected at advanced stages when treatments are less effective, contributing to poor outcomes.

Emerging epidemiological studies have highlighted the role of lifestyle modifications in tumor onset and progression. Advances in molecular biology and genomics have enabled the identification of new biomarkers and therapeutic targets, leading to innovative approaches including immunotherapy, targeted therapy, and combination therapies to overcome resistance. This narrative review emphasizes integrated prevention strategies, including lifestyle interventions, summarizes progress in understanding recalcitrant tumor pathophysiology, and evaluates current and experimental treatments to improve survival rates and quality of life for patients.

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Impact statement: This review investigates the primary factors that render recalcitrant tumors incurable and evaluates prospective strategies for enhancing early diagnosis, prevention, and the overcoming of therapeutic resistance.

Key words: *Recalcitrant tumor; nutrition; immuno-checkpoint inhibitor; replication stress response; tumor stiffness.*

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INTRODUCTION

Recalcitrant tumors constitute a highly aggressive and challenging category of neoplasms, characterized by their plasticity, which enables them to develop novel mechanisms and adopt phenotypes that confer resistance to conventional therapies. The overall 5-year survival rate for patients with recalcitrant tumors is less than 20% (1-5). Although these tumors account for approximately 20-25% of annual cancer diagnoses globally, they are responsible for nearly half of all cancer-related deaths (6). Pancreatic ductal adenocarcinoma (PDAC), small cell lung

cancer (SCLC), glioblastoma (GBM), hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and esophageal cancers are classified as recalcitrant tumors and represent the most lethal tumor types. Despite originating in different organs and being driven by distinct genetic alterations, these neoplasms share several common characteristics: 1) a high risk associated with unhealthy lifestyles, such as smoking, alcohol consumption, and obesity; 2) nonspecific and silent symptoms; 3) a lack of markers and diagnostic techniques for early detection of the disease; and 4) an absence of specific molecular targets (**Figure 1**).

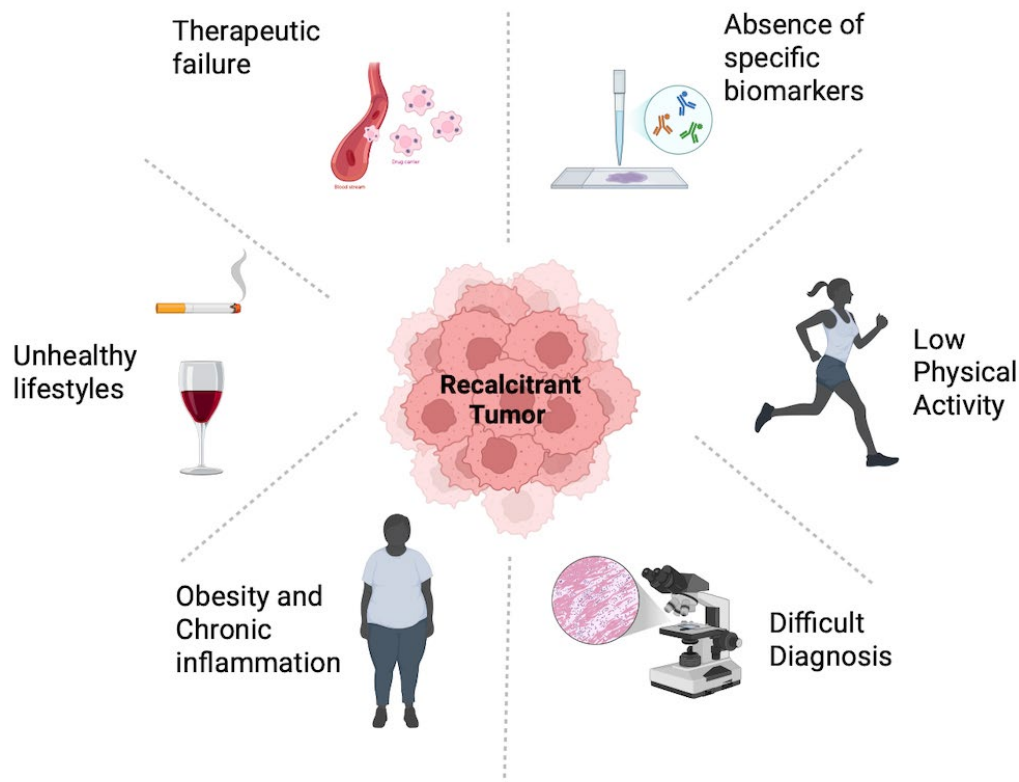


Figure 1. Risk factors driving the onset and progression of recalcitrant tumors. Schematic overview of the principal contributing factors.

LIFESTYLE AND RECALCITRANT CANCERS

Smoking and obesity are significant shared risk factors for various recalcitrant cancers because of their contribution to chronic inflammation, metabolic alteration, and DNA damage (7, 8). Obesity exacerbates cancer development and progression via several mechanisms. The rapid expansion of adipose tissue is not supported by adequate vascularization, leading to hypoxia, adipocyte death, and macrophage recruitment.

These immune cells release proinflammatory cytokines, establishing chronic inflammation, generating oxidative stress, and increasing the risk of DNA damage and oncogenic mutations (9, 10). Obesity-induced insulin resistance and hyperinsulinemia result in elevated IGF-1 levels and activation of the pro-oncogenic PI3K/Akt/mTOR signaling pathway, promoting the proliferation of transformed cells. Excess adipose tissue supports tumor growth by releasing fatty acids that serve as substrates for beta-oxidation, increase reactive oxygen species production,

and providing intermediate metabolites essential for proinflammatory factor synthesis while reducing precursors of anti-inflammatory factors. Additionally, obesity-induced metabolic changes lead to hormonal imbalances and altered adipokine synthesis, characterized by the overproduction of leptin, which promotes cell division and tumor survival, and a deficiency of adiponectin, a hormone with antitumor and anti-inflammatory properties, further exacerbating inflammation (11). Chronic inflammation, hormonal dysregulation, and lipid overload contribute to the expansion and maintenance of cancer stem cells (CSCs) (12).

Tobacco primarily contributes to cancer development by inducing loss-of-function mutations in tumor suppressor genes and gain-of-function mutations in oncogenes. These genes are crucial for regulating cell growth and maintaining genomic stability. These mutations compromise the mechanisms that regulate cellular proliferation, facilitating the initiation and progression of malignancy. Chemical compounds in tobacco smoke, such as polycyclic aromatic hydrocarbons and nitrosamines, form DNA

adducts that cause replication errors, increasing the likelihood of mutations in genes critical for cell cycle control and apoptosis (13).

Smoking and obesity are significant independent risk factors for PDAC (7, 8). Tobacco smoke promotes PDAC onset by inducing KRAS mutations and HDAC4 expression, thereby enhancing tumor invasion and metastasis (14). Visceral adipose tissue (VAT) and intrapancreatic fat deposition (IPFD) exceeding 10% are associated with PDAC as both risk prognostic factors, promoting cancer cell proliferation and immune evasion through chronic inflammation, cytokine release, extracellular vesicles (EVs), insulin resistance, and hyperinsulinemia, which drive pancreatic cancer initiation and progression (15-17). Both smoking and obesity often accelerate carcinogenesis, with the risk of pancreatic cancer in current smokers with a body mass index (BMI) ≥ 30 kg/m² being up to five-fold higher (18).

Smoking is the leading risk factor for SCLC, with 95-98% of cases occurring in current or former smokers, whereas never-smokers account for approximately 2% of cases (19, 20). In SCLC, tobacco carcinogens cause inactivating mutations in TP53 and RB1 (13, 21), whereas nicotine promotes progression and migration through activation of the CXCR4/CXCL12 pathway (22).

