Chapter-4

Unveiling the Landscape of Cancer: From Therapeutic Targets to their Inhibition

Authors

Geet Madhukar
Department of Molecular
Cellular and Biomedical Sciences
University of New Hampshire, 46 College Rd.,
Durham, NH 03824, USA

Naidu Subbarao
School of Computational and Integrative Sciences
Jawaharlal Nehru University
New Delhi, 110067, India
Email: geet85_sit@jnu.ac.in, nsrao@mail.jnu.ac.in

Abstract

Cancer remains a pervasive global health challenge, characterized by uncontrolled cell growth, invasion, and metastasis. Despite significant advancements in medical science, the burden of cancer continues to escalate, with projections indicating a substantial rise in cases in the coming years. Globally recognized databases, programs, and platforms such as IMRD, National Cancer Registry Programme, India and GLOBOCAN help to better recognize the gravity of the burden that cancer represents. India, in particular, faces a concerning increase in cancer incidence, necessitating urgent interventions. Chemotherapy remains pivotal, but challenges such as drug toxicity and resistance underscore the need for innovative therapeutic strategies. It is essential to understand the collective pathways in cancer, as delineated by Hanahan and Weinber. These pathways intricately connect with hallmark characteristics of cancer cells, driving tumorigenesis through various signaling cascades and cellular processes. Targeting specific molecular events within these pathways offers promising avenues for improved treatment outcomes. Therefore, unraveling the complex relationship between collective pathways and cancer hallmarks is crucial for advancing precision medicine and mitigating the global burden of cancer.

Keywords: Cancer Targeted Therapy, Current Drug Targets, Potential Drug Targets, Small Molecule Inhibitors.

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1. INTRODUCTION

Cancer represents a spectrum of diseases characterized by uncontrolled cell growth, invasion of surrounding tissues, and propagation to distant organs via bloodstream and lymphatic systems [1]. Although originating from diverse organs and tissues, cancers share common features, including abnormal cellular proliferation, with contributing factors such as chemical exposures, genetic predispositions, and lifestyle influences remaining significant [2]. Despite remarkable progress in medical science, the global burden of cancer continues to escalate. GLOBOCAN 2020 data revealed staggering figures, with approximately 19.3 million new cancer cases worldwide (excluding nonmelanoma skin cancer) and nearly 10.0 million cancer-related deaths. Notably, female breast cancer emerged as the most diagnosed cancer, with approximately 2.3 million new cases, while lung cancer maintained its position as the leading cause of cancer mortality, claiming around 1.8 million lives. Projections suggest a worrisome trajectory, with the global cancer burden anticipated to soar to 28.4 million cases by 2040, signifying a 47% increase from 2020, with transitioning countries predicted to bear the brunt of this rise [3]. A real-world research database known as IQVIA Medical Research Data (IMRD) having NHS Health Research Authority approval for medical research and treatment analysis provides valuable insights into primary care managed diseases and could prove beneficial in identifying the improved treatment for cancer patients [4].

In India, the statistics are equally concerning, with an estimated 1,461,427 new cancer cases reported in 2022, resulting in a crude rate of 100.4 per 100,000 people. Furthermore, the projected 12.8% increase in cancer incidence by 2025 compared to 2020 underscores the urgent need for effective interventions to curb this trend [5].

Chemotherapy maintains its central role, particularly in addressing metastasized cancer cells, emphasizing the need to advance the development of pharmaceutical and biological agents to prevent cancer propagation and reduce organ dysfunction. There are major challenges such as drug toxicity and resistance to ongoing efforts to uncover promising therapeutic options beyond conventional treatments [6], [7]. Research has been going on to devise a method

to optimize the drug dosage, iMRD is one such method that determine an individual's tailored dose for chemotherapy and could provide the optimal dose for patients with noncurable cancers such as metastatic pancreas cancer [8], [9]. However, it is still in very initial phases has not been extensively explored in different cancers and requires further research before it can be implemented. Addressing the treatment challenges requires a transformation in approaches to cancer therapy, with the need to explore the fundamental pathophysiology of cancer, as well. This requires the exploration of collective pathways in cancer, as understanding these complex molecular mechanisms is crucial for developing targeted treatments. The collective pathways in cancer are connected to the hallmark characteristics of cancer, as outlined by Hanahan and Weinberg [10], [11], [12], [13]. These hallmarks represent fundamental biological capabilities acquired by cancer cells during tumorigenesis, driven by alterations in signaling pathways and cellular processes. Cancer cells activate signaling pathways such as PI3K-AKT-mTOR [14] [15], [16], [17], [18] [19]and Ras-Raf-MEK-ERK [20], [21], [22] to sustain proliferative signaling, evade growth suppressors by disabling tumor suppressor pathways like p53 [23], [24] and Rb [25], [26], and resist cell death through mechanisms involving Bcl-2 family proteins [27]. They achieve replicative immortality by activating telomerase or alternative lengthening of telomeres (ALT) pathways, induce angiogenesis by stimulating Vascular Endothelial Growth Factor (VEGF) and Hypoxia-Inducible Factor (HIF) signaling [28], [29], and activate invasion and metastasis programs through pathways like epithelial-mesenchymal transition (EMT) [30], [31], [32] and matrix metalloproteinases (MMPs) [33], [34]. Cancer cells also avoid immune destruction by hijacking immune checkpoint signaling [35] and promoting immune tolerance and deregulate cellular energetics by reprogramming metabolism to support increased proliferation. Additionally, they accumulate genetic alterations through dysregulation of DNA damage response (DDR) [36], [37], [38] and repair pathways [39], [40], leading to genomic instability and heterogeneity. Tumor-promoting inflammation further contributes to tumor progression through pathways involving NF-κB and cytokines like TNF-α and IL-6 [41], [42], [43], [44]. Therefore, understanding the complex relationship between these collective pathways and cancer hallmarks is crucial for developing targeted therapies aimed at disrupting specific molecular events driving tumor growth and progression, ultimately improving cancer treatment outcomes [13], [11].

2. TARGETED THERAPY

The targeted therapies exemplify the precision medicine approach in cancer treatment, where therapies are tailored to the specific molecular characteristics of individual tumors (Table 1). By selectively targeting key pathways and molecular targets driving cancer progression, targeted therapies

offer the potential for improved efficacy and reduced toxicity compared to traditional cytotoxic chemotherapy. Several clinically approved drug targets in humans have been identified (Table 2), however, resistance to targeted therapies can develop over time, highlighting the need for ongoing research to identify new targets and combination strategies to overcome resistance and improve patient outcomes [45], [46], [47], [48]

Table 1: List of Some Approved Small Molecules and Monoclonal Antibodies for Cancer Treatment.

Compound	Commercial name	Target(s)	Indications	Comments	References
Gefitinib	IRESSA	EGFR (Epidermal Growth Factor Receptor)	NSCLC (non-small cell lung cancer)	For patients with tumors harboring EGFR exon 19 deletions or exon 21 (L858R) substitution mutations	[49] [50]
Sunitinib	SUTENT	VEGFR (Vascular Endothelial Growth Factor Receptor)	RCC (renal cell carcinoma), GIST (gastrointestinal stromal tumor)	For adult patients at high risk of recurrent RCC following nephrectomy.	[50]
Lorlatinib	LORBRENA	ALK (Anaplastic Lymphoma Kinase)	NSCLC	for patients with ALK-positive metastatic NSCLC	[50]
Venetoclax	VENCLEXTA	BCL-2 (B-cell lymphoma 2)	CLL (Chronic Lymphocytic Leukemia), AML(acute myeloid leukemia)	Combine azacitidine, decitabine, or low dose cytarabine (LDAC) for the treatment of newly diagnosed AML in	[50]

				adults aged 75 years or older, or those with comorbidities that prevent the use of intensive induction chemotherapy.	
Enasidenib	IDHIFA	IDH2 (Isocitrate Dehydrogenase 2)	AML	For patients with relapsed or refractory AML	[50]
Rucaparib	RUBRACA	BRCA	Advanced Ovarian Cancer	For patients who have undergone treatment involving two or more rounds of chemotherapy.	[50]
Ponatinib	ICLUSIG	BCR-ABL gene mutation, T315I	CML, Ph+ ALL (Philadelphia chromosome positive acute lymphoblastic leukemia)		[50][51]
Palbociclib	IBRANCE	CDK(Cyclin-Dependent Kinase)	Breast Cancer	Approved in combination with fulvestrant	[50]
Talazoparib	TALZENNA	PARP	Prostate Cancer	Approved in combination with enzalutamide	[50]
Olaparib	LYNPARZA	PARP	Prostate Cancer	Approved in combination with abiraterone	[50][52]

				and prednisone	
Trametinib	MEKINIST	MEK (Mitogen-Activated Protein Kinase Kinase)	Solid Tumors	Approved in combination with dabrafenib (Tafinlar)	[53]
Vismodegib	ERIVEDGE	SMO (Smoothened)	BCC (Basal Cell Carcinoma)	for patients with locally advanced basal cell cancer who are not candidates for surgery or radiation and for patients with metastatic disease	[54]
Lenvatinib	LENVIMA	VEGFR, FGFR (Fibroblast Growth Factor Receptor)	Thyroid Cancer, RCC	Approved in combination with pembrolizumab	[55]
Idelalisib	ZYDELIG	PI3K (Phosphatidylinositol 3-Kinase)	CLL, Follicular Lymphoma		[56], [57], [58]
Regorafenib	STIVARGA	VEGFR, PDGFR, RAF (Rapidly Accelerated Fibrosarcoma)	HCC (hepatocellular carcinoma), colorectal cancer	The expanded approval is for the treatment of patients with HCC whose tumors have stopped responding to a similar	[59], [60], [61]

