

Supplementary Table S2. *Clinical trials evaluating treatment with CDK4/6 inhibitors in combination with other pharmacologic agents.* Only trials including one of the currently approved CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib and trilaciclib) are included. All data were compiled from ClinicalTrials.gov in August 2021.

Combination drug(s)	Tumor type	Clinical development
AKT inhibitors		
Capivasertib (AZD5363) + Endocrine therapy	HR+/HER2- breast cancer	Phase III
Ipatasertib + Endocrine therapy	HR+/HER2- breast cancer	Phases I, II and III
ALK inhibitors		
Ceritinib	ALK+ neuroblastoma ALK+ NSCLC	Phase I
Androgen-directed therapy		
Abiraterone + prednisolone	Advanced cancers Castration-resistant prostate cancer	Phases I and I/II
Bicalutamide	AR+ breast cancer AR+ TNBC	Phase I/II
Enzalutamide	RB+ castration-resistant prostate cancer	Phase I/II
Bicalutamide + Goserelin + Leuprolide	RB+ hormone-sensitive prostate cancer	Phase II
BCL2 inhibitors		
APG-2575	HR+/HER2- breast cancer	Phase I/II
Venetoclax + Endocrine therapy	BCL2+ HR+ breast cancer	Phase I
BCR-ABL/SRC inhibitors		
Bosutinib + Endocrine therapy	HR+/HER2- breast cancer	Phase I
BRAF inhibitors		
LGX818	BRAF-mutant melanoma KRAS- or BRAF-mutant NSCLC	Phase I/II
LXH254	NRAS-mutant melanoma Melanoma	Phases I and II
Sorafenib	Refractory leukemia	Phase I
BTK inhibitors		
Ibrutinib	Mantle cell lymphoma	Phase II
CDK2 inhibitors		
PF-07104091 +/- Endocrine therapy	SCLC NSCLC Ovarian cancer TNBC HR+/HER2- breast cancer	Phase II
Chemotherapy		
Capecitabine	HER2- breast cancer	Phase I
Carboplatin	HNSCC Solid tumors	Phases I and II
Cisplatin	Solid tumors p16INK-altered HPV- HNSCC	Phases I and II
CPX-351	Acute myeloid leukemia	Phase I/II
Decitabine	Refractory leukemia	Phase I
Docetaxel	NSCLC	Phase II
Docetaxel + Prednisone	Castration-resistant prostate cancer	Phase I/II

Doxorubicin	Soft tissue sarcoma	Phase I
Gemcitabine	Solid tumors	Phase I
	Lymphoma	
	NSCLC	
Nab-paclitaxel	Pancreatic ductal adenocarcinoma	Phase I
	HR+/HER2- breast cancer	
Paclitaxel +/- Endocrine therapy	Breast cancer	Phases I, I/II and II
	Solid tumors	
Pemetrexed	NSCLC	Phase I
Topotecan	SCLC	Phase I/II
5-FU + oxaliplatin	Solid tumors	Phase I
Combination chemotherapy regimens		
Carboplatin + etoposide/topotecan	SCLC	Phases I/II and III
Cytarabine, doxorubicin, prednisone/prednisolone, vincristine, pegaspargase, methotrexate, hydrocortisone	Pediatric acute lymphoblastic leukemia	Phase I
	Pediatric lymphoblastic lymphoma	
Epirubicin + cyclophosphamide + paclitaxel	TNBC	N.A.
Gemcitabine + carboplatin	TNBC	Phases II and III
Irinotecan + temozolomide	Pediatric/young adult solid tumors	Phase I
Topotecan + cyclophosphamide	Pediatric/young adult solid tumors	Phase I
Paclitaxel + carboplatin	Ovarian cancer	Phase I
	Fallopian tube Peritoneal cancer	
Topotecan + temozolomide	Pediatric/young adult recurrent malignancies	Phase I/II
EGFR inhibitors		
Cetuximab	CDKN2A-altered/HPV- HNSCC	Phases II and III
	HNSCC	
	CRC	
Nazartinib (EGF816)	EGFR-mutant NSCLC	Phase I
Necitumumab	NSCLC	Phase I
Osimertinib	EGFR-mutant NSCLC	Phase II
ERK1/2 inhibitors		
LY3214996	Solid tumors	Phases I and II
	GBM	
Ulixertinib (BVD-523)	Pancreatic cancer	Phase I
	Solid tumors	
FGFR inhibitors		
Erdafitinib + Endocrine therapy	HR+/HER2- FGFR+ breast cancer	Phase I
Rogaratinib (BAY1163877) + Endocrine therapy	HR+/HER2- FGFR+ breast cancer	Phase I
Glucocorticoids		
Dexamethasone	B-cell acute lymphoblastic leukemia	Phase I
	Refractory leukemia	
HAT inhibitors		
PF-07248144	Solid tumors	Phase I
HDAC inhibitors		
Abexinostat + Endocrine therapy	HR+ breast cancer	Phase I
	Gynecologic cancers	