Obesity (BMI ≥ 30 kg/m²) and high-fat diets are linked to aggressive GBM, reduced survival, and higher disease risk, especially in patients with abdominal obesity (23, 24). Excess adipose tissue supplies substrates for membrane synthesis and ATP production via beta oxidation. Cholesterol-rich macrophages promote tumor growth and suppress local immunity (25). High-fat diets reduce brain hydrogen sulfide (H₂S) production, fostering tumor growth and enriching cancer stem cells (26). Additionally, upregulation of the fat mass and obesity-associated (FTO) gene, a brain-expressed demethylase, supports GBM progression and therapeutic resistance through metabolic reprogramming and m6A RNA/DNA demethylation (27).

Obese individuals have an 89% higher risk of HCC than those of normal weight. Adult weight gain leads to nonalcoholic steatohepatitis (NASH), characterized by remodeling of the liver microenvironment, which predisposes individuals to HCC. The accumulation of lipids, chronic inflammation mediated by interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), and insulin resistance collectively promote HCC development by exacerbating oxidative stress and DNA damage (28). Additionally, smok-

ing increases the risk of HCC by 21-86%, with obesity further amplifying this effect (29).

Obesity doubles the risk of intrahepatic cholangiocarcinoma (ICC) and increases the risk of extrahepatic cholangiocarcinoma (ECC) by 1.3-fold (30). Smoking is a moderate risk factor, increasing the risk by 40-100% depending on the biliary site. Tobacco carcinogens, after hepatic metabolism and biliary excretion, damage bile duct epithelial cells, facilitate gallstone formation, and induce chronic inflammation of the biliary epithelium by modulating adipokine levels, specifically increasing leptin and decreasing adiponectin (31).

Obesity is the primary risk factor for esophageal adenocarcinoma and is linked to gastroesophageal reflux disease (GERD). Increased abdominal pressure promotes GERD, leading to Barrett's esophagus, a precancerous condition. Systemic inflammation and insulin dysregulation independently activate oncogenic pathways, contributing to carcinogenesis (32). Smoking increases the risk of squamous cell carcinoma and adenocarcinoma by inducing genetic mutations in the esophageal mucosa (33).

In contrast, physical activity (PA) lowers cancer risk in the general population and is incorporated into programs aimed at preventing second primary cancers. For patients undergoing tumor treatment, PA enhances the quality of life by reducing chemotherapy side effects, sarcopenia, and cancer recurrence, while improving fitness and providing emotional and psychological benefits (34). The mechanisms, optimal levels, and effective doses of PA in oncology remain unclear; however, exercise modulates key GBM progression pathways, including the RTK/PI3K/Akt/mTOR signaling, angiogenesis, and metabolic reprogramming pathways. Additionally, PA promotes cytotoxic T cell and natural killer (NK) cell infiltration while reducing immunosuppressive cells such as Tregs and MDSCs (35).

THE SILENT SYMPTOMATOLOGY OF RECALCITRANT CANCER

Recalcitrant tumors are often asymptomatic or present with nonspecific symptoms during their early stages, complicating early detection and diagnosis. These subtle and often vague signs are frequently misinterpreted as benign or transient conditions, leading to delays in patients seeking medical attention and, consequently, in diagnosis. The nonspecific nature of early symptoms results in many patients

remaining asymptomatic or experiencing mild discomfort that does not immediately raise concern, thereby allowing the disease to progress unnoticed. For instance, PDAC typically manifests with insidious symptoms that may develop intermittently over several years before a formal diagnosis is made. This delayed presentation is partly attributed to the pancreas's retroperitoneal anatomical location, which limits early symptom development, and the current lack of specific early biomarkers for PDAC, making screening and early detection particularly challenging (36). Similarly, SCLC is often called a "silent" disease because its early respiratory symptoms – such as coughing, wheezing, or chest discomfort – are nonspecific. These symptoms are easily attributed to common respiratory infections or chronic conditions, which contribute to delayed diagnosis and treatment initiation (37). GBM also frequently manifests with early-stage symptoms that are subtle and nonspecific, including mild headaches, fatigue, and cognitive alterations, which are often erroneously attributed to stress, general fatigue, or other benign neurological conditions. The brain's exceptional capacity to adapt and compensate for slowly progressive tumor growth can obscure these initial indicators, thereby further impeding prompt diagnosis (38). In the case of HCC and CCA, the early stages are typically asymptomatic or present with vague systemic symptoms such as fatigue, decreased appetite, or weight loss (39, 40). In esophageal cancers, initial symptoms such as intermittent dysphagia, heartburn, hoarseness, cough, and weight loss may be easily mistaken for benign gastrointestinal disorders, including GERD or esophageal irritation (41). Overall, the common thread among these malignancies is the predominance of silent or nonspecific clinical presentations during their early stages of development. This shared characteristic underscores the critical need for heightened clinical vigilance, improved screening strategies, and the development of more sensitive and specific biomarkers to facilitate early detection and improve patient outcomes.

THE CHALLENGE OF EARLY DIAGNOSIS

Approximately one-third of patients with recalcitrant tumors are diagnosed incidentally during emergency hospital admissions, often at an advanced stage due to the nonspecific nature of the symp-

toms. Early detection is especially difficult because of the lack of specific biomarkers and challenges in identifying precursor or premalignant lesions using routine clinical imaging.

High-grade pancreatic intraepithelial neoplasia (PanIN), an early precursor lesion, is mainly detected via histopathology, as conventional imaging and biomarkers such as CA19-9 lack specificity for early malignant changes (36). SCLC diagnosis relies on minimally invasive sampling, such as bronchoscopy or fine-needle aspiration, often yielding small specimens that are extensively necrotic, which may lead to misdiagnosis and erroneous identification as treatable neoplasms. Unlike non-small cell lung cancer, no early detection biomarkers exist for SCLC, and computed tomography (CT) scans may miss small lesions or fail to distinguish them from other conditions (37). Early GBM detection is challenging because of tumor infiltration into normal brain tissue and the limited permeability of contrast agents across the blood-brain barrier. Consequently, magnetic resonance imaging (MRI) cannot reliably differentiate between low-grade and atypical GBM forms. Molecular heterogeneity within GBM tumors complicates early detection, as no single biomarker reliably indicates initial-stage disease, hindering the identification of universal markers (38). Pre-HCC lesions under 10 mm are often undetectable by MRI or CT and may mimic regenerative nodules in cirrhotic livers. Biomarkers such as alpha-fetoprotein (AFP) show low sensitivity for detecting small HCC (40). Pre-neoplastic biliary lesions, such as biliary intraepithelial neoplasia (BillIN) and intraductal papillary neoplasms of the bile duct (IPNB), resemble inflammatory changes and are difficult to detect because of their location. Brush cytology during endoscopic retrograde cholangiopancreatography (ERCP) has low sensitivity (< 50%) because desmoplastic tumors yield limited amounts of tissue. Serum markers, such as CA19-9, lack specificity because their levels increase with benign biliary inflammation (39). Early esophageal tumors may be missed by conventional endoscopy, requiring advanced imaging such as Lugol's iodine chromoendoscopy for precancerous lesion identification (41) (**Table 1**). The potential of liquid biopsy combined with multiomic technologies offers a promising approach for early detection of tumors that evade traditional screening. Liquid biopsy analyzes tumor-derived components in bodily fluids, such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and EVs. While widely used in advanced cancer management,

Table 1. Major diagnostic challenges and current biomarker approaches across recalcitrant tumors.