				targeted therapy	
Cabozantinib	CABOMETYX	MET, VEGFR, RET	Thyroid Cancer, HCC	For adults and pediatric patients aged 12 and above with advanced thyroid cancer unresponsive to VEGFR-targeted therapy and ineligible for radioactive iodine, treatment is recommended.	[62], [63], [64]
Ruxolitinib	JAKAFI	JAK1, JAK2 (Janus Kinase 1, 2)	Myelofibrosis, Polycythemia Vera		[65], [66], [67]
Afatinib	GIOTRIF	EGFR	NSCLC		[68]
Ibrutinib	IMBRUVICA	BTK (Bruton's tyrosine kinase)	CLL, SLL (small lymphocytic lymphoma)	Approved in combination with rituximab	[69], [70], [71]
Alectinib	ALECENSA	ALK	ALK-positive NSCLC		[72], [73]
Brigatinib	ALUNBRIG	ALK	ALK-positive NSCLC		[74], [75], [76]
Panobinostat	FARYDAK	HDAC (Histone deacetylase)	Multiple myeloma	For patients whose cancer has progressed after treatment with at least	[77], [78], [79], [80]

				two prior standard therapies.	
Dasatinib	SPRYCEL	BCR-ABL, SRC (Proto-Oncogene Tyrosine-Protein Kinase Src)	CML, Ph+ ALL		[81], [82], [83]
Tamoxifen	NOLVADEX	Estrogen Receptor	Breast Cancer		[84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94], [95]
Dabrafenib	TAFINLAR	BRAF (V-Raf Murine Sarcoma Viral Oncogene Homolog B)	Melanoma, NSCLC, and thyroid cancer.	Approved in combination with trametinib	[81], [96], [97]
Crizotinib	XALKORI	ALK, ROS1	NSCLC	For adult and pediatric patients 1 year of age and older	[98], [99]
Everolimus	AFINITOR	mTOR (Mammalian Target of Rapamycin)	RCC, Breast Cancer		[100], [101], [102]
Nivolumab	OPDIVO	PD-1	Various cancers including melanoma, HNSCC		[103], [104], [105]
Pembrolizumab	KEYTRUDA	PD-1 (Programmed cell death protein 1)	Various cancers including melanoma, NSCLC		[55], [106], [107], [108], [109]

Isatuximab -irfc	SARCLISA	CD38	Multiple myeloma	Approved in combination with carfilzomib and dexamethasone	[110], [111], [112]
Sacituzumab govitecan -hziy	TRODELVY	TROP-2 (Tumor-associated calcium signal transducer 2)	Triple-negative breast cancer		[113], [114], [115], [116]
Tafasitamab -cxix	MONJUVI	CD19	Diffuse large B-cell lymphoma	Approved in combination with lenalidomide (REVLIMID)	[117], [118], [119], [120]
Belantamab mafodotin -blmf	BLENREP	BCMA	Multiple myeloma	On March 20, 2023, FDA revoked biologics license for BLENREP due to the failure of the confirmatory DREAMM–3 trial to meet its primary endpoint, which was to establish superior progression-free survival.	[121], [122], [123], [124]

Naxitamab -gqgk	DANYELZA	GD2	High-risk neuroblastoma and refractory osteomedullary disease	Approved in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for pediatric patients aged one year and above, as well as adult patients experiencing relapsed or refractory high-risk neuroblastoma.	[125], [126], [127], [128]
Dostarlimab -gxly	JEMPERLI	PD-1	Endometrial cancer	Approved in combination with chemotherapy	[129], [130], [131], [132], [133]
Amivantamab -vmjw	RYBREVANT	EGFR, cMET	NSCLC with EGFR exon 20 insertion mutations	Approved in combination with carboplatin and pemetrexed for the first-line treatment of NSCLC	[134], [135], [136], [137]
Loncastuximab tesirine -lpyl	ZYNLONTA	CD19	Diffuse large B-cell lymphoma	Zynlonta is an intravenous, CD19-directed antibody and alkylating	[130], [138], [139], [140]

				agent conjugate	

Table 2: List of Clinically Approved Drug Targets in Humans, Accompanied by Compounds Documented in the ChEMBL Database (as of February 2024).

CHEMBL ID	Name	UniProt Accessions	Type	Organism	Compounds	Activities
CHEMBL1163126	Serine/threonine-protein kinase ICK	Q9UPZ9	SINGLE PROTEIN	Homo sapiens	426	484
CHEMBL1615382	Nuclear receptor coactivator 3	Q9Y6Q9	SINGLE PROTEIN	Homo sapiens	240	240
CHEMBL1764945	PHD finger protein 13	Q86YI8	SINGLE PROTEIN	Homo sapiens	2	2
CHEMBL1795185	Bromodomain testis-specific protein	Q58F21	SINGLE PROTEIN	Homo sapiens	278	549
CHEMBL1795198	STE20-related kinase adapter protein alpha	Q7RTN6	SINGLE PROTEIN	Homo sapiens	261	270
CHEMBL2021752	Kinesin-like protein KIF20B	Q96Q89	SINGLE PROTEIN	Homo sapiens	6	32
CHEMBL2046267	Anoctamin-1	Q5XXA6	SINGLE PROTEIN	Homo sapiens	180	229
CHEMBL2052032	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphata	P60484	SINGLE PROTEIN	Homo sapiens	4	4

	se and dual-specificity protein phosphatase PTEN					
CHEMBL206	Estrogen receptor alpha	P03372	SINGLE PROTEIN	Homo sapiens	7671	15446
CHEMBL2093866	Estrogen receptor	Q92731 P03372	PROTEIN FAMILY	Homo sapiens	1788	3070
CHEMBL2095161	Peroxisome proliferator-activated receptor gamma/Nuclear receptor coactivator 3	P37231 Q9Y6Q9	PROTEIN-PROTEIN INTERACTION	Homo sapiens	749	749
CHEMBL2106	Fructose-bisphosphate aldolase A	P04075	SINGLE PROTEIN	Homo sapiens	1	1
CHEMBL2146355	Protein CIP2A	Q8TCG1	SINGLE PROTEIN	Homo sapiens	7	21
CHEMBL2150837	ATPase family AAA domain-containing protein 2	Q6PL18	SINGLE PROTEIN	Homo sapiens	369	586
CHEMBL2295562	Dual specificity protein phosphatase 26	Q9BV47	SINGLE PROTEIN	Homo sapiens	14	14
CHEMBL2363065	Mitochondrial complex I (NADH dehydrogenase)	P03923 O95299 O00217 P03901 P56556 P03886 O95139	PROTEIN COMPLEX	Homo sapiens	13	28

		O00483 Q86Y39 P17568 P03891 O75306 P03915 P51970 O43674 P03905 P03897 O14561 O15239 O43181 O43676 O43677 O43678 O43920 O75251 O75380 O75438 O75489 O95167 O95168 O95169 O95178 O95182 O95298 O96000 P19404 P28331 P49821 P56181 Q16718 Q16795 Q8N183 Q9BU61 Q9NRX3 Q9NX14 Q9P032 Q9P0J0 Q9UI09 Q9Y375 Q9Y6M9				
CHEMBL 2364701	26S proteasome	Q99460 P49721 P20618	PROTEIN COMPL	Homo sapiens	65	143

		P28074 P28062 P28065 P28072 O00487 P25786 P25787 P25788 P25789 P28066 P60900 O14818 Q8TAA3 P40306 A5LHX3 P49720 P28070 Q99436 Q16186 P35998 P62191 P43686 P62333 P17980 P62195 Q13200 O43242 O00232 O00231 Q15008 P51665 Q9UNM6 P55036 P48556 P60896	EX			
CHEMBL 242	Estrogen receptor beta	Q92731	SINGLE PROTEIN	Homo sapiens	4863	8979
CHEMBL 3038485	Beta-N-acetyl-D-hexosaminidase-A/B	P07686 P06865	PROTEIN FAMILY	Homo sapiens	50	71
CHEMBL 3112376	Alpha-ketoglutarate-dependent	Q96Q83	SINGLE PROTEIN	Homo sapiens	75	100

	dioxygenase alkB homolog 3					
CHEMBL3580482	Mucin-16	Q8WXI7	SINGLE PROTEIN	Homo sapiens		
CHEMBL3580494	Mucin-1	P15941	SINGLE PROTEIN	Homo sapiens	10	26
CHEMBL3627582	Testis-specific serine/threonine-protein kinase 6	Q9BXA6	SINGLE PROTEIN	Homo sapiens	15	17
CHEMBL3632454	Kinesin-like protein KIF15	Q9NS87	SINGLE PROTEIN	Homo sapiens	32	55
CHEMBL3713916	Ovarian cancer G-protein coupled receptor 1	Q15743	SINGLE PROTEIN	Homo sapiens	71	279
CHEMBL3774295	Lysine-specific demethylase 5B	Q9UGL1	SINGLE PROTEIN	Homo sapiens	561	755
CHEMBL3831285	Interleukin 13 receptor	P24394 P78552	PROTEIN COMPLEX	Homo sapiens		
CHEMBL3879825	tRNA-dihydrouridine (20) synthase [NAD(P)+]-like	Q9NX74	SINGLE PROTEIN	Homo sapiens	1	1
CHEMBL3883304	Aurora kinase A/Targeting protein for Xklp2	O14965 Q9ULW0	PROTEIN COMPLEX	Homo sapiens	23	24
CHEMBL3885521	Baculoviral IAP repeat-	P03372 Q13490	PROTEIN COMPL	Homo sapiens	4	7

