Table S1. Clinical trials of ivosidenib in cancer diseases with the status of not yet recruiting, recruiting, and active not recruiting.

NCT Number	Title	Phase	Status	Disease	Intervensions
NCT03564821	A Phase 1 Study of IDH1 Inhibition Using Ivosidenib as Maintenance Therapy for IDH1-mutant Myeloid Neoplasms Following Allogeneic Stem Cell Transplantation	1	Active, not recruiting	Myeloid Neoplasms with IDH1 mutation undergoing hematopoietic stem cell transplantation	Ivosidenib
NCT04955938	A Phase Ib Study of Fedratinib With IDH Inhibition in Advanced-Phase, IDH-Mutated Ph-Negative Myeloproliferative Neoplasms	1	Recruiting	IDH-Mutated Ph-Negative Myeloproliferative Neoplasms	Fedratinib plus Ivosidenib, Fedratinib plus Enasidenib
NCT04056910	Phase II Study of IDH1 Inhibitor Ivosidenib and Nivolumab in IDH1 Mutant Gliomas and Advanced Solid Tumors	2	Recruiting	Advanced solid tumors (nonresectable or metastatic) or enhancing gliomas with IDH1 mutation	Ivosidenib plus Nivolumab
NCT02074839	A Phase I, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects With Advanced Hematologic Malignancies With an IDH1 Mutation	1	Recruiting	R/R Acute Myeloid Leukemia, Untreated Acute Myeloid Leukemia, Hematologic Malignancie, Myelodysplastic Syndromes with IDH1 mutation	Ivosidenib
NCT04195555	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase 2 Subprotocol of AG-120 (Ivosidenib) in Patients With Tumors Harboring IDH1 Mutations	2	Recruiting	Advanced solid tumors, lymphoma, histiocytic disorders with IDH1 mutation	Ivosidenib
NCT03471260	Phase Ib/II Investigator Initiated Study of the IDH1-Mutant Inhibitor Ivosidenib (AG120) With the BCL2 Inhibitor Venetoclax +/- Azacitidine in IDH1-Mutated Hematologic Malignancies	1b/2	Recruiting	Acute Myeloid Leukemia, R/R Acute Myeloid Leukemia, Hematopoietic and Lymphoid System Neoplasm, Myelodysplastic Syndrome, Myeloproliferative Neoplasm with IDH1 mutation	Ivosidenib plus Azacitidine plus Venetoclax

NCT02073994	A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects With Advanced Solid Tumors, Including Glioma, With an IDH1 Mutation	1	Active, not recruiting	Cholangiocarcinoma Chondrosarcoma Glioma Other Advanced Solid Tumors with IDH1 mutation	Ivosidenib
NCT04493164	Phase II Investigator Sponsored Study of CPX-351 in Combination With Ivosidenib for Patients With IDH1 Mutated Acute Myeloid Leukemia or High-Risk MDS	2	Recruiting	Acute myeloid leukemia, R/ R Acute Myeloid Leukemia, Myelodysplastic Syndrome, Myeloproliferative Neoplasm with IDH1 mutation	Ivosidenib plus Liposome-encapsulated Daunorubicin-Cytarabine (CPX-351)
NCT04176393	A Phase 1, Multicenter, Single-Arm Study Evaluating Pharmacokinetic, Pharmacodynamic, Safety, and Clinical Efficacy of Orally Administered Ivosidenib in Chinese Subjects With Relapsed or Refractory Acute Myeloid Leukemia With an IDH1 Mutation	1	Active, not recruiting	R/R Acute Myeloid Leukemia with IDH1 mutation	Ivosidenib
NCT04250051	Phase 1 Trial of Ivosidenib and FLAG Chemotherapy in Relapsed/Refractory IDH1+ Acute Myeloid Leukemia (AML)	1	Not yet recruiting	R/R Acute Myeloid Leukemia, R/R Myelodysplastic Syndrome, R Myeloproliferative Neoplasm with IDH1 mutation	Ivosidenib
NCT04774393	Phase 1b/2 Study of Oral Decitabine/Cedazuridine (ASTX727) and Venetoclax in Combination With the Targeted Mutant IDH1 Inhibitor Ivosidenib or the Targeted Mutant IDH2 Inhibitor Enasidenib	1b/2	Recruiting	R/R Acute Myeloid Leukemia with IDH1 mutation	Decitabine/cedazuridine (ASTX727) plus Venetoclax plus Ivosidenib or Enasidenib
NCT05010772	Oral Decitabine-Based Maintenance Therapy in Patients With AML in Remission	1	Recruiting	Acute Myeloid Leukemia	Decitabine plus Enasidenib or Gilteritinib or Ivosidenib or Venetoclax
NCT02677922	A Phase 1b/2 Open-label, Randomized Study of 2 Combinations of Isocitrate	1b/2	Active, not recruiting	Newly diagnosed Acute Myeloid Leukemia with IDH1 or IDH2 Mutation	Oral Ivosidenib plus Subcutaneous