TUMOR TYPE	MAIN DIAGNOSTIC CHALLENGES	LIMITATIONS OF CURRENT IMAGING OR SAMPLING	CURRENT BIOMARKERS OR DIAGNOSTIC ADJUNCTS	KEY UNRESOLVED NEEDS
Pancreatic ductal adenocarcinoma (PDAC)	Nonspecific and intermittent symptoms; retroperitoneal location; precursor PanIN lesions are predominantly microscopic.	Standard imaging does not reliably identify high-grade PanIN or very small early lesions.	CA19-9 has insufficient specificity to distinguish benign pancreatic disease from early malignancy and limited value for early detection.	Prospective validation in high-risk cohorts; discrimination from pancreatitis and other benign conditions; standardized pre-analytical and analytical workflows.
Small-cell lung cancer (SCLC)	Bronchoscopic or fine-needle specimens may be small or necrotic; histologic overlap with carcinoid tumors, basaloid squamous-cell carcinoma, and lymphoma may complicate classification.	CT may miss small early-stage lesions and may not reliably distinguish malignancy from other thoracic conditions.	No established biomarker is available for population-level early detection.	Validation in limited-stage disease; distinction from other lung neoplasms; reproducibility across cohorts and sequencing platforms.
Glioblastoma (GBM)	Infiltrative growth, marked intratumoral heterogeneity, and radiologic overlap with abscess, tumefactive demyelination, or stroke impede early recognition.	MRI is the standard modality but may not reliably distinguish early or atypical lesions; the blood-brain barrier limits contrast-agent effectiveness.	No universal circulating biomarker is established for early detection.	A sufficiently sensitive noninvasive assay; differentiation from benign neurologic conditions; tumor-specific validation of plasma <i>versus</i> cerebrospinal-fluid approaches.
Hepatocellular carcinoma (HCC)	Small dysplastic nodules in cirrhotic livers may resemble regenerative nodules and lack the vascular features of overt HCC.	MRI and CT frequently fail to detect nodules <10 mm; 20-30% may remain undetected. Biopsy of small lesions in cirrhotic liver is technically difficult.	Alpha-fetoprotein (AFP) has low sensitivity for small or early HCC.	Discrimination of early HCC from cirrhosis, dysplasia, and inflammation; clinically validated thresholds; longitudinal surveillance studies.
Cholangiocarcinoma (CCA)	BilIN and intraductal papillary neoplasms may resemble inflammatory biliary changes; deep-seated and desmoplastic lesions yield limited cellular material.	ERCP brush cytology has low sensitivity (<50%); MRI/MRCP may not reliably distinguish early intrahepatic CCA from benign lesions or metastases.	CA19-9 has limited sensitivity for early disease and may be elevated in benign biliary inflammation; no reliable blood-based screening test is established.	Reliable distinction between malignant and benign biliary strictures; validation in high-risk populations; standardization by anatomical subtype.
Esophageal cancer	Early lesions may be asymptomatic and subtle, delaying clinical recognition.	Conventional endoscopy may miss early lesions; enhanced endoscopic techniques are required for improved visualization of precancerous changes.	Non valid circulating biomarker is currently established for early detection.	Separate validation for squamous-cell carcinoma and adenocarcinoma; discrimination from inflammatory or premalignant conditions; sensitivity in stage I disease.

its early diagnostic application faces several biological and technical challenges. Early tumors release biomarkers at low levels, making it difficult to distinguish cancer-specific signals from those of normal cell-free DNA. Integrating molecular data – including mutation analysis, DNA methylation, early-stage proteins and enzymatic biomarkers, and lipid changes – may help overcome some of these limitations and detect molecular signals before tumors are visible on imaging (42, 43).

THERAPEUTIC FAILURE IN RECALCITRANT TUMORS

At the molecular level, these tumors exhibit alterations in MYC or RAS oncogenes. RAS mutations are present in PDAC tumors in 90-95% of cases and in CCA in 7-25% of cases (44, 45). In contrast, RAS is overexpressed either directly through genetic alterations or indirectly through the activation of other pathways, such as EGFR and MET, in HCC, GBM, and esophageal cancer (46). MYC is overexpressed in 42% of PDAC cases, 50% of SCLC cases, 30-70% of HCC cases, 60-80% of GBM, and 20-25% of esophageal cancer cases (47-51). Oncogene activation is often associated with mutations in tumor suppressor genes, including TP53 and CDKN2A. TP53 mutations occur in 75-80% of PDAC cases, 90% of SCLC cases, 20-50% of HCC cases, 30-35% of GBM cases, 10-50% of CCA cases, and 72-80% of esophageal cancer cases (52-57). Deletion or mutation of CDKN2a is observed in 60-95% of PDAC tumors, 60% of GBM cases, 6-30% of HCC cases, 15-30% of CCA cases, and 12-25% of esophageal cancers (58-62). Hyperactivation of MYC and RAS, coupled with the inactivation of TP53 and CDKN2A, confers stemness characteristics to cells and induces metabolic reprogramming, epigenetic remodeling, and genetic instability (**Figure 2**). This cellular transformation influences the tumor microenvironment by promoting phenotypic reprogramming through cytokines, growth factors, and cell-cell interactions, thereby establishing an immunosuppressive milieu that facilitates immune evasion.

THE CHALLENGE OF UNDRUGGABLE PROTEINS

MYC inhibitors face significant clinical challenges due to the absence of a conventional binding site, ren-

dering them “undruggable” by standard small-molecule drugs. Unlike other enzymes, MYC does not possess a deep “pocket” that accommodates drug binding. Additionally, high-molecular-weight drugs have difficulty accessing the nucleus. Although numerous candidates have demonstrated promising *in vitro* binding affinities, they have failed clinically because of off-target effects and poor selectivity. Given that MYC regulates essential processes in healthy cells, such as proliferation and metabolism, its complete inhibition results in severe side effects (63).

The failure of RAS inhibitors in clinical trials is attributed to the complex biology of the protein, including the absence of binding pockets, high GTP/GDP affinity, and tumor adaptation through alternative pathways. While early farnesyltransferase inhibitors were unsuccessful due to isoform resistance, contemporary KRAS G12C inhibitors face challenges with resistance mechanisms, such as mutations, bypass pathway activation, and tumor rewiring, necessitating combination therapies for durable responses. Because RAS signaling is required for proliferation and survival in normal cells, complete inhibition can damage healthy tissues. Efforts to target downstream RAS signals have often failed due to side effects in normal tissues and feedback mechanisms that require intolerable doses (64). Pharmaceutical research has advanced with the development of next-generation anti-RAS agents, such as daraxonrasib, which significantly improves outcomes in patients with pancreatic cancer. In the phase 3 RASolute 302 trial, daraxonrasib approximately doubled median overall survival rate (65). Daraxonrasib inhibits RAS in its active, GTP-bound state, overcoming the limitations of earlier inhibitors that targeted the inactive [RAS(OFF)] form. Daraxonrasib functions as a pan-RAS inhibitor, effectively targeting a broad spectrum of activating mutations beyond the KRAS G12C specificity of previous drugs. Moreover, it forms a complex with cyclophilin A, which binds RAS with high affinity, resulting in sustained protein inactivation (65).

Owing to the challenges in directly targeting RAS and MYC, research has shifted toward developing molecules that modulate the downstream pathways affected by these oncogenes and tumor suppressors (TP53, CDKN2A), including cell cycle regulation, genomic stability, DNA damage response, epigenetic remodeling, metabolism, immune modulation, and extracellular matrix composition.