	containing protein 2/Estrogen receptor		EX			
CHEMBL3885534	LKB1-STRAD-MO25 complex	Q15831 Q7RTN6 Q9Y376	PROTEIN COMPLEX	Homo sapiens	2	2
CHEMBL3886	Mixed lineage kinase 7	Q9NYL2	SINGLE PROTEIN	Homo sapiens	1295	1473
CHEMBL4105704	Obg-like ATPase 1	Q9NTK5	SINGLE PROTEIN	Homo sapiens	188	188
CHEMBL4148	L-type amino acid transporter 3	O75387	SINGLE PROTEIN	Homo sapiens	7	7
CHEMBL4295936	Cancer-related nucleoside-triphosphatase	Q9BSD7	SINGLE PROTEIN	Homo sapiens	1	2
CHEMBL4295952	X antigen family member 1	Q9HD64	SINGLE PROTEIN	Homo sapiens	1	1
CHEMBL4296022	Melanoma-associated antigen 4	P43358	SINGLE PROTEIN	Homo sapiens	20	38
CHEMBL4296073	Lysine-specific demethylase 5A/5B	P29375 Q9UGL1	PROTEIN FAMILY	Homo sapiens	88	101
CHEMBL4296614	Bromodomain and extra-terminal motif (BET)	P25440 O60885 Q58F21 Q15059	PROTEIN FAMILY	Homo sapiens		
CHEMBL4523318	Glycerol-3-phosphate acyltransf	Q53EU6	SINGLE PROTEIN	Homo sapiens	1	6

	erase 3					
CHEMBL 4523506	START domain-containing protein 10	Q9Y365	SINGLE PROTEIN	Homo sapiens	9	9
CHEMBL 4523509	Spindlin-1	Q9Y657	SINGLE PROTEIN	Homo sapiens	23	66
CHEMBL 4523606	Speckle-type POZ protein/PTEN	P60484 O43791	PROTEIN-PROTEIN INTERACTION	Homo sapiens	1	4
CHEMBL 4523643	A-kinase anchor protein 13/Transforming protein RhoA	P61586 Q12802	PROTEIN COMPLEX	Homo sapiens	1	1
CHEMBL 4523681	Protein cereblon/Estrogen receptor	P03372 Q96SW2	PROTEIN-PROTEIN INTERACTION	Homo sapiens	22	39
CHEMBL 4523713	Protein cereblon/Cullin-4A/Estrogen receptor	P03372 Q96SW2 Q13619	PROTEIN-PROTEIN INTERACTION	Homo sapiens	2	8
CHEMBL 4523721	Estrogen receptor/E3 ubiquitin-protein ligase XIAP	P03372 P98170	PROTEIN-PROTEIN INTERACTION	Homo sapiens	2	3
CHEMBL 4523726	VHL/Estrogen receptor	P03372 P40337	PROTEIN-PROTEIN INTERACTION	Homo sapiens	17	39

CHEMBL 4523754	VHL/Cullin-2/Estrogen receptor alpha	P03372 P40337 Q13617	PROTEIN-PROTEIN INTERACTION	Homo sapiens	37	138
CHEMBL 4662941	Melanoma-associated antigen 3	P43357	SINGLE PROTEIN	Homo sapiens		
CHEMBL 4742282	Cereblon/ Small EDRK-rich factor 2	Q96SW2 P84101	PROTEIN-PROTEIN INTERACTION	Homo sapiens	1	1
CHEMBL 4802034	HEC1/NEK2	P51955 O14777	PROTEIN-PROTEIN INTERACTION	Homo sapiens	1	2
CHEMBL 4804257	Cancer/testis antigen 1	P78358	SINGLE PROTEIN	Homo sapiens		
CHEMBL 4896	PDZ-binding kinase	Q96KB5	SINGLE PROTEIN	Homo sapiens	954	995
CHEMBL 4899	Mitogen-activated protein kinase kinase kinase 8	P41279	SINGLE PROTEIN	Homo sapiens	392	453
CHEMBL 5169155	Kita-kyushu lung cancer antigen 1	Q5H943	SINGLE PROTEIN	Homo sapiens	1	4
CHEMBL 5169192	YTH domain-containing family protein 1	Q9BYJ9	SINGLE PROTEIN	Homo sapiens	2	2
CHEMBL 5169204	Palmitoyltransferase ZDHHC2	Q9UIJ5	SINGLE PROTEIN	Homo sapiens	11	13

CHEMBL 5389	Targeting protein for Xklp2	Q9ULW 0	SINGLE PROTEI N	Homo sapiens	6	6
CHEMBL 5393	ATP-binding cassette sub-family G member 2	Q9UNQ 0	SINGLE PROTEI N	Homo sapiens	2009	4860
CHEMBL 5578	Cyclin-dependent kinase 2-associated protein 1	O14519	SINGLE PROTEI N	Homo sapiens	33	33
CHEMBL 5639	Serine/thr eonine-protein kinase WNK2	Q9Y3S1	SINGLE PROTEI N	Homo sapiens	380	570
CHEMBL 5660	Kinetocho re protein NDC80 homolog	O14777	SINGLE PROTEI N	Homo sapiens	5	14
CHEMBL 5877	Beta-hexosamin idase subunit beta	P07686	SINGLE PROTEI N	Homo sapiens	75	131
CHEMBL 5990	Breast cancer type 1 susceptibil ity protein	P38398	SINGLE PROTEI N	Homo sapiens	15823	15908
CHEMBL 612260	Colon cancer cell line		CELL-LINE	Homo sapiens	28	54
CHEMBL 612700	KATO III stomach cancer cell lines		CELL-LINE	Homo sapiens	95	114
CHEMBL 613895	Ovarian cancer cell line		CELL-LINE	Homo sapiens	74	102
CHEMBL 614005	Renal cancer cell line		CELL-LINE	Homo sapiens	42	66

CHEMBL 614648	Tumor cancer cell line		CELL-LINE	Homo sapiens	10	10
CHEMBL 614788	Breast cancer cell lines		CELL-LINE	Homo sapiens	35	85
CHEMBL 614790	Lung cancer cell line		CELL-LINE	Homo sapiens	22	22

3. COLLECTIVE PATHWAYS IN CANCER

PI3K/Akt/m TOR Pathway and Inhibition

Unregulated activation of the PI3K/Akt/mTOR pathway leads to several hallmarks of cancer, including sustained growth signaling, inhibition of apoptosis, continual angiogenesis, increased tissue invasion and metastasis and insensitivity to antigrowth signals. PI3Ks are a group of intracellular lipid kinases that catalyze the phosphorylation of phosphatidylinositol and phosphoinositides at the 3′-hydroxyl group [14]. They are categorized into three classes (I–III), each playing distinct roles in signal transduction. Class I PI3Ks, further divided into class IA and IB, are activated by growth factor receptor tyrosine kinases and G-protein-coupled receptors, respectively [19]. The class IA PI3K is a heterodimer composed of a p85 regulatory subunit (encoded by PIK3R1, PIK3R2, and PIK3R3 genes) and a p110 catalytic subunit (encoded by PIK3CA, PIK3CB, and PIK3CD genes). Class II PI3Ks only consist of a p110-like catalytic subunit (encoded by PIK3C2A, PIK3C2B, and PIK3C2G genes), while class III PI3K comprises a single catalytic member, Vps34 (encoded by PIK3C3 gene), which interacts with the adapter protein Vps15 (encoded by PIK3R4 gene) [18], [141].

The roles of PI3K classes are broadly categorized into cell signaling (class I and II) and membrane trafficking (class II and III). Class IA PI3Ks, particularly the p110α isoform, are heavily implicated in human cancer, with mutations or amplifications of the PIK3CA gene found across various malignancies [14], [141]. Inhibition of p110α isoform in breast cancer as well as head and neck cancer has shown increased tumorigenesis [14], [141]. Furthermore, other class IA isoforms such as p110 and p110 also play modulatory roles in cancer. Preclinical data indicates functional redundancy among class IA PI3Ks, where a small fraction of total activity is sufficient for cell survival and proliferation. Inhibition of specific isoforms such as p110 may cause upregulation of alternative pathways such as the ERK pathway.

Activation of PI3K leads to the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to produce PI(3,4,5)P3 (PIP3), which triggers downstream signaling. Akt, a member of the AGC protein kinase family, is activated by PI3K/Akt pathway and regulates various cellular processes including apoptosis, cell cycle, and immune modulation [18]. Akt activation inhibits proapoptotic factors and promotes cell survival. Additionally, Akt modulates NFκB transcription factor, preventing its negative regulation by IκB family proteins. Akt also activates mTOR pathway, promoting tumorigenesis, cell cycle progression, and inhibition of apoptosis [141].