	Dehydrogenase (IDH) Mutant Targeted Therapies Plus Azacitidine: Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus SC Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia Harboring an IDH1 or an IDH2 Mutation, Respectively, Who Are Not Candidates to Receive Intensive Induction Chemotherapy				(SC) azacitidine, Oral Enasidenib plus Subcutaneous (SC) azacitidine
NCT04278781	Phase II Study of AG-120 in IDH1 Mutant Chondrosarcoma	2	Recruiting	Advanced/metastatic or recurrent Chondrosarcoma with IDH1 mutation	Ivosidenib
NCT05209074	A Phase I, Single-Center, Open-Label, Dose De-escalation and Expansion Study Ivosidenib + mFOLFIRINOX in Patients With Resectable Pancreatic Adenocarcinoma	1	Not yet recruiting	Pancreatic Ductal Adenocarcinoma	Ivosidenib plus mFOLFIRINOX
NCT02632708	A Phase 1, Multicenter, Open-Label, Safety Study of AG-120 or AG-221 in Combination With Induction Therapy and Consolidation Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation	1	Active, not recruiting	Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation	Ivosidenib or Enasidenib with 2 types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and 2 types of AML consolidation therapies (mitoxantrone with etoposide or cytarabine).
NCT04088188	A Phase I, Multi-Center, Open Label, Dose De-Escalation and Expansion Study of Gemcitabine and Cisplatin With AG120 or Pemigatinib for Advanced Cholangiocarcinoma	1	Recruiting	Advanced Cholangiocarcinoma	Gemcytabine and Cisplatin plus Ivosidenib, Gemcytabine and Cisplatin plus Pemigatinib
NCT03173248	A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination With Azacitidine in Subjects ≥ 18 Years of Age With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation	3	Active, not recruiting	Newly Diagnosed Acute Myeloid Leukemia, Untreated Acute Myeloid Leukemia, Acute Myeloid Leukemia Arising From Myelodysplastic	Ivosidenib plus azacitidine

				Syndrome (MDS) with IDH1 mutation	
NCT03343197	A Phase 1, Multicenter, Randomized, Controlled, Open-Label, Perioperative Study of AG-120 and AG-881 in Subjects With Recurrent, Non-Enhancing, IDH1 Mutant, Low Grade Glioma	1	Active, not recruiting	Glioma with IDH1 mutation	Ivosidenib or AG-881
NCT03839771	A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Study of Ivosidenib or Enasidenib in Combination With Induction Therapy and Consolidation Therapy Followed by Maintenance Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome With Excess Blasts-2, With an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy.	3	Recruiting	Newly Diagnosed Acute Myeloid Leukemia, Myelodysplastic Syndrome With Excess Blasts-2 with IDH1 mutation or IDH2 mutation	Ivosidenib plus chemotherapy, Enasidenib plus chemotherapy
NCT03503409	A Single-arm Phase II Multicenter Study of IDH1 (AG 120) Inhibitor in Patients With IDH1 Mutated Myelodysplastic Syndrome	2	Recruiting	Myelodysplastic Syndromes with IDH1 mutation	Ivosidenib

Table S2. Clinical trials of enasidenib in cancer diseases with the status of not yet recruiting, recruiting, and active not recruiting.

NCT Number	Title	Phase	Status	Disease	Intervensions
NCT01915498	A Phase 1/2, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-221 in Subjects With Advanced Hematologic Malignancies With an IDH2 Mutation	1/2	Active, not recruiting	Advanced Hematologic Malignancies With an IDH2 Mutation	Enasidenib
NCT04092179	Phase Ib/II Study of IDH2 Inhibitor Enasidenib in Combination With BCL2 Inhibitor Venetoclax in Patients With IDH2-Mutated Myeloid Malignancies (ENAVEN-AML)	1b/2	Recruiting	R/R Acute Myeloid Leukemia with IDH2 Mutation	Enasidenib plus Venetoclax
NCT04281498	A Phase II Open-label Study of Combined Ruxolitinib and Enasidenib in Patients With Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis With an IDH2 Mutation	2	Recruiting	Accelerated/Blast-phase Myeloproliferative Neoplasm or Chronic-phase Myelofibrosis With an IDH2 Mutation	Ruxolitinib plus Enasidenib
NCT04955938	A Phase Ib Study of Fedratinib With IDH Inhibition in Advanced-Phase, IDH-Mutated Ph-Negative Myeloproliferative Neoplasms	1	Recruiting	IDH-Mutated Ph-Negative Myeloproliferative Neoplasms	Fedratinib plus Ivosidenib, Fedratinib plus Enasidenib
NCT03515512	A Phase I Study of IDH2 Inhibition Using Enasidenib as Maintenance Therapy for IDH2-mutant Myeloid Neoplasms Following Allogeneic Stem Cell Transplantation	1	Active, not recruiting	Acute Myeloid Leukemia, Chronic Myelomonocytic Leukemia with IDH2 mutation	Enasidenib
NCT04522895	IDH2-Post-Allo-Trial: Enasidenib as Consolidation or Salvage Therapy for Patients With IDH2 Mutated AML or MDS Following Allogeneic Blood Stem Cell Transplantation	2	Recruiting	Acute Myeloid Leukemia, Myelodysplastic Syndromes, Chronic Myelomonocytic Leukemia in remission after allo-SCT or relapsed after allo-SCT with IDH2 mutation	Enasidenib
NCT04203316	An Open-Label Feasibility Study to Assess the Safety and Pharmacokinetics of Enasidenib in Pediatric Patients With Relapsed/Refractory Acute	2	Recruiting	R/R Acute Myeloid Leukemia with IDH2 mutation	Enasidenib