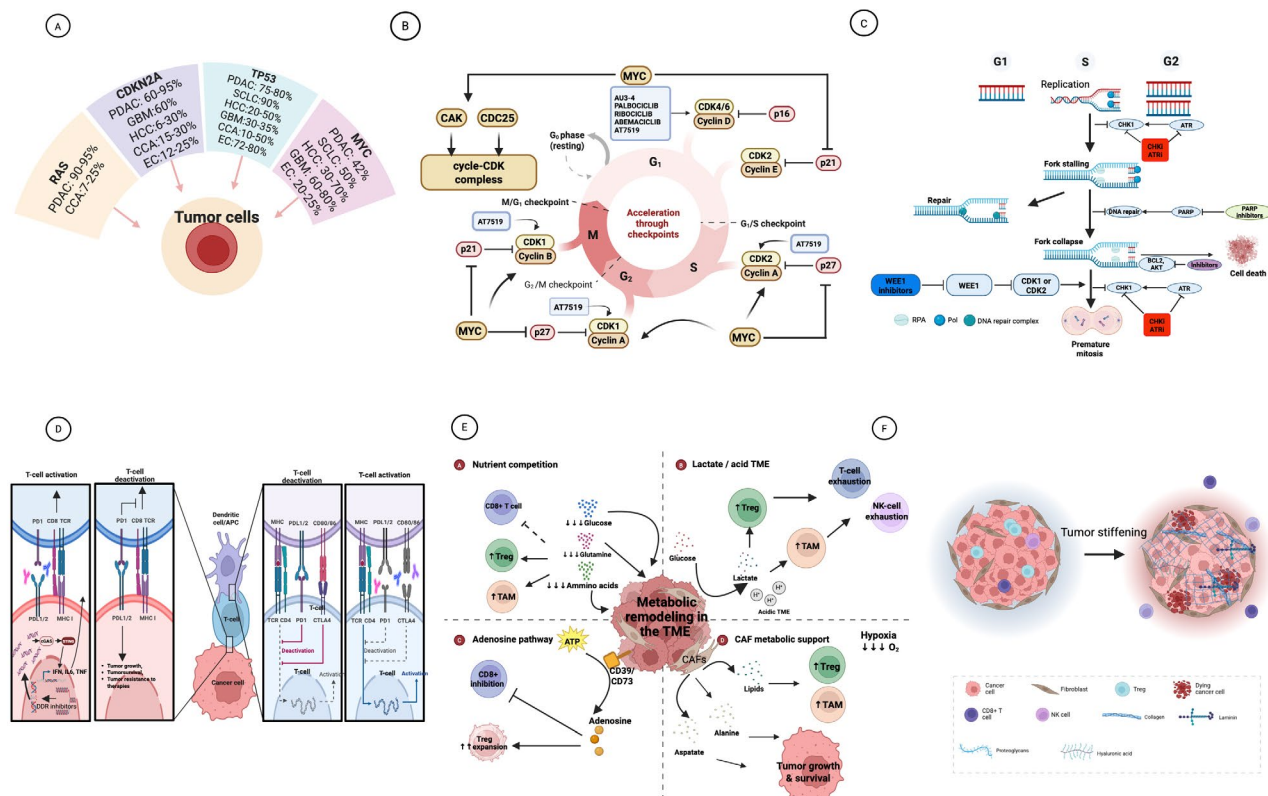


Figure 2. Molecular and microenvironmental alteration in recalcitrant tumors and their potential therapeutic targeting.

(A) Mutations in oncogenes and tumor suppressor genes are prevalent in recalcitrant tumors. **(B)** CDK inhibitors restrict cell-cycle progression in recalcitrant tumors. **(C)** Recalcitrant tumors enhance DDR expression to prevent replication fork stalling and promote tumor cell proliferation. **(D)** Recalcitrant tumors evade immune recognition by recruiting immunosuppressive cells, which, in collaboration with cancer cells, induce exhaustion in effector CD8 T cells through the expression of immune checkpoint proteins. Inhibiting the DDR pathway with inhibitors targeting WEE1, ATM, and ATR can enhance the efficacy of immune checkpoint inhibitors by stalling replication fork and activating the cGAS-STING-mediated interferon pathway through the release of cytosolic DNA. **(E)** Cancer cells remodel the tumor microenvironment and foster an immunosuppressive, tumor-supportive environment by employing the following strategies: a) nutrient deprivation leading to exhaustion of effector T cells and natural killer cells; b) increasing glycolytic metabolism and lactate production, which induces immunosuppressive M2 TAM polarization and Treg differentiation and proliferation; c) CD39 convert ATP/ADP to AMP, whereas CD37 convert AMP to adenosine, promoting Treg expansion and T cell exhaustion; d) reprogramming cancer-associated fibroblasts (CAFs) to release amino acids (alanine and aspartate) to support tumor growth in a hypoxic environment, provide lipid-derived energy substrates, and promote Treg and TAM expansion. **(F)** Recalcitrant tumors reprogram CAFs to synthesize and release more extracellular matrix and lysyl oxidase (LOX), which crosslinks collagen and elastin, creating a stiff barrier that impedes lymphocyte infiltration into the tumor.

LIMITATIONS OF CONVENTIONAL THERAPIES IN RECALCITRANT TUMORS

CDK inhibitors

The ineffectiveness of Cyclin-Dependent Kinase (CDK) inhibitors, particularly CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, in the treatment of resistant tumors poses a substantial challenge in the field of oncology. The limited efficacy of CDK inhibitors is largely attributable to mechanisms of intrinsic and acquired resistance.

Clinical trials of CDK4/6 inhibitors, such as palbociclib, in resistant PDAC have yielded limited success as stand-alone therapies. This limitation is attributed to the rapid emergence of adaptive resistance mechanisms. PDAC cells bypass CDK4/6 inhibition by elevating cyclin D1 and E levels and activating alternative pathways, notably the PI3K/mTOR and MEK pathways. Clinical trials have revealed that although palbociclib inhibits tumor proliferation, it simultaneously enhances metastasis and invasion by inducing epithelial-to-mesenchymal transition (EMT). Furthermore, trials with nonspecific CDK inhibitors, including CDK9 inhibitors, flavopiri-

dol, and dinaciclib, have shown unacceptable toxicity and poor efficacy (66).

In SCLC, CDK inhibitors have yielded mixed results, with earlier generations proving ineffective in addressing relapsed or resistant cases. Initial “pan-CDK” inhibitors, such as flavopiridol and roscovitine, failed in clinical trials due to toxicity and insufficient specificity. Although trilaciclib has demonstrated efficacy in mitigating chemotherapy-induced myelosuppression, its effectiveness as an anticancer agent is constrained because its function is to protect healthy bone marrow rather than to target resistant tumors. Recent CDK9 inhibitors, such as KB-0742, have shown preclinical potential by targeting transcriptional mechanisms, offering an approach to overcome resistance beyond cell cycle regulation (67).