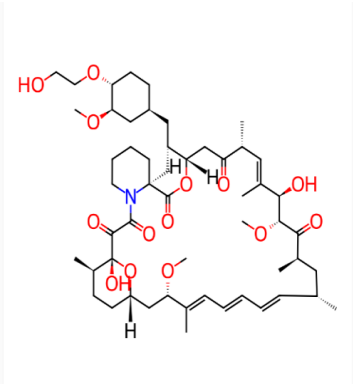
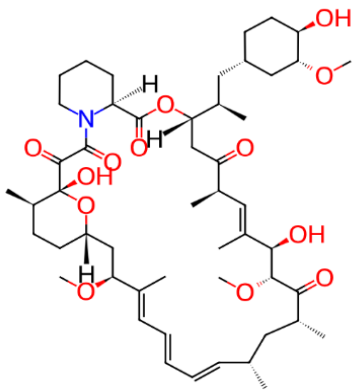
Dysregulation of the PI3K/Akt/mTOR pathway is well-documented in cancer, with somatic mutations and gene amplifications found in various cancers [14], [19], [18], [141] Mutations in PIK3CA are prevalent in hepatocellular [142], breast [143], [144], and colon cancers [145], [146], while PTEN loss is common in glioblastoma [147], [148], [149], [150], prostate [151], [152], breast [153], [154], [155], melanoma [156], and gastric cancers [157]. Akt amplifications and mutations have been identified in several cancers, contributing to constitutive activation of the pathway.

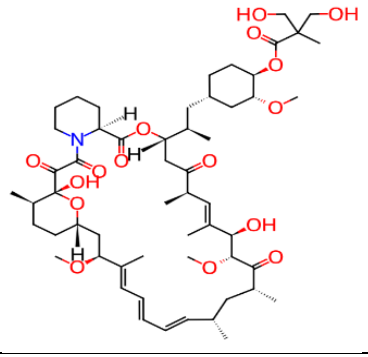
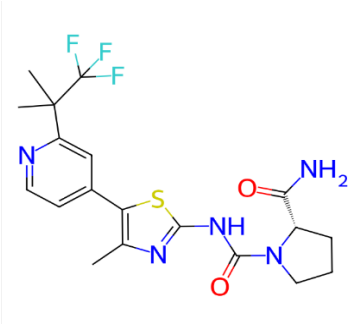
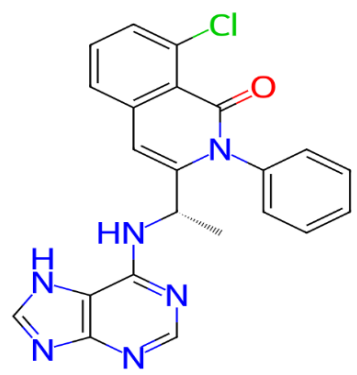
Increased activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway leads to numerous hallmarks of cancer, including acquired growth signal autonomy, inhibition of apoptosis, sustained angiogenesis, increased tissue invasion and metastasis and insensitivity to antigrowth signals. Therefore, this pathway is an attractive target for novel anticancer therapies.

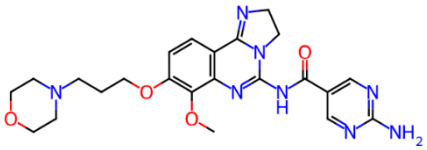
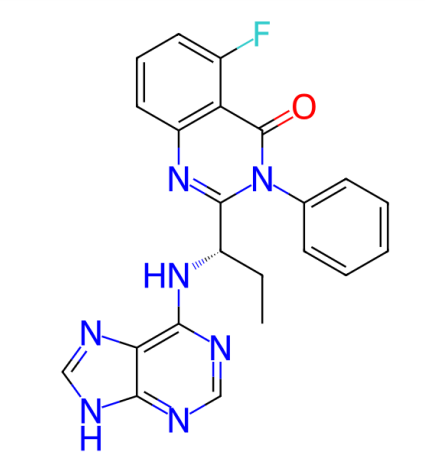
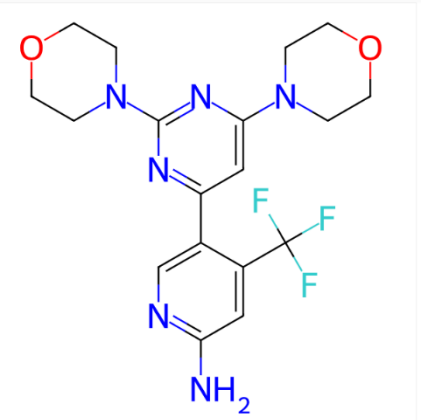
Targeted Therapy Against the PI3K/Akt/mTOR Pathway

Targeted therapies in cancer treatment emphasis on interrupting specific molecular pathways or targets that are critical for tumor development and survival while reducing damage to normal cells. These therapies often exploit vulnerabilities in cancer cells that arise from genetic mutations or unregulated signaling pathways [14], [18]. During the past years, the targeted treatment of various cancers such as NSCLC [158], breast cancer [159], oral cancer [18], [19], pancreatic cancer etc has been developed, and tyrosine kinase inhibitors (TKIs) has been extensively explored (Table 3). TKIs target receptor tyrosine kinases, which play key roles in PI3K-AKT-mTOR signaling pathways and blocks the activity of these kinases, inhibiting downstream signaling and impeding cancer cell proliferation and survival.

Table 3: List of Known TKIs Targeting PI3K/Akt/mTOR Pathway

Sl.no	Compounds	Commercial Name	Structure	Specificity	Description	References
1	Everolimus	Afinitor		mTOR inhibitor	Similar to Temsirolimus, it inhibits mTOR and has been approved for various cancers, including advanced breast cancer, pancreatic neuroendocrine tumors, and RCC.	[100], [101], [105]
2	Sirolimus	Rapamune		mTOR inhibitor	Sirolimus inhibits the mTOR pathway, exerting antiproliferative and antiangiogenic effects in cancer cells. Recently, U.S. Food and Drug Administration (FDA) approved sirolimus protein-bound particles for malignant perivascular epithelioid cell tumor.	[160], [161]

3	Temsirolimus	Torisel		mTOR inhibitor	It inhibits mTOR and is used for the treatment of advanced RCC (kidney cancer).	[15], [102], [162]
4	Alpelisib	Piqray		PI3K inhibitor	It selectively inhibits the alpha isoform of PI3K and is approved for hormone receptor-positive, HER2-negative breast cancer with PIK3CA mutations.	[14], [18], [163]
5	Duvelisib	Copiktra		PI3K inhibitor	It inhibits both the delta and gamma isoforms of PI3K and is approved for certain types of blood cancers, including CLL and follicular lymphoma.	[164], [165]

6	Copanlisib	Aliqopa		PI3K inhibitor	This is another PI3K inhibitor approved for the treatment of relapsed follicular lymphoma.	[166], [167]
7	Idelalisib	Zydelig		PI3K inhibitor	It is an FDA approved inhibitor that inhibits the delta isoform of PI3K and is used for the treatment of certain types of blood cancers, such as chronic lymphocytic leukemia (CLL) and follicular lymphoma.	[56], [57], [58]
8	Buparlisib	BKM120		PI3K inhibitor	This is a pan-PI3K inhibitor that has been studied in clinical trials for various solid tumors, including breast cancer and glioblastoma.	[168], [169]

Ras-Raf-MEK-ERK Pathway and Inhibition

The mitogen-activated protein kinase (MAPK) signaling pathway has highly conserved central regulators of cell proliferation, cell cycle progression, and survival, which are activated in response to numerous extracellular signals. While primarily transmitting mitogenic signals, this pathway is involved in numerous cancers beyond cutaneous melanomas. Colorectal cancer [170], [171], lung cancer [172], [173], pancreatic cancer [174], thyroid cancer [175], [176], ovarian cancer [177], [178], breast cancer [179], [180], [181], [182], prostate cancer [183], [184], HNSCC [18], [19], [185], brain tumors like glioblastoma [186], [187], [188], and liver cancer [189], [190], [191], [192] are among the malignancies where the MAPK pathway dysregulation plays a significant role. The unusual activation of this pathway contributes to tumor initiation, progression, and metastasis across these cancer types, emphasizing its potential as a therapeutic target [20], [21], [22].

Upon activation by membrane receptors, RAS recruits RAF kinases to the plasma membrane, resulting in a cascade wherein RAF phosphorylates MEK. Active MEK, in turn, phosphorylates ERK, which can translocate to the nucleus to modulate transcription factors and cytosolic targets essential for cell functions. MEK and ERK exist in isoforms, MEK1/2 and ERK1/2, respectively, with MEK displaying narrow substrate specificity while ERK exhibits broad specificity [20], [21], [193].

RAS is a key upstream regulator that undergoes activation through a series of events involving GRB2-SOS complexes at the cell membrane. This activation culminates in RAF activation and subsequent signaling cascade initiation. The pathway is tightly regulated by negative feedback mechanisms and interacts with the RAS-PI3K-AKT-mTOR pathway, leading to cross-inhibition and convergence on shared substrates [20]. Understanding the intricate regulation and interactions of the RAS-RAF-MEK-ERK pathway is crucial for devising effective therapeutic strategies for cancer treatment.