	Myeloid Leukemia (R/R-AML) With an Isocitrate Dehydrogenase-2 (IDH2) Mutation				
NCT03720366	A Phase 1, 2-Part, Multicenter, Open-Label, 3-Arm Study to Determine the Effect of Enasidenib (CC-90007) on the Pharmacokinetics of Single Oral Doses of Caffeine, Dextromethorphan, Fexofenadine, Flurbiprofen, Midazolam, Omeprazole, Pioglitazone, and Rosuvastatin in Patients With Acute Myeloid Leukemia	1	Active, not recruiting	Acute Myeloid Leukemia with IDH2 mutation	Enasidenib plus Arm 1 probe or Arm 2 probe or Arm 3 probe
NCT03728335	Pilot Trial of Enasidenib (AG-221) Maintenance Post Allogeneic Hematopoietic Cell Transplantation in Patients With IDH2 Mutation	1	Recruiting	Acute Myeloid Leukemia with IDH2 mutation following donor stem cell transplant	Enasidenib
NCT04774393	Phase 1b/2 Study of Oral Decitabine/Cedazuridine (ASTX727) and Venetoclax in Combination With the Targeted Mutant IDH1 Inhibitor Ivosidenib or the Targeted Mutant IDH2 Inhibitor Enasidenib	1b/2	Recruiting	R/R Acute Myeloid Leukemia with IDH1 mutation	Decitabine/cedazuridine (ASTX727) plus Venetoclax plus Ivosidenib or Enasidenib
NCT02577406	A Phase 3, Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of AG-221 (CC-90007) Versus Conventional Care Regimens in Older Subjects With Late Stage Acute Myeloid Leukemia Harboring an Isocitrate Dehydrogenase 2 Mutation	3	Active, not recruiting	R/R Acute Myeloid Leukemia with IDH2 mutation	Enasidenib
NCT05010772	Oral Decitabine-Based Maintenance Therapy in Patients With AML in Remission	1	Recruiting	Acute Myeloid Leukemia	Decitabine plus Enasidenib or Gilteritinib or Ivosidenib or Venetoclax
NCT02677922	A Phase 1b/2 Open-label, Randomized Study of 2 Combinations of Isocitrate Dehydrogenase (IDH) Mutant Targeted Therapies Plus Azacitidine: Oral AG-120 Plus Subcutaneous Azacitidine and Oral AG-221 Plus SC Azacitidine in Subjects With Newly Diagnosed Acute Myeloid Leukemia Harboring an IDH1 or an IDH2	1b/2	Active, not recruiting	Newly diagnosed Acute Myeloid Leukemia with IDH1 or IDH2 Mutation	Oral Ivosidenib plus Subcutaneous (SC) azacitidine, Oral Enasidenib plus Subcutaneous (SC) azacitidine

	Mutation, Respectively, Who Are Not Candidates to Receive Intensive Induction Chemotherapy				
NCT02632708	A Phase 1, Multicenter, Open-Label, Safety Study of AG-120 or AG-221 in Combination With Induction Therapy and Consolidation Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation	1	Active, not recruiting	Newly Diagnosed Acute Myeloid Leukemia With an IDH1 and/or IDH2 Mutation	Ivosidenib or Enasidenib with 2 types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and 2 types of AML consolidation therapies (mitoxantrone with etoposide or cytarabine).
NCT05282459	A Phase Ib/II, Single Center, Open-Label, Safety and Efficacy Study to Improve Anemia in Subjects on Enasidenib With Lower Risk Myelodysplastic Syndrome and Non-proliferative Chronic Myelomonocytic Leukemia Without an IDH2 Mutation	1b/2	Recruiting	Myelodysplastic Syndrome and Non-proliferative Chronic Myelomonocytic Leukemia Without an IDH2 Mutation	Enasidenib mesylat
NCT03383575	Targeted Therapy With the IDH2-Inhibitor Enasidenib (AG221) for High-Risk IDH2-Mutant Myelodysplastic Syndrome	2	Active, not recruiting	IDH2-mutant Myelodysplastic Syndrome	Enasidenib in combination with azacitidine
NCT03744390	A Single-arm Phase II Multicenter Study of IDH2 (AG-221) Inhibitor in Patients With IDH2 Mutated Myelodysplastic Syndrome	2	Recruiting	Myelodysplastic Syndrome, Acute myeloblastic Leukemia with IDH 2 mutation	Enasidenib
NCT03839771	A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled Study of Ivosidenib or Enasidenib in Combination With Induction Therapy and Consolidation Therapy Followed by Maintenance Therapy in Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome With Excess Blasts-2, With an IDH1 or IDH2 Mutation, Respectively, Eligible for Intensive Chemotherapy	3	Recruiting	Newly Diagnosed Acute Myeloid Leukemia, Myelodysplastic Syndrome With Excess Blasts-2 with IDH1 or IDH2 mutation	Ivosidenib plus chemotherapy, Enasidenib plus chemotherpy

Table S3. Selected *in vitro* and *in vivo* research of inhibitors in cancer cell energy metabolic pathway.

Enzyme/Transporter	Inhibitor	Type of research	Type of cancer	References
Glycolysis and glucose transporters				
GLUT1	WZB117	*In vitro*	non–small cell lung cancer (A549, H1299) breast cancer (MCF7)	Liu et al. 2012 [1]
		In vivo	xenograft model of non–small cell lung cancer (A549)	
GLUT2	Polyphenolic Floretin	*In vitro*	breast cancer (MDA-MB-231)	Wu et al. 2018 [2]
			colon cancer (COLO205)	Lin et al. 2016 [3]
GLUT4	Ritonavir	*In vitro*	multiple myeloma (L363, JJN3, KMS11)	Dalva-Aydemir et al. 2015 [4]
		In vivo	xenograft model of multiple myeloma (KMS11-GFP)	
HK2	2-DG	*In vitro*	ovarian cancer (SKOV3, IGROV1, IGROV-R10) mesothelioma (MSTO-211H, NCI-H28) glioblastoma (U251, GLI15) head and neck squamous cancer (SCC12B2, SQ2OB, SCC61) liver cancer (HepG2) colon cancer (HT29D4)	Zhang et al. 2006 [5]
	3-BP	*In vitro*	malignant peripheral nerve sheath tumor (S462, NSF1, T265)	Linke et al. 2020 [6]
			mesothelioma (NCI-H28)	Philippe et al. 2012 [7]
			nasopharyngeal carcinoma (HNE1, CNE-2Z)	Zou et al. 2015 [8]
	BNBZ	*In vitro*	pancreatic cancer (SW1990)	Zheng et al. 2021 [9]
		In vivo	xenograft models of pancreatic cancer (SW1990) colon adenocarcinoma (SW480)	