The use of CDK inhibitors in GBM treatment poses a significant therapeutic challenge. Although alterations in the CDK4/6-Rb axis occur in 80% of cases, outcomes remain suboptimal because of limited BBB penetration and drug resistance. Current efforts are focused on molecules with superior pharmacokinetic profiles and combination therapies to overcome resistance. Zotiraciclib (TG02), an oral multi-CDK inhibitor targeting CDK9 and reducing the expression or levels of c-MYC and MCL-1, is being assessed in phase Ib trials (NCT03224104) alongside temozolomide or radiotherapy, following limited efficacy as a monotherapy in recurrent GBM (PFS-6 of 6.7%). Abemaciclib, known for its superior BBB permeability, is being evaluated in clinical trials for patients exhibiting alterations in the Rb pathway. AU3-14, a novel CDK4/6 inhibitor with high brain penetration, delays resistance to temozolomide (TMZ) in preclinical models. AT7519, a selective inhibitor of CDK1, 2, 4, 6, and 9, induces apoptosis, pyroptosis, and cell cycle arrest in human GBM cells, as demonstrated in preclinical studies (68-70).

Clinical trials assessing the efficacy of CDK inhibitors as standalone treatments for advanced HCC have encountered notable obstacles. Despite promising results in preclinical studies, clinical trials of palbociclib have faced challenges owing to the emergence of compensatory pathways and resistance mechanisms. Notably, trials NCT04162301 and NCT02255461 were either discontinued or demonstrated limited efficacy when CDK4/6 inhibitors were used as monotherapies, as their cytostatic action was insufficient to combat aggressive tumors. Resistance arises from the activation of alternative pathways, such as PI3K/mTOR and MAPK, enabling tumors to

bypass CDK4/6 inhibitor-induced cell cycle arrest (71) (**Table 2**).

In cases of recalcitrant CCA, the efficacy of single-agent CDK4/6 inhibitors, such as palbociclib, is limited in both clinical and preclinical settings. These inhibitors have been observed to upregulate cIAP1/2 (Cellular Inhibitor of Apoptosis Proteins) through NF- κ B signaling pathways, thereby protecting tumor cells against apoptosis. Although these inhibitors induce temporary G0/G1 cell cycle arrest, tumors frequently circumvent this blockade, resulting in disease progression and the development of treatment resistance (72, 73) (**Table 2**).

Clinical trials investigating the use of CDK4/6 inhibitors as monotherapy for refractory esophageal cancer have demonstrated suboptimal outcomes. A significant number of upper gastrointestinal carcinomas exhibit intrinsic resistance attributed to cyclin E overexpression, which facilitates cell cycle progression despite CDK4/6 inhibition. Due to the limited clinical efficacy observed, plans to extend phase II trials for agents such as ribociclib in this context were discontinued (74) (**Table 2**).

Replication stress response (RSR) inhibitors

Replication stress (RS), resulting from the stalling or collapse of replication forks, is a hallmark of therapy-resistant cancers, including SCLC and pancreatic cancer. These tumors rely on the replication stress response (RSR), mediated by the ATR-CHK1 axis, to mitigate RS, prevent mitotic entry, and promote survival. Oncogene-driven RS, caused by MYC amplification or loss of TP53 and RB1, exacerbates replication stress, increasing the risk of fork collapse into lethal double-strand breaks (DSBs). Therapeutic inhibition of RSR components ATR, CHK1, and WEE1 induces replication catastrophe, which is a promising strategy for selectively targeting these malignancies (75). RSR inhibitors targeting ATR, WEE1, and CHK1 have emerged as promising therapeutic agents for PDAC, a cancer characterized by replication stress, KRAS mutations, and genomic instability (76-79). However, clinical trials have faced setbacks due to acquired drug resistance. Early trials combining CHK1 or ATR inhibitors with chemotherapy frequently resulted in dose-limiting toxicity (80-82). Consequently, the research focus is shifting toward combining these inhibitors with ICIs, as RSR defects can induce cytosolic DNA accumulation, thereby activating immune responses via the cGAS-STING pathway (83). Ongoing studies, including trial NCT06015659, are evaluating the WEE1 inhibitor azenosertib in combina-

tion with gemcitabine, alongside the identification of biomarkers that predict therapeutic response (84) (**Table 2**).

ATR inhibitors, such as berzosertib, show potential in treating SCLC because of the cancer's dependence on DNA repair mechanisms for rapid cell proliferation. Nevertheless, clinical trials addressing the recalcitrant nature of SCLC face significant challenges, including limited therapeutic responses, toxicity, and the development of resistance. Notably, clinical trials targeting RSR in SCLC have faced setbacks, as exemplified by the termination of a Phase II trial for berzosertib (M6620/VX-970) (85, 86). Furthermore, the ineffectiveness of prexasertib in treating SCLC was corroborated by the Phase II study NCT02735980 (87). Despite preclinical evidence suggesting that SCLC is an optimal target for these interventions, the clinical outcomes have been disappointing (**Table 2**).

GBM resistance to standard therapies is driven by glioma stem cells (GSCs) experiencing replication stress from transcription-replication collisions in long neural genes, which activate the ATR-CHK1 pathway, stabilizing replication forks and preventing genomic instability, enabling tumor survival against chemotherapy and radiotherapy (88). Targeting the RSR pathway is a promising approach to overcome drug resistance, with ATR inhibitors (AZD6738, M6620) being evaluated to sensitize GBM to radiotherapy and PARP inhibitors (89, 90). A Phase I trial is assessing the CHK1/CHK2 inhibitor triapine with radiotherapy in recurrent GBM (NCT06860594). Additionally, the antisense oligonucleotide TUG1-DDS, which targets the long noncoding RNA (lncRNA) Taurine Upregulated Gene 1 (TUG1), induces R-loop accumulation and DNA damage, suppressing tumor growth preclinically and supporting future clinical development (91) (**Table 2**).

Table 2. Selected clinical trials and therapeutic strategies in recalcitrant tumors.

TUMOR TYPE	THERAPEUTIC STRATEGY	AGENT(S) / REGIMEN	TRIAL IDENTIFIER	PHASE	MAIN MESSAGE (REVISED)
PDAC	CDK inhibition	Palbociclib	Not specified	Not specified	CDK4/6 inhibition showed limited clinical activity as monotherapy, consistent with rapid adaptive bypass signaling and lack of durable disease control in PDAC.
PDAC	RSR inhibition	Azenosertib + gemcitabine	NCT06015659	Phase II	This trial reflects a biomarker-oriented strategy to exploit replication stress in second-line advanced PDAC, but efficacy remains under investigation.
PDAC	ICI + DDR/RSR targeting	PARP inhibitor + PD-1/PD-L1 blockade	NCT04548752; NCT04493060; NCT03330405	Not consistently specified	These studies test whether DDR-targeted therapy can increase tumor immunogenicity and sensitize selected PDAC subsets, particularly BRCA-mutated or platinum-sensitive disease, to immunotherapy.
PDAC	TME/adenosine axis	Quemliclustat + etrumadenant + SBRT-based neoadjuvant therapy	NCT06048484 (AIRPanc)	Phase II	This study evaluates whether adenosine-pathway blockade plus radiotherapy and immunotherapy can remodel the immunosuppressive PDAC microenvironment in surgically eligible disease.