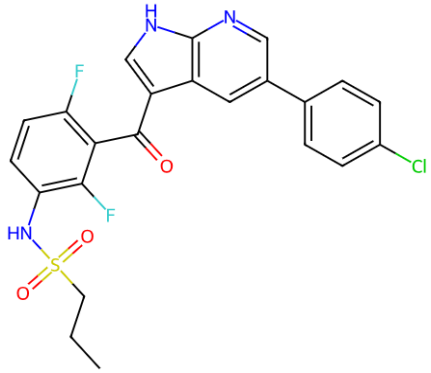
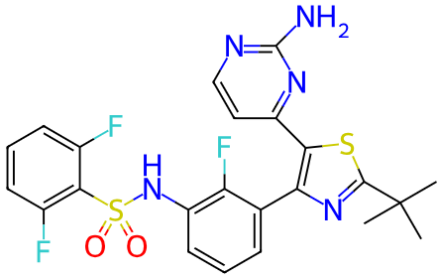
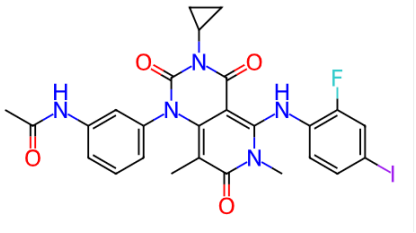
Targeted Therapy against RAS-RAF-MEK-ERK Pathway

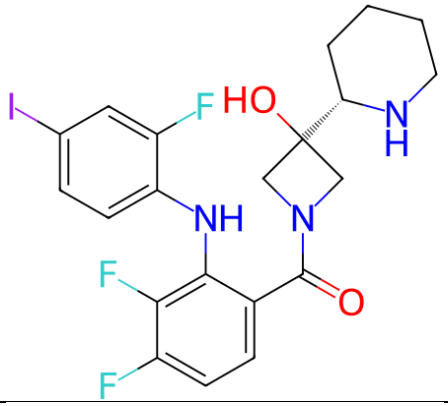
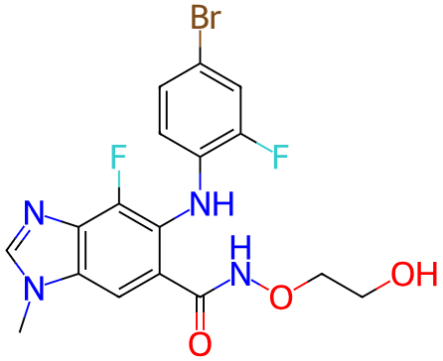
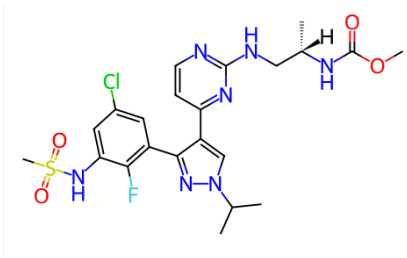
Targeted therapy against the RAS-RAF-MEK-ERK pathway represents a compelling strategy in cancer treatment, particularly for malignancies where this pathway is disrupted. Numerous approaches have been devised to inhibit key elements of this pathway at different stages. Efforts to target RAS, although challenging due to its elusive binding pocket, involve the development of small molecule inhibitors and interventions targeting upstream regulators of RAS activation [194], [195], [196]. Inhibition of RAF kinases, including BRAF, has been achieved through small molecule inhibitors aimed at blocking their kinase

activity, showing promise in cancers harboring BRAF mutations like melanoma and colorectal cancer [197], [198], [199]. MEK inhibitors have also been developed to disrupt MEK-mediated phosphorylation of ERK, demonstrating efficacy in various cancers such as melanoma, NSCLC and HNSCC[185], [200], [201], [202] (Table 4). While direct inhibition of ERK remains challenging, ongoing research explores inhibitors targeting ERK or its upstream regulators. Combinatorial approaches, simultaneously targeting multiple pathway components, are under investigation to combat resistance mechanisms and enhance therapeutic outcomes [201], [202]. Moreover, biomarker-driven strategies are being explored to identify patient subsets likely to benefit most from targeted therapy against the RAS-RAF-MEK-ERK pathway. Despite obstacles like drug resistance and toxicity, targeted therapy against this pathway offers significant potential in cancer treatment and remains an active area of research in oncology.

The Ras-Raf-MEK-ERK and PI3-AKT-mTOR pathway are also triggered by the activation of Fibroblast growth factors (FGF) and FGF receptor (FGFRs) signaling, causing receptor dimerization, phosphorylation of receptor kinases, and subsequent activation of gene transcription [203]. Therefore, developing anti-FGFR treatment strategies could be efficient in addressing different cancers [204], [205]. Several small molecules, including Lucitanib, Dovitinib, and Lenvatinib, are currently being studied in preclinical trials to assess their effectiveness in cancer treatment [203].

Table 4: List of Known TKIs Targeting RAS-RAF-MEK-ERK Pathway

Sl.no	Compounds	Commercial Name	Structure	Specificity	Description	References
1	Vemurafenib	Zelboraf		BRAF	Inhibits mutant BRAF kinase and is used in the treatment of BRAF V600E mutation-positive metastatic melanoma.	[199]
2	Dabrafenib	TAFINLAR		BRAF	Another inhibitor of mutant BRAF kinase, primarily used in BRAF V600E mutation-positive metastatic melanoma and NSCLC.	[200], [201]
3	Trametinib	Mekinist		MEK1 MEK2	Targets MEK1 and MEK2, approved for use in metastatic melanoma with BRAF V600E or V600K mutations, as well as in combination therapy for NSCLC with BRAF V600E mutation.	[200], [201], [202], [203]

4	Cobimetinib	Cotellic		MEK1 MEK2	Also inhibits MEK1 and MEK2 and is used in combination with vemurafenib for the treatment of BRAF V600 mutation-positive metastatic melanoma.	[204], [205], [206], [207]
5	Binimetinib	Mektovi		MEK1 MEK2	A selective inhibitor of MEK1 and MEK2, approved for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.	[208], [209]
6	Encorafenib	Braftovi		BRAF	Inhibits mutant BRAF kinase and is used in combination with binimetinib for the treatment of unresectable or metastatic melanoma with BRAF V600E or V600K mutations.	[209], [210], [211], [212]

Tumor Suppressor Pathways and Inhibition

The onset of cancer, known as malignant transformation, is primarily due to the activation of oncogenes or the deactivation of tumor suppressor genes (TSGs), resulting in unrestricted cell development and survival. TSGs are pivotal in maintaining normal cell functions and preventing the formation of tumors [220], [221], [222], [223]. Key TSGs like RB1 and p53 oversee essential cellular processes such as halting cell division, triggering cell aging, repairing DNA damage, and inducing cell death in response to various stresses [224], [225], [226]. Alterations in TSGs, including mutations or deletions, are essential in the development of different types of cancers. For instance, mutations in genes like PTEN (prostate cancer), APC (colon cancer), MADR2 (colon cancer), BRCA1 and BRCA2 (breast and ovarian cancer), and SPINOPHILIN (lung, colorectal, gastric, glioblastoma, and breast cancer) are linked to various cancers, disrupting the normal functions of TSGs, and leading to unregulated cell growth and survival [220], [227], [228]. Normally, TSG-encoded proteins restrict cell proliferation or survival, and their malfunction causes tumor formation by removing key negative regulatory mechanisms. For example, p53 is an extensively studied TSG, which is crucial for regulating cell cycle progression and triggering cell death in response to DNA damage [229]. The loss of p53 function disrupts DNA damage-induced cell cycle arrest and cell death, resulting in increased mutation rates and genetic instability, common characteristics of cancer cells [230]. Furthermore, loss of p53 function contributes to tumor resistance to chemotherapy and interferes with cell death induced by various stimuli [229], [230], [231]. In most cancers, the p53 tumor suppressor pathway is inactive. Promising anticancer therapies aim to restore p53 function through methods such as gene therapy delivery of p53, RNA interference targeting p53 inhibitors, and the use of small molecules designed to activate p53 [232]. Until January 2023, there are no FDA-approved small molecule activators of p53 for cancer therapy. However, various small molecules targeting the p53 pathway are under investigation in clinical trials [233]. Another tumor suppressor, PTEN counters the effects of PI 3-kinase and Akt, which promote cell survival. Inactivation of PTEN increases cell survival and contributes to tumor growth [234]. Similarly, proteins from INK4 and PTEN genes regulate cell division and act as inhibitors of cell proliferation. Additionally, TSGs produce proteins that regulate the expression of genes involved in cell growth and division. Disruption of these TSGs can lead to abnormal expression of growth-promoting factors, fueling tumor cell proliferation. Moreover, TSGs like Rb and INK4 govern the progression of the cell cycle, and their malfunction results in uncontrolled cell division [228], [234], [235]. Therefore, alterations in TSGs significantly contribute to cancer development and progression by promoting uncontrolled cell growth, survival, and genetic instability. Understanding the roles and regulation of TSGs is

essential for developing effective strategies for cancer prevention and treatment. Some promising small molecules stabilizers and activators of p53 currently in preclinical trials for cancer treatment are as follows:

1. **Nutlin-3:** Nutlin-3 is a small molecule inhibitor of the interaction between p53 and its negative regulator, MDM2 [236]. By blocking this interaction, Nutlin-3 stabilizes p53, leading to its activation and subsequent induction of apoptosis in cancer cells [237]. Nutlin-3 has shown efficacy in preclinical models of various cancers, including leukemia, lymphoma, and solid tumors such as melanoma, breast cancer, head and squamous cell carcinoma and others [236], [237], [238].