ALDOA	UM0112176	*In vitro*	non-small cell lung cancer (KLN205, hNSCLC) pancreatic adenocarcinoma (BxPC3)	Gizak et al. 2019 [10]
	Bisphosphonate-based inhibitor (Compound 2)	*In vitro*	cervical cancer (Hela)	Heron et al. 2018 [11]
GAPDH	KA	*In vitro*	melanoma (SK-MEL28, UACC-62, SK-MEL2, M14, SK-MEL5) breast cancer (BT-474) lung cancer (NCI-H522) multiple myeloma (RPMI -8226)	Liberti et al. 2017 [12]
		In vivo	orthotopic breast cancer model (BT-474)	
	DC-1563	*In vitro*	breast cancer (BT-549, MCF-7, MDA-MB-231) colon cancer (HCT116) lung cancer (A549)	Li et al. 2020 [13]
PGK1	NG52	*In vitro*	glioma (U87, U251)	Wang et al. 2021 [14]
		In vivo	glioma patient-derived xenografts model	
PGAM1	PGMI-004A	*In vitro*	non-small cell lung carcinoma (H1299) acute myelogenous leukemia (KG-1a) head and neck squamous cell carcinoma (LN212) myelogenous leukemia (K562) erthroleukemia (HEL) eosinophilic leukemia (EOL1) acute monocytic leukemia (Molm14)	Hitosungi et al. 2012 [15]
		In vivo	xenograft model (H1299)	
	HKB99	*In vitro*	non-small cell lung cancer (PC9, HCC827, H1975, A549, HCC827ER-erlotynib resistant cells)	Huang et al. 2019 [16]

		In vivo	xenograft model (PC9, HCC827, HCC827ER)	
	MJE2	*In vitro*	breast cancer (MDA-MB-231)	Evans et al. 2005 [17]
	EGCG	*In vitro*	non-small cell lung carcinoma (H1299) breast cancer (MDA-MB-231)	Li et al. 2017 [18]
	Xanthone derivatives	*In vitro*	non-small cell lung carcinoma (H1299) breast cancer (MCF-7) pancreatic cancer (PANC-1)	Wang et al. 2018 [19]
	KH3	*In vitro*	pancreatic cancer (SW1990, PANC-1, AsPC-1, MIA PaCa-2)	Wen et al. 2019 [20]
		In vivo	orthotopic mouse model of pancreatic ductal adenocarcinoma (MIA PaCa-2)	
			patient-derived xenograft models of pancreatic ductal adenocarcinoma	
ENO2	Phosphonoacetohydroxamate	*In vitro*	glioblastoma (D-423- cells with ENO1 deletion)	Muller et al. 2012 [21]
	POMHEX	*In vitro*	glioblastoma (D-423- cells with ENO1 deletion)	Lin et al. 2020 [22]
	SF2312	*In vitro*	glioblastoma (D-423- cells with ENO1 deletion)	Leonard et al. 2016 [23]
PKM2	Metformin	*In vitro*	osteosarcoma (HOS; metformin increases sensitivity of cells to cisplatin)	Shang et al. 2017 [24]
			bladder cancer (T24, UMUC3; metformin increases sensitivity of cells to pirarubicin)	Su et al. 2018 [25]
	Benserazide	*In vitro*	melanoma (SK-MEL5, SK-MEL28)	Zhou et al. 2020 [26]
		In vivo	xenograft model of melanoma (SK-MEL5, SK-MEL28)	
	Shikonin	*In vitro*	bladder cancer (T24, RT112; shikonin potentiates the responses of cells to cisplatin)	Wang et al. 2017 [27]
		In vivo	syngeneic mouse model of bladder cancer (MB49)	

		In vitro	cholangiocarcinoma (KKU-055, KKU-100, KKU-213A)	Thonsri et al. 2020 [28]
		In vitro	esophageal cancer (EC109, EC9706)	Tang et al. 2018 [29]
		In vivo	mice model of esophageal cancer (EC109)	
	Resveratrol	*In vitro*	cervical cancer (Hela) colon cancer (DLD1) breast cancer (MCF-7)	Wu et al. 2016 [30]
			melanoma (MV3, A375)	Zhao et al. 2018 [31]
	Vitamin K	*In vitro*	cervical cancer (Hela)	Chen et al. 2012 [32]
	Gliotoxin	*In vitro*	glioblastoma (U87,U251) acute promyelocytic leukemia (HL-60) chronic myelogenous leukemia (K-562) breast cancer (MCF-7) non-small cell lung cancer (H1975) prostate cancer (PC-3) colon cancer (HCT116) cervical cancer (Hela)	Tang et al. 2020 [33]
	Compound 3k	*In vitro*	colon cancer (HCT116) cervical cancer (Hela) lung cancer (H1299)	Ning et al. 2017 [34]
Pyruvate and it`s further fate				
LDHA	Oxamate	*In vitro*	gastric cancer (SGC7901, BGC823)	Zhao et al. 2015 [35]
			medulloblastoma (UW402, Res256)	Valvona et al. 2018 [36]
			cervical cancer (SW756, C33A)	Stone et al. 2019 [37]
			hepatocarcinoma (Dt81Hepa1-6)	Cassim et al. 2018 [38]
			non-small cell lung cancer (H1299, A549)	Qiao et al. 2021 [39]
	Gossypol	*In vitro*	melanoma (SK-MEL19, SK-MEL28) leukemia (K562)	Shelley et al. 1999 [40]