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TUMOR TYPE	THERAPEUTIC STRATEGY	AGENT(S) / REGIMEN	TRIAL IDENTIFIER	PHASE	MAIN MESSAGE (REVISED)
PDAC	TME/CXCL12 axis	NOX-A12 (olaptesed pegol) + pembrolizumab	NCT03168139	Phase I/II	This trial investigates stromal chemokine blockade as a strategy to improve immune-cell trafficking and overcome CAF-mediated immune exclusion.
PDAC	Autophagy inhibition	Hydroxychloroquine + gemcitabine/nab-paclitaxel	NCT01978184	Phase II	This randomized trial tested autophagy inhibition as a metabolic vulnerability in resectable PDAC; clinical benefit appears modest and insufficient to establish HCQ as an effective standard strategy.
SCLC	CDK/DDR interface	Trilaciclib	Not an antitumor efficacy trial in this context	Approved supportive-care use	Trilaciclib should not be framed as an active antitumor strategy; its clinical value in SCLC is myelopreservation during chemotherapy rather than direct tumor control.
SCLC	RSR inhibition	Prexasertib (LY2606368)	NCT02735980	Phase II	Prexasertib monotherapy showed limited efficacy in extensive-stage SCLC despite strong biological rationale, underscoring the gap between replication-stress dependency and clinical benefit.
SCLC	DDR inhibition	Berzosertib + topotecan	DDRiver SCLC 250	Phase II	The combination represents an attempt to potentiate topotecan through ATR inhibition in platinum-resistant SCLC, but available evidence remains preliminary and does not yet support practice change.
SCLC	ICI + PARP inhibition	Olaparib + durvalumab	MEDIOLA	Phase I/II	The regimen was tolerable but did not achieve the desired level of antitumor activity, highlighting the need for biomarker-guided combination strategies in relapsed SCLC.
SCLC	CHK1 inhibition + immunotherapy	Prexasertib + anti-PD-L1	NCT03495323	Early-phase/clinical exploration	This program is hypothesis-generating and should be described as translation of strong preclinical synergy into early clinical testing, not as evidence of established efficacy.
GBM	Multi-CDK inhibition	Zotiraciclib (TG02)	NCT03224104	Phase Ib / early clinical program	Zotiraciclib-based regimens illustrate continued interest in transcriptional CDK targeting in GBM, but clinical activity to date remains limited and investigational.

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TUMOR TYPE	THERAPEUTIC STRATEGY	AGENT(S) / REGIMEN	TRIAL IDENTIFIER	PHASE	MAIN MESSAGE (REVISED)
GBM	RSR inhibition	Triapine + radiotherapy	NCT06860594	Phase I	This first-in-human combination explores whether checkpoint kinase inhibition can radiosensitize recurrent glioblastoma while remaining tolerable in the CNS setting.
GBM	PARP inhibition	Talazoparib + chemotherapy (TAC-GReD)	NCT04740190	Early-phase trial	This trial targets DDR-deficient recurrent high-grade glioma, testing whether PARP inhibition can exploit molecularly defined DNA-repair vulnerability.
GBM	ICI	Nivolumab-based programs	Not specified	Phase III	Large randomized trials of checkpoint blockade in GBM failed to demonstrate meaningful survival improvement, reinforcing the immune-cold biology of this disease and the need for rational combinations.
HCC	CDK4/6 inhibition	Palbociclib	NCT04162301; NCT02255461	Early-phase	Clinical development of CDK4/6 inhibition in advanced HCC has been constrained by limited efficacy and pathway compensation, indicating that cytostatic monotherapy is unlikely to be sufficient.
HCC	RSR inhibition	WEE1/CHK1 pathway-targeted regimens	NCT04158336	Ongoing clinical trial	This trial exemplifies the strategy of leveraging high replication stress in HCC, but outcome data remain immature and should be presented as investigational.
CCA/BTC	RSR inhibition	ATR/CHK1/WEE1/ PARP-targeted programs	NCT04298021; NCT03878095; NCT02576444	Early-phase trials	These studies collectively reflect an exploratory DDR-targeting approach in biliary tract malignancies, especially in genomically selected or treatment-refractory settings.
CCA/BTC	PARP inhibition	Olaparib	NCT04042831	Phase II	The manuscript should correct the registry number to NCT04042831; this phase II study evaluates olaparib in metastatic biliary tract cancer with DNA-repair alterations.
CCA/BTC	ICI + chemotherapy	Durvalumab + gemcitabine/ cisplatin	Not specified	Phase III	TOPAZ-1 established chemo-immunotherapy as a clinically meaningful standard in advanced biliary tract cancer, although absolute survival gains remain modest and resistance remains common.

(Continued on next page)

TUMOR TYPE	THERAPEUTIC STRATEGY	AGENT(S) / REGIMEN	TRIAL IDENTIFIER	PHASE	MAIN MESSAGE (REVISED)
CCA/BTC	ICI-based combination	Nivolumab + gemcitabine/ cisplatin or nivolumab + ipilimumab	Not specified	Randomized Phase II	BitT-01 supports continued evaluation of immune-based combinations in untreated advanced biliary cancer, but its results should be interpreted as signal-seeking rather than definitive practice-changing evidence.
Esophageal cancer	CDK4/6 inhibition	Palbociclib	Phase II trial in advanced esophageal or gastric cancer	Phase II	Palbociclib monotherapy showed limited efficacy in upper gastrointestinal cancers, consistent with intrinsic cell-cycle bypass mechanisms such as cyclin E upregulation.
Esophageal cancer	ICI	Nivolumab vs chemotherapy	ATTRACTION-3	Phase III	ATTRACTION-3 demonstrated an overall survival advantage for nivolumab over chemotherapy in previously treated advanced esophageal squamous cell carcinoma, validating immune checkpoint blockade in a subset of patients.
Esophageal cancer	ICI	Pembrolizumab vs chemotherapy	KEYNOTE-181	Phase III	KEYNOTE-181 showed that benefit from pembrolizumab is concentrated in biomarker-enriched populations, supporting patient selection rather than indiscriminate monotherapy use.

PDAC: pancreatic ductal adenocarcinoma; SCLC: small-cell lung cancer; GBM: glioblastoma; HCC: hepatocellular carcinoma; CCA/BTC: cholangiocarcinoma/biliary tract cancer; RSR: replication stress response; DDR: DNA damage response; ICI: immune checkpoint inhibitor; TME: tumor microenvironment.

Tumors exhibiting a “High Replication Stress” profile, such as HCC, are associated with poorer survival outcomes but demonstrate increased sensitivity to therapies targeting the ATR-CHK1-WEE1 pathway (92-94). Agents such as ceralasertib (AZD6738) and elimusertib (BAY1895344) are currently being evaluated in early phase clinical trials for advanced solid tumors, including those resistant to standard treatments (95, 96). Preclinical studies have shown that ATR inhibition in high-risk HCC suppresses tumor progression and modulates antitumor immune response (92). Inhibitors of WEE1 and CHK1 induce mitotic catastrophe in cancer cells, further supporting their therapeutic potential. Ongoing trials (NCT04158336) are investigating these agents as monotherapies or

in combination with chemotherapy and immune checkpoint inhibitors to exploit high replication stress (97, 98). Additionally, research is progressing toward integrating RSR inhibitors with radiotherapy or immunotherapy to reverse the immunosuppressive tumor microenvironment characteristics of resistant HCC.

In CCA, ongoing clinical trials are investigating inhibitors of RSR proteins, including ATR, CHK1, WEE1, and PARP as potential strategies (NCT04298021, NCT03878095, NCT02576444) (99). Of particular interest, the PARP inhibitor olaparib is currently under evaluation in Phase II clinical trials (NCT04042831) for metastatic biliary tract cancer characterized by mutations in DNA repair genes (**Table 2**).

Gastroesophageal adenocarcinomas with high chromosomal instability and TP53 mutations in 72-90% of cases are particularly sensitive to CHK1 inhibitors (100). Clinical trials have indicated that the combination of these inhibitors with chemotherapy enhances therapeutic efficacy. The ATR inhibitor VX-970 (berzosertib) sensitizes esophageal cancer cells to chemotherapy and radiotherapy in preclinical models (101). Other ATR inhibitors, including ceralasertib and elimusertib (BAY 1895344), are under clinical evaluation for advanced solid tumors with DNA damage response defects (102, 103) (**Table 2**).