2. **RITA (Reactivation of p53 and Induction of Tumor cell Apoptosis):** RITA is another small molecule that stabilizes and activates p53 by disrupting its interaction with MDM2 [232]. Preclinical studies have demonstrated the ability of RITA to induce apoptosis in cancer cells harboring wild-type p53, making it a potential candidate for p53-targeted cancer therapy [239], [240], [241]. It has been investigated on various cancer types such as breast cancer, oral cancer, colorectal cancer, and glioblastoma among others [94], [242], [243], [244], [245].

3. **PRIMA-1 and PRIMA-1Met (APR-246):** PRIMA-1 and its methylated derivative, PRIMA-1Met, are small molecules that reactivate mutant p53 by restoring its wild-type conformation and function [246], [247], [248]. These compounds have shown efficacy in preclinical models of various cancers with mutant p53, including ovarian cancer, colorectal cancer, and prostate cancer [249], [250], [251], [252].

4. **MIRA-1:** MIRA-1 is a small molecule that stabilizes p53 by inhibiting its interaction with MDMX, another negative regulator of p53 [253]. Preclinical studies have demonstrated the ability of MIRA-1 to induce apoptosis and inhibit tumor growth in various cancer models, including breast cancer and neuroblastma [253].

5. **Tenovin-6:** Tenovin-6 is a small molecule that activates p53 by inhibiting the activity of SIRT1, a histone deacetylase that negatively regulates p53 [254]. Preclinical studies have shown that Tenovin-6 can induce apoptosis and inhibit tumor growth in various cancer models, including lung cancer and uveal cancer [254], [255], [256].

Telomerase Pathway and Inhibition

In cancer, telomerase plays a crucial role in enabling unlimited proliferation and immortalization of malignant cells. The upregulation of telomerase activity is a hallmark of many cancer types, providing cancer cells with the capability to maintain telomere length and evade replicative senescence, a natural barrier to uncontrolled cell growth [257], [258], [259]. The dysregulation of telomerase expression and activity is often observed in various stages of cancer development, contributing to tumor initiation, progression, and metastasis [258]. One of the primary mechanisms by which cancer cells achieve telomerase upregulation is through alterations in the expression of telomerase components, particularly telomerase reverse transcriptase (TERT). TERT is frequently overexpressed in cancer cells, driven by genetic alterations such as amplifications, mutations, or epigenetic modifications within the TERT promoter region. These alterations result in enhanced transcriptional activation of TERT, leading to increased telomerase activity and telomere maintenance in cancer cells [258], [259], [260]. Moreover, signaling pathways involved in cell growth, survival, and oncogenesis can modulate TERT expression and telomerase activity. For instance, oncogenic pathways such as PI3K/Akt, Wnt/β-catenin, and NF-κB have been implicated in promoting TERT transcription, thereby promoting telomerase activity and telomere elongation in cancer cells [261], [262]. Conversely, tumor suppressor pathways like p53 and Transforming growth factor beta (TGF-β) act as negative regulators of TERT expression, exerting tumor-suppressive effects by inhibiting telomerase activity and inducing telomere shortening [263]. In addition to transcriptional regulation, post-translational modifications and protein-protein interactions can influence telomerase function in cancer. Alterations in the composition and activity of the shelterin complex, which interacts with telomerase and regulates its access to telomeres, can impact telomerase-mediated telomere maintenance in cancer cells. Dysregulation of shelterin proteins, such as TRF1, TRF2, and POT1, can disrupt telomere structure and function, leading to genomic instability and promoting tumorigenesis. Several compounds have been investigated for their potential to target telomerase activity and telomere maintenance in cancer therapy [264], [265], [266], [267]. Imetelstat (GRN163L) is a synthetic oligonucleotide designed to competitively inhibit telomerase by binding to the RNA component (TERC) of the telomerase enzyme. This binding prevents the addition of telomeric repeats onto chromosome ends, inducing telomere shortening and eventual cell death. Imetelstat has shown promising results in preclinical and clinical studies across various cancers, particularly hematological malignancies and solid tumors [268], [269]. Similarly, BIBR1532 acts as a non-nucleoside small molecule inhibitor of telomerase, interfering with its catalytic activity. By disrupting telomerase function, BIBR1532 induces telomere shortening and cellular senescence in cancer cells.

Preclinical investigations are ongoing to explore its potential as a therapeutic agent for cancer treatment [270], [271], [272]. HIV/AIDS treatmentido-3′-deoxythymidine (AZT), also known as zidovudine, primarily utilized in HIV/AIDS treatment, has demonstrated inhibitory effects on telomerase activity. AZT acts as a competitive substrate for the telomerase enzyme, interfering with its function and leading to reduced telomere length. Preclinical studies have suggested potential antitumor effects of AZT, highlighting its candidacy as an adjunct therapy for cancer treatment [273], [274], [275].

Overall, these compounds represent promising avenues for targeting telomerase activity and telomere maintenance in cancer therapy, offering potential strategies to combat cancer progression and enhance therapeutic outcomes.

ALT Pathway and Inhibition

The ALT pathway represents a unique mechanism for maintaining telomere length in cancer cells, distinct from the more common telomerase pathway. ALT is characterized by homology-directed telomere synthesis, primarily achieved through homologous recombination (HR) [276]. In ALT-positive cells, telomeres undergo recombination events, where segments of telomeric DNA are exchanged between sister chromatids or non-homologous chromosomes, allowing telomere extension without telomerase involvement [258]. Central to ALT functioning is the chromatin remodeling complex comprising ATRX (Alpha Thalassemia/Mental Retardation Syndrome X-Linked) and DAXX (Death-Domain Associated Protein), essential for depositing histone variant H3.3 at telomeric regions [276], [277]. Mutations or loss of ATRX and DAXX are common in ALT-positive cancers, contributing to dysregulated telomere maintenance. In cancer treatment, targeting the ALT pathway has emerged as a potential therapeutic strategy. While ALT-specific inhibitors are less studied than those targeting telomerase, various approaches have been explored. One promising avenue is inhibiting the ATRX and DAXX complex to disrupt H3.3 deposition at telomeres and ALT-associated telomere maintenance [277], [278]. However, developing specific inhibitors for ATRX and DAXX remains challenging.

VEGF Pathway and Inhibition

The VEGF family members play critical roles in angiogenesis, the formation of new blood vessels essential for various physiological and pathological processes. Among these members, VEGF-A stands out as a major contributor to angiogenesis [29], [279], [280]. It is ubiquitously expressed in vascular tissues, macrophages, tumor cells, and other cell types. Its binding to

VEGF Receptor-2 (VEGFR-2) triggers dimerization, autophosphorylation, and activation of downstream signaling pathways, pivotal for endothelial cell proliferation, migration, and angiogenic functions[281]. Upon binding to VEGFR-2, VEGF-A initiates the activation of phospholipase C γ (PLC-γ), which hydrolyzes phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) to generate inositol triphosphate (IP3) and diacylglycerol (DAG). IP3 induces intracellular Ca^{2+} release, enhancing vascular permeability, while DAG activates protein kinase C (PKC), facilitating endothelial cell proliferation via the Raf1-MEK1/2-ERK1/2 pathway [281]. Additionally, VEGF-A binding to VEGFR-2 leads to phosphorylation of phosphoinositide 3-Kinase (PI3K), which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3-phosphate (PIP3). PIP3 induces phosphorylation of serine/threonine-specific protein kinase (AKT), activating endothelial nitric oxide synthase (eNOS) to produce nitric oxide (NO), further promoting endothelial cell proliferation and migration [29], [281]. Other members of the VEGF family, such as VEGF-B, VEGF-C, VEGF-D, and Placental Growth Factor (PIGF), also contribute to angiogenesis and vascular remodeling through binding to their respective receptors. VEGF-B predominantly binds to VEGFR-1 and Neuropilin-1 (NRP-1), influencing tumor angiogenesis and ischemic conditions. VEGF-C and VEGF-D mainly interact with VEGFR-3, playing crucial roles in lymphangiogenesis. VEGF-D is particularly implicated in tumor metastasis to regional lymph nodes. Furthermore, PIGF primarily binds to VEGFR-1, regulating blood vessel growth and maturation by modulating endothelial and parietal cell proliferation. The elevation of VEGF has been observed across various tumor types, both benign and malignant, such as juvenile hemangioma, glioblastoma multiforme, melanoma, breast, lung, head and neck, ovarian, gastrointestinal tract, and renal carcinomas. In a subgroup of melanoma patients, heightened VEGF levels have been shown to correspond with tumor thickness. Another study indicated that VEGF enhances the mitogenic potential in stromal cells, including immune cells, derived from human tumor biopsies [279]. Research also indicates that VEGF plays a multifaceted role in tumors, not only promoting angiogenesis but also directly impacting cancer cells [282]. VEGF can facilitate tumor development and progression by engaging with receptors expressed on tumor cells, either through autocrine or paracrine mechanisms. In addition to tyrosine kinases, neuropilins (NRPs) also play a vital role in mediating VEGF's effects on tumor cells by regulating the function and transportation of growth factor receptors and integrins [281], [283]. In lung cancer, autocrine VEGF has been observed to activate mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) and PI3K/AKT signaling pathways, promoting cell proliferation in non-small cell lung cancer (NSCLC). Furthermore, NRP1 has been identified as a key regulator in VEGF-driven NSCLC cell proliferation. However, studies have demonstrated that blocking endogenous VEGF with bevacizumab, a VEGF antibody, did not