			cervical cancer (Sihas) lung cancer (H69)	
			glioma (U373, U138, U87, HS683)	Coyle et al. 1994 [41]
			breast cancer (MCF-7)	Gilbert et al. 1995 [42]
			prostate cancer (PC-3, LNCaP, DU-145)	Volate et al. 2010 [43]
			colon cancer (HCT116, DLD-1)	Lan et al. 2015 [44]
		In vitro	head and neck squamous carcinoma (UM-SCC-17B, UM-SCC-1)	Wolter et al. 2006 [45]
		In vivo	orthotopic xenograft model of head and neck squamous carcinoma (UM-SCC-17B, UM-SCC-1)	
	FX11	*In vitro*	prostate cancer (PC-3, DU-145)	Xian et al. 2015 [46]
			gallbladder cancer (GBC-SD, NOZ, SGC-996)	He et al. 2018 [47]
			neuroblastoma (SK-N-AS, SK-N-SH, IMR-32, LAN-1, BE(2)-C)	Rellinger et al. 2017 [48]
		In vitro	renal carcinoma (RCC4) breast cancer (MCF-7) B-lymphoma (P493)	Le et al. 2010 [49]
		In vivo	xenograft model of human B-lymphoma (P493) and pancreatic cancer (P198)	
	Quinoline-3-sulfonamides	*In vitro*	hepatocellular carcinoma (SNU398)	Billiard et al. 2013 [50]
	NHI-1	*In vitro*	pancreatic cancer (PANC-1, MIA PaCa-2)	Granchi et al. 2011 (a) [51]
			ovarian cancer (ADDP, A2780/cOHP) colorectal cancer (H630) mesothelioma (NIH-H2452, NIH-H2052, MSTO-211H, NIH-H28)	Granchi et al. 2011 (b) [52]
	Galloflavin	*In vitro*	endometrial cancer (ECC-1, Ishikawa cells)	Han et al. 2015 [53]

			Burkitt lymphoma (Raji, Daudi, Louckes)	Vettraino et al. 2013 [54]
			breast cancer (MCF-7, MCF-Tam, MDA-MB-231)	Farabegoli et al. 2012 [55]
			liver cancer (PLC/PRF/5)	Manerba et al. 2017 [56]
MCT1	AZD3965	*In vitro*	Burkitt lymphoma (Raji) Non Hodgkin's lymphoma (SU-DHL-10) Diffuse large B cell lymphoma (WSU-DLCL-2)	Curtis et al. 2017 [57]
		In vivo	xenograft model of Burkitt`s lymphoma (Raji)	
	BAY-8002	*In vitro*	Burkitt`s lymphoma (Raji, Daudi)	Quanz et al. 2018 [58]
		In vivo	xenograft model of Burkitt`s lymphoma (Raji)	
PDK	DCA	*In vitro*	liver cancer (HepG2; sensitize cells to doxorubicin)	Korga et al. 2019 [59]
		In vitro	lung cancer (A549; resensetize sells to paclitaxel)	Sun et al. 2017 [60]
		In vitro	bladder cancer (HTB-9, HTB-5)	Woolbright et al. 2018 [61]
		In vivo	mouse xenograft model of bladder cancer (HTB-9)	
The pentose phosphate pathway				
G6PD	DHEA	*In vitro*	cervical cancer (Hela)	Fang et al. 2016 [62]
	6-AN	*In vitro*	ovarian cancer (C13)- overcomes resistance to cisplatin	Catanzaro et al. 2015 [63]
			ovarian cancer (SKOV3/DDP))- overcomes resistance to cisplatin	Xu et al. 2018 [64]
			renal cancer (ccRCC)- overcomes resistance to cisplatin	Lucarelli et al. 2015 [65]
			cell lung cancer (A549/DDP))- overcomes resistance to cisplatin	Hong et al. 2018 [66]

			bladder cancer (T24, TCCSUP)- overcomes resistance to cisplatin	Chen et al. 2018 [67]
			melanoma (A375, SB2, M8)- potentiated the cytotoxic effects of metformin	Arbe et al. 2020 [68]
	Polydatin	*In vitro*	nasopharyngeal carcinoma (CNE) cervical cancer (HeLa) hepatoma (SMMC-7721) epidermal carcinoma (A431)	Liu et al. 2011 [69]
			acute monocytic leukemia (MOLT-4)	Wang et al. 2016 [70]
		In vitro	head and neck squamous carcinoma (UMSCC103)	Mele et al. 2018 [71]
		In vivo	orthotopic xenograft model of head and neck squamous carcinoma (UMSCC103)	
		In vitro	liver cancer (HepG2, SMMC-7721)	Jiao et al. 2018 [72]
		In vivo	xenograft model of liver cancer (HepG2)	
	ZA	*In vitro*	bladder cancer (T24)	Wang et al. 2015 [73]
Glutamine as TCA anaplerotic substance				
GLS	JHU-083	*In vitro*	medulloblastoma (D425MED)	Hanaford et al. 2019 [74]
		In vivo	xenograft model of medulloblastoma (D425MED)	
	BPTES	*In vitro*	glioblastoma (D54-R132H IDH1 mutation)	Seltzer et al. 2010 [75]
			lymphoblastoid cell line (P493)	Le et al. 2012 [76]
			pancreatic cancer (8988T)	Son et al. 2013 [77]
			breast cancer (MCF10A-NeuT, SK-BR-3, MDA-MB-453)	Qie et al. 2014 [78]
			non-small cell lung cancer (NCI-H647, NCI-H1703)	van den Heuvel et al. 2012 [79]
	CB-839	*In vitro*	breast cancer (HCC1806, MDA-MB-231)	Gross et al. 2014 [80]