Immune checkpoint inhibitors

Many recalcitrant tumors exhibit an immunologically “cold” phenotype with low T-cell infiltration and abundant immunosuppressive cells, facilitating immune evasion and resistance to immunotherapy. Evaluating immune checkpoints remains crucial for developing combination therapies to convert cold tumors into “hot” tumors.

PDAC is characterized by a dense stroma, known as a desmoplastic reaction, which prevents immune cells from accessing the cancer cells. The tumor microenvironment (TME) contains immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs), which inhibit cytotoxic T cell infiltration. Dense stroma causes poor vascularization, creating a hypoxic and acidic environment that kills or exhausts effector T cells (104). PDACs have a low-to-intermediate mutational burden, resulting in fewer neoantigens and limited immune recognition (105). Consequently, ICIs show minimal efficacy in resistant PDAC and are FDA-approved only for patients with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) (~0.5-1%) (106). Meta-analyses have indicated that combining ICIs with chemotherapy provides modest benefits over chemotherapy alone (107). Clinical trials are evaluating ICI and RSR inhibitor combinations in resistant PDAC, focusing on PARP and PD-1/PD-L1 inhibitors in BRCA-mutated or platinum-sensitive cases (NCT04548752, NCT04493060, and NCT03330405). The Phase II POLAR study assessed ATR inhibitors to counteract PARP inhibitor resistance linked to ATR/CHK1 pathway hyperactivation (108) (**Table 2**). Despite a high tumor mutational burden from smoking-induced DNA damage, SCLC exhibits an immune-cold microenvironment with low immune infiltration, enabling immune evasion (109). Nonetheless, ICIs have improved treatment efficacy, with

the Phase III IMpower133 (Atezolizumab) and CASPIAN (Durvalumab) trials demonstrating the efficacy of ICI-chemotherapy combinations in extensive-stage SCLC (110). The MEDIOLA trial of olaparib plus durvalumab in relapsed SCLC showed tolerability but failed to meet primary efficacy endpoints, underscoring the need for biomarker-based patient selection (111). Prexasertib (Chk1 inhibitor) combined with anti-PD-L1 induced significant tumor regression in SCLC mouse models, achieving complete regression in up to 60% of cases, prompting early phase clinical evaluation (NCT03495323) (112) (**Table 2**). GBM is an immunologically cold tumor characterized by low T cell infiltration and an immunosuppressive microenvironment driven by M2-type TAMs and Tregs. Its low mutational burden contributes to poor ICI monotherapy outcomes, as shown in the Check-Mate 143, 498, and 548 trials (113-116). Additionally, the blood-brain barrier restricts the delivery of therapeutic antibodies, further limiting the engagement of the immune system. Current approaches focus on combination therapies, neoadjuvant use, and novel checkpoint targets. RSR defects are emerging biomarkers for predicting responses. Preclinical studies are assessing whether ATR inhibitors can prevent radiation-induced CD8+ T-cell depletion and target glioma stem cells with high replication stress (117, 118). Clinical trials are evaluating PARP inhibitors, such as talazoparib, combined with chemotherapy in high-grade gliomas (NCT04740190) (119) (**Table 2**). Recalcitrant HCC is an immunologically cold tumor characterized by poor T cell infiltration, high immunosuppression, and limited responses to ICIs despite arising in a chronically inflamed liver. Tumors exploit liver immune tolerance by accumulating M2-type TAMs, Tregs, and CAFs, which hinder immune cell infiltration (120). Many HCCs have few neoantigens, rendering them “invisible” to immune recognition (121). ICIs have changed HCC treatment, particularly in advanced cases that fail conventional therapies. Although atezolizumab plus bevacizumab is the first-line treatment for advanced HCC, ongoing trials are exploring combination and neoadjuvant therapies to overcome drug resistance (122). Clinical trials are evaluating RSR inhibitors in patients with advanced HCC. Patients with HBV-associated HCC show increased sensitivity to DNA damage, making DNA damage repair (DDR) inhibitors suitable for immunotherapy in this subpopulation (123). RSR inhibitors, including ATR inhibitors ceralasertib and berzosertib, combined with anti-PD-1/PD-L1, show promise in enhancing T cell activation in preclinical

models (102). Prexasertib and adavosertib (WEE1 inhibitor) have been evaluated in refractory solid tumors, showing potential benefits in Phase I trials (124, 125) in HCC with genomic signatures of chromosomal instability (CIN).

CCA is an immunologically cold tumor characterized by poor T cell infiltration, an immunosuppressive microenvironment, desmoplasia, and low antigenicity, leading to resistance to standard immunotherapy (126). In relapsed or advanced CCA, immune checkpoint inhibitors (durvalumab, nivolumab, and pembrolizumab) modestly improve overall survival compared to gemcitabine/cisplatin chemotherapy (1-2 months) (127-130). Combining ICIs with RSR inhibitors, including PARP inhibitors (olaparib) and ATR inhibitors (camonsertib), is under clinical investigation to enhance efficacy by targeting DNA repair mechanisms, increasing tumor mutational burden, and stimulating antitumor immune pathways (NCI-2020-05323, BIL-PPP) (131). While ICI monotherapy shows limited response rates (5-20%), combination strategies may improve outcomes in resistant CCA (**Table 2**).

Esophageal cancers are immunologically cold, characterized by an immunosuppressive microenvironment with Tregs and MDSCs and loss of MHC-I expression, enabling immune evasion (132). ICIs have improved treatment outcomes, with monotherapy and combination regimens (ATTRACTION-3, KEYNOTE-181) extending survival, although response rates remain 10-20% (133, 134). The combination of ICIs with RSR inhibitors is being investigated to enhance tumor immunogenicity and improve durable responses in resistant esophageal cancer (**Table 2**).

Remodeling of TME metabolism

Remodeling TME metabolism is essential for overcoming resistance in refractory tumors by reversing immunosuppression and inhibiting adaptive survival mechanisms under hypoxic and nutrient-deprived conditions. Tumor cells preferentially consume glucose, glutamine, and amino acids, thereby limiting the nutrients required for immune-cell activation and effector function. Lactic acid accumulation acidifies the TME, impairing the cytotoxic functions of NK cells and T lymphocytes. Extracellular ATP released during cellular stress is enzymatically converted to immunosuppressive adenosine via the action of CD39 and CD73. Under hypoxic conditions, refractory tumors depend on enhanced lipid biosynthesis and cholesterol accumulation to

evade immune surveillance and sustain their proliferation (135).

PDAC cells induce adjacent CAFs to undergo glycolysis, producing metabolites such as lactate and alanine that support tumor growth. This metabolic reprogramming generates a highly acidic and hypoxic TME that promotes aggressive tumor phenotypes. Fibroblast Activation Protein (FAP)-expressing CAFs secrete CXCL12, thereby inhibiting T cell infiltration, while inflammatory CAFs (iCAFs) release proinflammatory factors that facilitate immune evasion and tumor progression (136-138). Several clinical trials have investigated therapies targeting the TME. Study NCT06048484 evaluates stereotactic body radiation therapy (SBRT) combined with quemli-clustat, a CD73 inhibitor, and etrumadenant, an A2A/B receptor antagonist, aiming to block the adenosine pathway exploited by tumors for immune suppression (139). A Phase I/II trial (NCT03168139) assessed pembrolizumab in combination with NOX-A12, a CXCL12 inhibitor, targeting chemokine secretion from FAP-positive CAFs to impede tumor progression (140). Another trial focused on inhibiting the CSF1R/FAK pathway to reprogram MDSCs and TAMs, thereby enhancing T cell-mediated tumor eradication (141). PDAC also depends on macropinocytosis and autophagy for survival under nutrient deprivation, making these pathways potential therapeutic targets (142). Although hydroxychloroquine (HCQ) is the only autophagy inhibitor clinically tested in PDAC (NCT01978184), tolerated doses may paradoxically enhance macropinocytosis, thereby limiting its efficacy (143) (**Table 2**). Novel macropinocytosis inhibitors, including ivermectin, tyrphostin A9, and pyrimethamine, are currently under preclinical investigation in combination with autophagy blockers (144). Additional preclinical studies are exploring nutrient restriction strategies, such as vitamin B6 depletion, to inhibit PDAC growth (145). Despite promising preclinical results, translation to human trials remains challenging because of stromal heterogeneity.