effectively inhibit NSCLC cell line growth, indicating that VEGF alone may not sustain lung cancer cell proliferation in vitro [281], [284]. It is suggested that the development of NSCLC is influenced by various factors within the tumor microenvironment (TME). Consequently, in isolated cell lines lacking tumor angiogenesis or TME, blocking VEGF alone might not sufficiently impede tumor cell growth. It is plausible that VEGF-VEGFR-targeted therapy also modulates the TME to counteract immunosuppression, thereby restraining tumor growth [281]. Hence, it is hypothesized that combining immunotherapy with VEGF-VEGFR-targeted therapy could potentially yield more favorable therapeutic outcomes for NSCLC [281]. Targeting the VEGF pathway has emerged as a promising therapeutic strategy in cancer treatment. Monoclonal antibodies such as bevacizumab [244], [245], aflibercept [246], and ramucirumab [245], along with small molecule tyrosine kinase inhibitors like sunitinib [247], sorafenib [247], pazopanib [247], axitinib [248], regorafenib [249], cabozantinib [247], and Lenvatinib [248], have been developed to inhibit VEGF-mediated angiogenesis. These inhibitors disrupt tumor vascularization, depriving cancer cells of essential nutrients and oxygen, thereby impeding tumor growth and metastasis. Several of these molecules are in various clinical phases, including phase III trials for indications such as colorectal cancer, RCC, and HCC.

HIF Pathway and Inhibition

The rapid division of cancer cells leads to the proliferation of tumor tissue, which occurs independently of angiogenesis, the process of forming new blood vessels. Consequently, due to limited blood vessel availability, certain regions within the tumor experience consistently low oxygen levels, termed chronic hypoxia [285], [286]. Within this hypoxic TME, three key proteins known as HIFs play crucial roles. Among them, HIF-1 and HIF-2 primarily oversee the transcription of genes triggered by hypoxia, while HIF-3 not only promotes gene expression but also dampens the activity of HIF-1 and HIF-2 [286]. HIF-1 is a dimer transcription factor, comprising α and β subunits.The α subunit is expressed in hypoxia, regulating gene expression, while β subunit is constitutively expressed in specific tissues. HIF-2/3α, analogous to HIF-1α, and HIF-1β, also known as ARNT, have isoforms (Arnt1, Arnt2, and Arnt3) [287]. HIF-1α and HIF2-α, structurally similar, are vital in hypoxia response, forming complexes with HIF-1β. The role of HIF-3α is unclear, but it may inhibit HIF-1α transcriptional activation [287]. HIF-1α plays a crucial role in tumor angiogenesis, being up-regulated in various cancers via genetic and environmental factors, including hypoxia. Studies demonstrate that in temporomandibular joint osteoarthritis (TMJ-OA) [288], hypoxia induces angiogenesis through up-regulation of HIF-1-VEGF-Notch pathways. Succinate is shown to expedite angiogenesis in rheumatoid arthritis by enhancing the HIF-

1α-VEGF pathway [289]. Mutated oncogenes like insulin, IGFs, Ras, and Src accelerate angiogenesis by inducing hypoxia-inducible factor expression. Conversely, mutated tumor suppressor genes like PTEN, p53, p14ARE, and notably pVHL stimulate the HIF-1α system, promoting angiogenesis [290], [291], [292]. pVHL deactivation stabilizes HIF-1α, leading to the transcriptional up-regulation of its downstream genes [293]. Subsequently, elevated HIF-1α, alongside P300CBP and HIF-1β, translocates to the nucleus, activating major angiogenesis-related genes such as VEGF, EGF, ANGPT, Tie-2, TIMP-1, Flt-1, and PAI-1 [293]. By targeting the adaptive response of cancer cells to hypoxia, these inhibitors hold potential for overcoming treatment resistance and enhancing the efficacy of anticancer treatments. PX-478 is currently in phase I clinical trials for advanced solid tumors, while topotecan is approved for various cancer types and is in clinical use [294], [295], [296], [297], [298].

EMT Process and Inhibition

The EMT process was initially observed in embryonic development and refers to a cellular reprogramming mechanism where epithelial cells adopt a mesenchymal phenotype [32], [30], [299], [300], [301]. EMT plays a crucial role in various biological processes such as development, wound healing, and the progression of malignancies, facilitating the acquisition of traits associated with more aggressive cancer phenotypes.Various signaling pathways can participate in the process of EMT, including the TGF-β , Bone morphogenetic protein (BMP), Receptor tyrosine kinase (RTK), Wnt/β-catenin, Notch, Hedgehog, Signal transducer and activator of transcription 3 (STAT3), ECM-mediated, and Hypoxia signaling pathways [302]. These pathways regulate gene expression by influencing key transcription factors such as Snail, Twist, and ZEB. Recent research indicates that Snail1 plays a significant role in the EMT process through multiple pathways. It targets E-cadherin, a pivotal gene in EMT, via several binding sites, influencing its expression levels and consequently promoting EMT and metastasis[302], [303]. Additionally, Snail1 regulates various proteins involved in cell-cell interactions and structural integrity, including Claudin, Occludin, Zona occludens 1, Cytokeratin 18, and Mucin 1. Furthermore, Snail1 governs the expression of MMPs, particularly MMP-2 and MMP-9, which are implicated in metastasis [302], [303], [304]. Moreover, Snail1 upregulates other EMT-related transcription factors like ZEB-1 and ZEB-2, amplifying the EMT process [303]. Immunohistochemical studies in prostate cancer patients reveal high Snail1 expression during initial tumor formation. Twist is a pivotal transcription factor in EMT belonging to the BHLH family. It includes Twist-1 and Twist-2, crucial for mesodermal layer development. Mutation of Twist in humans link to Saethre-Chotzen syndrome [302], [305], [306], [307]. Unlike Twist-2, the role of Twist-1 in cancer progression, metastasis, angiogenesis, and stemness is well-documented. High

Twist-1 expression correlates with cancer cell invasion, migration, and anoikis resistance, promoting EMT and metastasis. Anoikis is the programmed cell death by which epithelial cells become apoptotic by breaking from the extracellular matrix and their neighboring cells. This process acts as a barrier against metastasis[305], [307]. However, cancer cells resist anoikis due to molecular mechanisms during separation from the original sites and travelling in the circulatory and lymphatic system[302]. ZEB is another key EMT regulator that comprises of ZEB1 and ZEB2. It is crucial in embryogenesis, differentiation, and cancer progression. They repress E-cadherin expression, induce metastatic traits and regulate other genes involved in cell-cell interaction and polarity [302], [308]. Consequently, they enhance the expression of mesenchymal cell markers, diminish epithelial cell markers, ultimately inducing a phenotypic shift in epithelial cells towards mesenchymal stem cells [302]. Activation of EMT prompts tumor cells to undergo a series of physical alterations, including the dissolution of tight junctions, disruption of apical–basal polarity, and rearrangement of cytoskeletal structures [32], [299]. These changes collectively enable the cells to detach from their primary site, invade surrounding tissues, survive in the bloodstream, and ultimately establish metastases in distant organs. Furthermore, research has linked EMT to enhanced resistance against chemotherapy and immunotherapy, as it fosters interactions with tumor-associated stromal cells, which are known for their pro-tumorigenic effects [30], [299], [300], [301], [309]. Targeting EMT-related signaling pathways represents a promising therapeutic strategy to inhibit cancer metastasis and improve patient outcomes. Small molecule inhibitors of EMT-associated pathways, such as salinomycin [310], [311], zidovudine [312], mocetinostat [312], evodiamine [312], curcumin [312], and metformin [312] are a few molecules that have shown efficacy in preclinical models of cancer by suppressing EMT and attenuating metastatic spread [312]. By inhibiting the invasive and metastatic properties of cancer cells, these inhibitors offer potential for preventing or delaying disease progression and improving patient survival.