			lung cancer (A549)	Ruan et al. 2019 [81]
			colon cancer (HCT116)	
			kidney cancer (Caki-1)	
			pancreatic cancer (SW1990)	
			acute myeloid leukemia (Molm14, OCI-AML3, MV4;11)	Matre et al. 2014 [82]
	Compound 968	*In vitro*	non-small cell lung cancer (HCC827ER, NCI-H1975)	Xie et al. 2015 [83]
			glioblastoma (GBM1, GBM10, GBM14)	Kahlert et al. 2016 [84]
			ovarian cancer (Hey, SKOV3, IGROV-1; sensitize cells to paclitaxel)	Yuan et al. 2016 [85]
GDH	EGCG	*In vitro*	glioma (U251)	Zhang et al. 2016 [86]
		In vivo	xenograft model of glioma (U251)	
	R162	*In vitro*	lung cancer (NCI-H1299, A549) erythroleukemia (KG-1a, HEL) acute monocytic leukemia (MOLM-14) chronic myelogenous leukemia (K-562) breast cancer (SKBR3, MDA-MB-231)	Jin et al. 2015 [87]
		In vivo	xenograft model of non-small cell lung carcinoma (NCI-H1299)	
SLC1A5 (ASCT2)	GPNA	*In vitro*	lung cancer (A549)	Hassanein et al. 2013 [88]
			neuroblastoma (BE-2C)	Ren et al. 2015 [89]
			prostate cancer (PC-3)	Wang et al. 2015 [90]
			breast cancer (HCC1806)	van Geldermalsen et al. 2016 [91]
			endometrial carcinoma (Ishikawa, HEC1A, KLE)	Marshall et al. 2017 [92]

	V-9302	*In vitro*	colon cancer (HCT116, COLO205, HT29, RKO)	Schulte et al. 2018 [93]
		In vivo	xenograft model of colon cancer (HCT116, HT29)	
	Benzylserine	*In vitro*	endometrial carcinoma (Ishikawa, HEC1A, KLE, RL95-2)	Marshall et al. 2017 [92]
			breast cancer (HCC1806, MDA-MB-231)	van Geldermalsen et al. 2018 [94]
	Benzylcysteine	*In vitro*	gastric cancer (SGC-7901)	Sun et al. 2013 [95]
β-oxidation of fatty acids				
CPT1	Etomoxir	*In vitro*	prostate cancer (LNCaP, VCaP, PC-3)	Schlaepfer et al. 2014 [96]
		In vivo	xenograft model of prostate cancer (VCaP)	
		In vitro	nasopharyngeal carcinoma (CNE2-IR, HK1-IR + radiotherapy)	Tan et al. 2018 [97]
		In vivo	xenograft model of nasopharyngeal carcinoma (CNE2-IR)	
		In vitro	acute myeloid leukemia (OCI-AML3, MOLM13)	Samudio et al. 2010 [98]
			breast cancer (MCF-7, ZR751)	Jariwala et al. 2021 [99]
	ST1326	*In vitro*	Burkitt`s lymphoma (Raji)	Pacilli et al. 2013 [100]
		In vivo	xenograft model of Burkitt`s lymphoma (Raji)	
		In vitro	acute myeloid leukemia (U937, MOLM13, OCIAML2, HL60, HL60/MX2, KG1) acute lymphoid leukemia (CEM S, CEM R, CCFR-CEM, RAJI, MOLT4, RS4;11, JURKAT)	Ricciardi et al. 2015 [101]
	Oxyfenicine	*In vitro*	melanoma (HBL)	Mascagna et al. 1992 [102]
	Avocatin B	*In vitro*	acute myeloid leukemia (OCI-AML2)	Lee et al. 2015 [103]

CPT1/CPT2	Perhexiline	*In vitro*	chronic lymphocytic leukemia cell obtained from patients	Liu et al. 2016 [104]
		In vivo	chronic lymphocytic leukemia transgenic mouse model	
Fatty acids synthesis				
FASN	Orlistat	*In vitro*	head and neck squamous cell carcinoma (rSCC-61)	Mims et al. 2015 [105]
			glioma (LN229, LT68, MW21)	Grube et al. 2014 [106]
			colorectal cancer (HT-29)	Czumaj et al. 2019 [107]
			prostate cancer (LNCaP, PC-3)	Chuang et al. 2019 [108]
			pancreatic cancer (PANC-1)	Sokolowska et al. 2017 [109]
			hepatocellular carcinoma (Hep3B)	You et al. 2019 [110]
			gastrointestinal stromal tumor (GIST48, GIST430)	Li et al. 2017 [111]
		In vitro	T cell lymphoma (Dalton's lymphoma cells)	Kant et al. 2012 [112]
		In vivo	murine model of a transplantable T cell lymphoma of spontaneous origin, designated as Dalton's lymphoma (DL)	
		In vitro	melanoma (B16-F10 murine melanoma cells)	Carvalho et al. 2008 [113]
		In vivo	melanoma model for spontaneous metastasis (B16-F10 murine melanoma cells)	
		In vitro	non-small cell lung cancer (H1299, A549, LCC)	Zhou et al. 2021 [113]
		In vivo	mouse xenograft model of non-small cell lung cancer (LCC)	
		In vivo	cisplatin-resistant ovarian tumour xenograft model in mice (A2780cis)	Papaevangelou et al. 2018 [114]
	Cerulenin	*In vitro*	breast cancer (ZR-75-1, SKBR3, MCF-7)	Pizer et al. 1996 [115]