SCLC features a hypoxic environment that drives its drug resistance. Hypoxia induces glycolysis, with CAFs activating FGF/FGFR signaling to enhance glycolysis and lactate production in non-neuroendocrine SCLC cells. Targeting monocarboxylate transporters (MCTs) reduce TME acidification and immune suppression. FGFR inhibitors are being investigated to block FGF-mediated metabolic and phenotypic tumor progression (146). SCLC cells have reduced levels of n-3 fatty acids in their phospholipids com-

pared to healthy tissues, contributing to a pro-inflammatory TME that promotes tumor progression. CAF-driven lipid metabolism reprogramming creates a fat-rich, immunosuppressive niche that supports tumor survival under hypoxia (147). Antigen-presenting CAFs (apCAF) sequester CD8⁺ T cells or induce their differentiation into Tregs, impairing cytotoxic responses (148). Inhibition of phospholipase D1 (PLD1), which generates pro-tumor phosphatidic acid, reduces lung metastasis and sensitizes chemotherapy-resistant tumors in preclinical models (149).

The GBM TME is an adaptive ecosystem in which CAFs drive therapeutic resistance by producing metabolites, such as lactate and pyruvate, that promote tumor growth. CAFs and GBM-associated mesenchymal stem cells (GA-MSCs) enhance GSC stemness and supply amino acids, such as glutamine and aspartate, which are vital for tumor biosynthesis under hypoxia (150). Glutaminase inhibitors (e.g., CB-839) show limited efficacy because of poor blood-brain barrier penetration (151, 152). Monocarboxylate transporter 4 (MCT4) inhibitors offer a promising strategy for blocking lactate export from CAFs and disrupting tumor-stroma metabolic crosstalk (153). Emerging therapies aim to reprogram CAFs from pro-tumorigenic to tumor-suppressive phenotypes, rather than eliminating them, to minimize potential harm to healthy tissues (154).

HCC and CCA exhibit an immunosuppressive TME driven by nutrient competition, lactate accumulation, and hypoxia. CAFs promote metabolic crosstalk that supports tumor progression and immune evasion by inducing the Warburg effect and producing lactate and metabolites that enhance chemoresistance and suppress immunity (155). Metabolic reprogramming of CAFs generates a hypoxic, hypoglycemic, and acidic TME that impairs CD8⁺ T cell functions. CAFs increase fatty acid synthase (FASN) expression and secrete lipids to fuel HCC cells while supplying glutamine for proliferation and glutathione synthesis to reduce oxidative stress (156). Preclinical targeting of CAF metabolism reduces tumor burden, normalizes vasculature, and enhances CD8⁺ T cell infiltration by inhibiting CAF cytokines, fatty acid synthesis, and CD36-mediated lipid uptake (156).

Esophageal cancer cells exhibit high glucose uptake, depleting energy sources for effector T cells and producing lactate, which acidifies the TME, inducing T cell exhaustion and M2 macrophage polarization. CAFs enhance lipogenesis and secrete lipids, such as lysophosphatidylcholine, supporting tumor

metabolism via PI3K/AKT pathway activation. The metabolic exchange of aspartate and glutamate between tumor cells and CAFs sustains proliferation and redox balance under nutrient scarcity (157, 158). Targeting CAF metabolism with phosphodiesterase 5 (PDE5) inhibitors, such as sildenafil, restricts fibroblast transdifferentiation, sensitizing tumors to chemotherapy (159). Inhibitors of FASN and lipid transporter CD36 are also under investigation to disrupt CAF-mediated metabolic support (160, 161).

Physical activity is a viable strategy for modulating the TME in patients with cancer. Tumors resistant to ICIs are often characterized by low infiltration of antitumor immune cells and an immunosuppressive TME. Exercise enhances immune cell circulation and improves immunosurveillance. Recent studies have indicated that physical activity facilitates the mobilization and redistribution of immune cells into the TME, thereby augmenting antitumor immune responses and potentially improving the efficacy of ICIs (162).

Softening of the extracellular matrix

Extracellular matrix (ECM) remodeling is a critical factor in the progression of recalcitrant tumors, particularly solid malignancies such as PDAC and GBM. The dense ECM serves as a physical barrier, impeding drug delivery and immune cell infiltration while simultaneously promoting tumor survival and metastasis (163). Current clinical trials are focused on “normalizing” the ECM to overcome chemoresistance and enhance immunotherapy efficacy. One approach involves the degradation of barrier components using enzymes such as pegvorhialuronidase alfa (PEGPH20) to degrade hyaluronic acid or collagen, thereby reducing tumor interstitial pressure and facilitating drug delivery (164). Another strategy targets the inhibition of remodeling processes, with drugs such as pamrevlumab, an antibody targeting connective tissue growth factor (CTGF) was evaluated in Phase III trials for unresectable pancreatic cancer. The available clinical data did not demonstrate the expected benefits, suggesting that the projected therapeutic benefits were not fully achieved (165). Additionally, the modulation of matrix stiffness is being investigated through the inhibition of lysyl oxidase (LOX) to prevent collagen cross-linking, thus reducing the stiffness that supports tumor stem cell survival and metastasis (166). Despite historically disappointing outcomes, new generations of integrin inhibitors are being developed to block

the interaction between the extracellular matrix and surface receptors, thereby disrupting tumor survival signaling (167, 168).

CONCLUSIONS

Recalcitrant tumors represent a major challenge in oncology because of their resistance to conventional therapies, necessitating a comprehensive multidisciplinary approach to improve patient outcomes. Preventive strategies remain essential, with lifestyle modifications – such as abstaining from alcohol and tobacco, maintaining a balanced diet, and engaging in regular physical activity – serving as foundational measures to reduce cancer risk. Early detection is equally critical, and advancements in liquid biopsy combined with multiomic analyses offer promising avenues for identifying novel biomarkers that enable diagnosis at stages when therapeutic interventions are more effective. This potential for early intervention could significantly improve clinical outcomes by facilitating personalized treatment strategies tailored to the tumor's molecular profile.

Looking ahead, the future of oncology is centered on innovative therapeutic modalities targeting the TME and its pro-tumorigenic functions. Emerging pharmacological strategies, including proteolysis-targeting chimera (PROTAC) platforms, chimeric antigen receptor T cells (CAR T cells) engineered to recognize tumor-specific antigens, and immune modulation therapies, are anticipated to transform cancer treatment. These interventions aim to inhibit tumor progression and reprogram the TME to enhance antitumor immunity, thereby improving the efficacy of current therapies and patient survival outcomes. Until these advancements become widely accessible, maintaining a healthy lifestyle remains an accessible and effective strategy for cancer-risk reductions and overall health promotion.

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