MMPs and their Inhibition

MMPs play a crucial role in degrading matrix proteins extensively or selectively releasing cell surface-bound cytokines, growth factors, or their receptors. They are endopeptidases reliant on zinc ions (Zn^{2+}), found both intracellularly and bound to membranes and their activity impacts matrix integrity, cell behavior, phenotype, and tissue turnover. Traditionally, MMPs have been classified into collagenases, gelatinases, stromelysins, and membrane-type MMPs based on substrate specificity and cellular localization. However, some MMPs defy these categorizations [33]. Collagenases, such as MMP-1, MMP-8, and MMP-13, play vital roles in tissue remodeling by breaking down fibrillar and non-fibrillar collagens, promoting cellular

proliferation and migration, and contributing to cancer progression through mechanisms like EMT [34]. Gelatinases, including MMP-2 and MMP-9, target basement membrane collagens and non-fibrillar collagens, impacting cellular migration, collagen affinity, and inflammatory responses. Matrilysins, such as MMP-7, modulate the bioavailability of growth factors like TGF-β and IGF-1, induce apoptosis, and enhance cellular invasiveness. Stromelysins, including MMP-3 and MMP-10, are involved in epithelial-mesenchymal transition, angiogenesis, and cancer cell dissemination [34]. Membrane type MMPs (MT-MMPs), like MMP-14 and MMP-15, regulate cellular adhesion, migration, and extracellular matrix remodeling. Other MMPs, such as MMP-12 and MMP-19, exhibit diverse functions including plasminogen digestion, angiostatin release, and activation of growth factors. These MMPs collectively contribute to physiological processes like tissue development and repair but can also promote pathological conditions such as cancer metastasis when dysregulated [34]. The expression of MMPs is tightly regulated at both the transcriptional and post-translational levels, ensuring precise spatio-temporal distribution and action. In various cancer types, this regulation is often disrupted, implicating MMPs in cancer development and progression. Once a precancerous cell transitions into a cancerous state through EMT, it breaches the basement membrane (BM) and infiltrates the stromal extracellular matrix (ECM). This invasion is facilitated by the restructuring of integrin-containing cell-matrix adhesome structures and the recruitment of ECM-degrading MMPs [313]. Tumor-induced immune tolerance and an acidic microenvironment, stemming from altered metabolism characterized by lactate secretion and heightened expression of the proton efflux pump NHE1 in tumors, further promote invasion. However, the proteolytic degradation of matrix components in tumors can have both pro-tumorigenic and anti-tumorigenic effects. For instance, MMP8 (neutrophil collagenase) overexpression, which degrades type I, II, and III collagens, is linked to increased survival in oral squamous cell carcinoma patients but poor outcomes in ovarian or hepatocellular cancer patients. These contradictory findings underscore the challenges faced in clinical trials of MMP inhibitors [33], [313]. A well-documented record exists for MMP inhibitors that have demonstrated clinical efficacy. One such example is Periostat, a formulation of doxycycline administered at a sub-antimicrobial level, which has received approval from the FDA for treating periodontal disease. Additionally, numerous MMP inhibitors are currently undergoing clinical trials, aiming to address a range of conditions such as gastric cancer, diabetic foot ulcers, and multiple sclerosis [314]. Further research is needed to optimize the therapeutic potential of MMP inhibitors and overcome the obstacles to their clinical development in cancer therapy.

DDR, Repair Pathways and Inhibition

Genomic defects can trigger the DDR, causing cells to halt at checkpoints for repair, thereby safeguarding genome stability. The cell cycle regulation and control of various aspects such as centrosome cycle, mitotic onset, G2/M transition, and G1 progression by CDK1 can be turned off by phosphorylation through WEE1 or PKMYT1, especially in response to DNA damage to facilitate repair[36]. Activation of CDK1 involves binding with cyclin B, followed by its phosphorylation of Thr161, while CDC25 inhibits phosphorylation on Thr14 and Tyr15. Subsequently, the activated CDK1/cyclin B complex facilitates the translocation of cyclin-kinase complexes from the cytoplasm to the nucleus [36]. Cancer cells often exploit CDK1 activity, making it a target for therapy, particularly in conjunction with radiation. The study on hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer provides significant insights into the roles of CDK1 and WEE1. It has been demonstrated that during hyperthermia, the kinase CDK1 becomes hyperactivated, leading to marked changes in cellular dynamics, specifically causing replication arrest and precipitating early entry into mitosis. This disruption is identified as a pivotal mechanism through which hyperthermia influences cancer cells. Subsequent investigations into drug interactions have shown that inhibition of WEE1, a kinase that regulates the cell cycle, synergistically enhances the cytotoxic effects of hyperthermia on cancer cells. The efficacy of this combinatory approach—hyperthermia coupled with a WEE1 inhibitor—has been substantiated through in vivo experiments using a novel miniaturized device, which confirmed significant tumor reduction. These findings suggest that targeting CDK1 and WEE1 might refine and augment the therapeutic strategy of HIPEC in treating ovarian cancer, highlighting a promising direction for targeted cancer treatment [315]. CDK1 inhibitors like AZD5438 enhance radiation sensitivity in lung cancer and RO-3306 could promote activation of Bax in acute myeloid leukemia cells by promoting apoptosis and downstream p53 signaling [36], [316], [317]. Other inhibitors like taurine and JNJ-7706621 show promise in overcoming resistance to radiotherapy, particularly in TP53-deficient cancers. MEK162, a nonspecific inhibitor, prolongs DNA damage response in glioblastoma cells [318]. Various types of DNA damage have been reported previously, including single-strand breaks, double-strand breaks (DSBs), base damage, sugar damage, DNA cross-linking, and clustered damaged sites [39]. DSB is a common form of DNA damage which heightens the cancer risk, if not properly repaired. Two primary repair mechanisms address DSB: non-homologous end joining (NHEJ) and HR. HR repair (HRR) utilizes an intact chromosome as a template to accurately mend the damaged strand, ensuring precise repair [39], [319]. Conversely, NHEJ simply rejoins broken ends, potentially introducing errors due to nucleotide removal. Changes in DDR gene expression remain incompletely understood, but mutations or

dysfunction in DDR genes elevate cancer susceptibility [319]. Because of their rapid division cancer cells often have a diminished capacity for DDR. This makes them vulnerable to targeted DDR inhibition like ATR/DNA-PK inhibitors. This approach allows for the selective targeting of cancer cells, which possess compromised DDR, while leaving normal cells with intact DNA repair mechanisms unharmed. The inhibition of DDR holds promise as a potential game-changer in cancer treatment. DDR inhibitors exploit synthetic lethality, effectively eliminating cancer cells while sparing normal ones (for instance, ATR inhibitors in ATM-deficient cancers and WEE1 inhibitors in p53-mutated cells) [320]. Synthetic lethality arises when simultaneous deficiencies in multiple related genes lead to cell death or apoptosis, while individual deficiencies in one of these genes are manageable for cell survival. With the rapid progress in RNAi and CRISPR gene editing technologies, large-scale screening for synthetic lethal targets through single gene deletion has become possible, facilitating the discovery of new therapeutic targets for cancer [320]. PARP inhibitors have emerged as a promising class of anticancer agents, particularly in tumors with deficiencies in the HR repair pathway [320]. Olaparib, one of the leading PARP inhibitors, has undergone extensive clinical evaluation across multiple cancer types [321]. In ovarian cancer, Olaparib has demonstrated significant efficacy, especially in patients with BRCA1/2 mutations [322]. Clinical trials have shown improved progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients treated with Olaparib compared to standard chemotherapy or placebo. These trials have led to the approval of Olaparib for the maintenance treatment of ovarian cancer patients with BRCA mutations who have responded to platinum-based chemotherapy [323], [324]. Similarly, in breast cancer, Olaparib has shown promise, particularly in patients with BRCA1/2 mutations, including those with triple-negative breast cancer (TNBC). Clinical trials investigating Olaparib in metastatic breast cancer have demonstrated improved PFS compared to standard chemotherapy in patients with BRCA mutations. Beyond ovarian and breast cancers, Olaparib is being evaluated in clinical trials for various other cancer types, including pancreatic, prostate, and gastric cancers, among others [324]. These trials aim to assess the efficacy of Olaparib both as monotherapy and in combination with other anticancer agents.

CHK1 is an essential player in cell cycle regulation and DNA repair and operationally similar to Wee1 and CDK1 in coordinating cellular responses to DNA damage. By inhibiting CHK1, researchers aim to disrupt cancer cell survival and proliferation, making them more susceptible to treatments like radiation therapy [36]. While early CHK1 inhibitors like UCN-01 showed promise, their broad effects on other proteins limited their clinical use. Recent developments have yielded more selective inhibitors like LY2606368 [325], [326], [327] and PF-00477736 [328], [329], [330], which have demonstrated

efficacy in sensitizing cancer cells to radiation with fewer side effects [36], [331]. Novel inhibitors such as MK8776 [330], [332], [333], [334], [335] and CCT244747 [336], [337] offer additional promise by enhancing the effectiveness of radiotherapy while minimizing toxicity [36]. Combining CHK1 inhibitors with other targeted therapies, like WEE1 inhibitors, has shown synergistic effects, particularly in lymphoma treatment. However, as with any therapeutic approach, balancing safety and efficacy remains crucial for the successful clinical application of CHK1 inhibitors in cancer treatment [36].

4. CONCLUSION

The development of targeted therapies for cancer represents a significant advancement in the field of oncology. These therapies offer promising avenues for personalized treatment approaches, addressing specific molecular abnormalities driving tumor growth. By targeting key pathways and molecular targets, such as growth factors or signaling molecules, targeted therapies have shown efficacy in managing various types of cancer with potentially fewer side effects compared to traditional chemotherapy. However, challenges such as drug resistance and patient heterogeneity persist, highlighting the ongoing need for further research and refinement in this rapidly evolving field. Despite these challenges, targeted therapy continues to revolutionize cancer treatment, offering hope for improved outcomes and quality of life for patients worldwide.

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