			colon cancer (HT29, LoVo)	Chang et al. 2016 [116]
			retinoblastoma (Y79)	Deepa et al. 2011 [117]
			lung adenocarcinoma (A549, H1299)	Gouw et al. 2017 [118]
			bladder cancer (253J, 5637)	Jiang et al. 2012 [119]
		In vivo	xenograft model of drug-resistant ovarian cancer (OVCAR-3)	Pizer et al. 1996 [120]
		In vitro	colorectal cancer (HCT116, RKO)	Shiragami et al. 2013 [121]
		In vivo	xenograft model of colorectal cancer (HCT116)	
	C75	*In vitro*	prostate cancer (LNCaP, PC-3)	Rae et al. 2020 [122]
		In vitro	hepatocellular carcinoma (HepG2, SMMC7721)	Gao et al. 2006 [123]
	TVB-2640	*Clinical trial*	Phase 1 Study. Pharmacodynamic Effects of Fatty Acid Synthase (FASN) Inhibition With TVB-2640 in Resectable Colon Cancer and Other Resectable Cancers; a Window Trial.	NCT02980029
		Clinical trial	A Phase 2 Multi-center Pharmacodynamics Study of TVB-2640 in KRAS Mutant Non-small Cell Lung Carcinomas	NCT03808558
		Clinical trial	Phase 2 Trial to Evaluate the Efficacy of the FASN Inhibitor, TVB-2640, in Combination With Trastuzumab Plus Paclitaxel or Endocrine Therapy in Patients With HER2+ Metastatic Breast Cancer Resistant to Trastuzumab-Based Therapy	NCT03179904
		Clinical trial	A Phase 2 Investigator Initiated Study to Determine the Efficacy and Safety of TVB-2640 in Combination With Bevacizumab in Patients With First Relapse of High Grade Astrocytoma	NCT03032484

	TVB-3664	*In vitro*	colorectal cancer (Caco2, HT29)	Zaytseva et al. 2018 [124]
		In vivo	patient-derived xenograft model of colorectal cancer	
	TVB-3166	*In vitro*	lung cancer (CALU-6, NCI-H82, CALU-3, A427, NCI-H23, A549, NCI-H2347, NCI-H2122) colon cancer (T84, LS-1034, HCT116, SNU-C1, COLO205, NCI-H508, HT29, HT55) breast cancer (MDA-MB-231, MDA-MB-468, BT549, MCF7) ovarian cancer (OVCAR 5, CaOV4) prostate cancer (22RV1) Burkitt`s lymphoma (Raji, Daudi)	Ventura et al. 2015 [125]
		In vivo	xenograft model of pancreatic cancer (PANC-1) xenograft model of ovarian cancer (OVCAR-8) patient-derived xenograft model of non-small-cell lung cancer	
		In vitro	bladder cancer (T24, UMUC3)	Tao et al. 2019 [126]

GLUT1: glucose transporter 1; GLUT2: glucose transporter 2; GLUT4: glucose transporter 4; HK2: hexokinase type 2; 2-DG: 2-deoxyglucose; 3-BP: 3-bromopyruvate; BNBZ: benitrobenrazide; ALDOA: aldolase A; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; KA: koningic acid; MG: methylglyoxal; PGK1: phosphoglycerate kinase 1; PGAM1: phosphoglycerate mutase 1; EGCG: epigallocatechin-3-gallate; ENO2: γ-enolase; PK: pyruvate kinase; LDHA: lactate dehydrogenase isoform A; NHI-1: N-hydroxyindole, MCT1: monocarboxylate transporter 1; PDK: pyruvate dehydrogenase kinase; DCA: dichloroacetate; G6PD: glucose-6-phosphate dehydrogenase; DHEA: dehydroepiandosterone; 6-AN: 6-aminonicotinamide; ZA: zoledronic acid; GLS: glutaminase; GDH: glutamate dehydrogenase; SLC1A5: glutamine transporter; GPNA: L-γ-glutamyl-p-nitroanilide; CPT1: carnitine palmitoyltransferase 1; CPT2: carnitine acyltransferase 2; FASN: fatty acid synthase

Table S4. Examples of the inhibitors of the mitochondrial electron transport chain and ATP-synthase and their mechanisms of action in cancer cells.

Electron transport chain	Inhibiors	Mechanism of action	Cancer	Reference
Complex I	Metformin	Metformin reversibly inhibits mitochondrial complex I and reduces hypoxic activation of HIF-1α. Metformin causes inhibition of cancer cell proliferation in the presence of high glucose concentration in growth media and cancer cell death in conditions of low glucose availability.	lung cancer colorectal cancer	Wheaton et al. 2014 [127]
	IM156	IM156 inhibits mitochondrial complex I, which decreases NADH oxidation and activation of AMPK. IM156 indicates decrease in oxygen consumption rate.	lymphoma	Izreig et al. 2020 [128]
	Canagliflozin	Inhibition of proliferation of cancer cells is associated with inhibition of complex I, which causes reduction of ATP level and activation of AMPK.	lung cancer, prostate cancer	Villani et al. 2016 [129]
	BAY 87-2243	BAY 87-2243 causes induction of cancer cell death *in vitro* and reduction of tumor growth *in vivo* associated with complex I inhibition, which leads to oxygen consumption rate reduction and high level of ROS. In cancer cells maintained in the low glucose medium compound caused ATP depletion and induction of cancer cell death.	melanoma	Schöckel et al. 2015 [130]
	JCI-20679	JCI-20696 induces cancer cells growth inhibition mediated by the mitochondrial complex I inhibition.	panel of 39 cancer cell lines	Akatsuka et al. 2016 [131]
	Celastrol	Celastrol initiates apoptotic and necrotic cancer cell death through complex I inhibition which leads to ROS accumulation. Elevated level of ROS causes cell cycle arrest, inhibition of HSP90 function and JNK activation.	lung cancer, liver cancer	Chen et al. 2011 [132]
	AG311	AG311 causes complex I inhibition, HIF-1α stabilization, mitochondrial membrane depolarization, inhibition of tyrosine kinases and thymidylate synthase which leads to antitumor and antimetastatic effect on cancer cells.	breast cancer	Bastian et al. 2017 [133]
	Xanthohumol	Xanthohumol induces apoptosis of cancer cells through complex I inhibition, which leads to elevation of ROS level.	lung cancer, cervical cancer	Zhang et al. 2015 [134]

	Kalkitoxin	Kalkitoxin inhibits complex I, which causes decrease of oxygen consumption in cancer cells. This leads to inhibition of HIF-signaling and apoptosis of cancer cells. Moreover kalkitoxin targets tumor angiogenesis.	breast cancer	Morgan et al. 2015 [135]
	IACS-010759	Compound causes complex I inhibition, reduction of the activity of HIF-1 pathway and cancer cell apoptosis.	acute myeloid leukemia, ENO1 mutated glioblastoma	Molina et al. 2018 [136]
	CAI	Carboxyamidotriazole (CAI) inhibits complex I and causeses cancer cells growth reduction.	lung cancer	Stephenson et al. 2020 [137]
	Mubritinib	Mubritinib causes complex I inhibition.	acute myeloid leukemia	Baccelli et al. 2019 [138]
	MIBG	Meta-iodobenzylguanidine (MIBG) inhibits complex I and III of electron transport chain, causes reduction of the production of ATP and cancer cells death.	acute lymphoblastic leukemia	Cornelissen et al. 1995 [139]
	Verrucosidin	Verrucosidin causes complex I inhibition and induces cancer cell death in the hypoglycemic conditions.	breast cancer	Thomas et al. 2013 [140]
Complex II	α-Tocopheryl	α-Tocopheryl (α-TOS) inhibits succinate dehydrogenase (SDH) activity of complex II which, causes accumulation of ROS and cancer cell apoptosis.	breast cancer	Dong et al. 2008 [141]
	MitoVES	MitoVES causes inhibition of electron transfer from complex II to complex III, ROS accumulation and apoptosis of cancer cells.	acute T cell leukemia	Dong et al. 2011 [142]
	Atpenin A5 derivative	Atpenin A5 derivative inhibits complex II and leads to cancer cells death in both normoxic and hypoxic conditions.	prostate cancer	Wang et al. 2017 [143]
	Troglitazone	Inhibition of complex II by troglitazone causes massive apoptotic cancer cell death.	acute T cell leukemia	Soller et al. 2007 [144]

	DT-010	DT-010 inhibits complex II which leads to accumulation of ROS, loss of mitochondrial membrane potential, low ATP production and apoptosis of cancer cells.	breast cancer	Wang et al. 2016 [145]
Complex III	Atovaquone	Atovaquone targets the CoQ10-dependence of mitochondrial complex III which causes induction of oxidative stress, decreased oxygen consumption rate and death of cancer cells.	breast cancer	Fiorillo et al. 2016 [146]
	MIBG	MIBG inhibits complex I and III of electron transport chain, causes reduction of the production of ATP and cancer cells death.	acute lymphoblastic leukemia	Cornelissen et al. 1995 [139]
	Mahinine	Mahinine inhibits complex III of electron transport chain causes accumulation of ROS, induction of DNA damage response, Chk1/Chk2 upregulation and G0/G1 arrest of cancer cells.	glioblastoma	Bhattacharya et al. 2014 [147]
	Azoxystrobin	Azoxystrobin induces inhibition of complex III which leads to elevated level of ROS, loss of mitochondrial membrane potential and apoptosis of cancer cells.	oral cancer	Chen et al. 2020 [148]
Complex IV	Arsenic trioxide	Arsenic trioxide causes inhibition of complex IV which leads to accumulation of ROS, depolarization of mitochondrial membrane, decrease of ATP production and cancer cell death.	breast cancer	Sun et al. 2011 [149]
	Mitotane	Mitotane inhibits the activity of complex IV of electron transport chain which leads to cancer cell death.	adrenocortical carcinoma	Hescot et al. 2013 [150]
ATP-synthase	GBOXIN	Inhibition of ATP-synthase and death of cancer cells.	glioblastoma	Shi et al. 2019 [151]
	Angiostatin	Inhibition of ATP-synthase by the binding to α/β subunits.	colon cancer	Jung et al. 2007 [152]

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