Belinostat	TNBC Ovarian cancer	Phase I
Hedgehog pathway inhibitors		
Sonidegib	Pediatric/young adult brain tumors	Phase I
HER2-targeted therapies		
Neratinib	Solid tumors with HER family alterations or KRAS mutation	Phase I
Trastuzumab +/- pertuzumab +/- Endocrine therapy	HER2+ breast cancer HR+/HER2+ breast cancer	Phases I, I/II, II and III
Trastuzumab + lapatinib + Endocrine therapy	HR+/HER2+ breast cancer brain metastases	Phase II
Trastuzumab + Pyrotinib + Endocrine therapy	HR+/HER2- breast cancer	Phase II
Tucatinib + Endocrine therapy +/- trastuzumab	HR+/HER2+ breast cancer	Phases I and I/II
T-DM1 +/- Endocrine therapy	HER2+ breast cancer HR+/HER2+ breast cancer	Phases I, I/II and II
KN026 + Endocrine therapy	HER2+ breast cancer	Phase I/II
PF-06804103 + Endocrine therapy	HER2+ breast cancer Gastric cancer	Phase I
HIF-2α inhibitors		
MK-6482	Clear-cell renal cell carcinoma	Phase I
Hormone therapy		
Endocrine therapy	HR+/HER2- breast cancer	FDA-approved
Endocrine therapy	Ovarian cancer Endometrial cancer Fallopian tube cancer Peritoneal cancer	Phases I and II
IGF1R inhibitors		
Ganitumab	Ewig sarcoma	Phase II
IGF1/2 inhibitors		
Xentuzumab +/- Endocrine therapy	Lung cancer HR+/HER2- breast cancer	Phase I
Immune checkpoint inhibitors (PD-1 or PD-L1 blockers)		
Atezolizumab	Castration-resistant prostate cancer Solid tumors	Phase II
Atezolizumab + Endocrine therapy	HR+/HER2- breast cancer	Phase I/II
Avelumab +/- Endocrine therapy	HR+ breast cancer AR+ breast cancer	Phases I and II
Durvalumab + Endocrine therapy	HR+ breast cancer	Phase I
INCMGA00012	Liposarcoma	Phase II
LY3300054	Solid tumors	Phase I
Nivolumab +/- Endocrine therapy	HPV- HNSCC HNSCC Hepatocellular carcinoma HR+/HER2- breast cancer	Phases I/II and II
Pembrolizumab +/- Endocrine therapy	Gastroesophageal adenocarcinoma HNSCC NSCLC HR+/HER2- breast cancer	Phases I and II

Spartalizumab (PDR001) +/- Endocrine therapy	HNSCC Melanoma Ovarian cancer HR+ breast cancer	Phases I and II
JAK1/2 inhibitors		
Ruxolitinib	Myelofibrosis	Phase I
KRAS G12C inhibitors		
LY3537982	Solid tumors	Phase I
Sotorasib	Solid tumors	Phase I
MDM2 inhibitors		
HDM201	Advanced solid tumors Liposarcoma	Phases I and II
MEK inhibitors		
Binimetinib	KRAS-mutant NSCLC KRAS/NRAS-mutant CRC Pancreatic cancer TNBC	Phases I, I/II and II
MEK162	NRAS-mutant melanoma	Phase I/II
PD-0325901	KRAS-mutant NSCLC KRAS-mutant solid tumors	Phase I/II
Trametinib	Solid tumors Melanoma Pediatric/young adult brain tumors	Phases I and II
Metabolic modulators		
Hydroxychloroquine +/- Endocrine therapy	HR+ breast cancer Breast cancer	Phases I, I/II and II
Talaglenestat	Solid tumors	Phase I/II
mTOR inhibitors		
Everolimus (RAD001) +/- Endocrine therapy	Pediatric diffuse pontine glioma High-grade glioma Pancreatic cancer GBM Neuroendocrine tumors Brain tumors Dedifferentiated liposarcoma Leiomyosarcoma HR+/HER2- breast cancer	Phases I, I/II and II
Multi-RTK inhibitors		
Sunitinib	Renal cell carcinoma	Phase I
Multiple drug combinations		
Atezolizumab + Entinostat + Ipatasertib + Endocrine therapy	HR+/HER2- breast cancer	Phase I/II
Avelumab + Cetuximab	HNSCC	Phase I
Binimetinib + Encorafenib	BRAF-mutant melanoma	Phase I/II
Cetuximab + LY3214996	CRC	Phase I/II
Dexamethasone +/- everolimus	Acute lymphoblastic leukemia	Phase I
Etoposide/Carboplatin + Atezolizumab	SCLC	Phase II
Inavolisib (GDC-0077) +/- Endocrine therapy +/- Metformin	PIK3CA-mutant solid tumors	Phase I

LGX818 + MEK162	BRAF-mutant melanoma BRAF-mutant solid tumors	Phases I/II and II
GnRH agonist + Endocrine therapy + Talazoparib +/- Atezolizumab	Homologous recombination-deficient HR+/HER2- breast cancer	Phase II
Platinum-based chemotherapy + Avelumab	Bladder cancer	Phase II
Ruxolitinib + PIM447	Myelofibrosis	Phase I
NOTCH inhibitors		
Crenigacestat (LY3039478)	Solid tumors	Phase I
PARP inhibitors		
Niraparib	HR+/HER2- breast cancer	Phase I
Olaparib	Ovarian cancer	Phase I
Olaparib + Endocrine therapy	BRCA-mutant HR+/HER2- breast cancer	Phase I
Talazoparib	Solid tumors	Phase I
PI3K inhibitors		
Alpelisib (BYL719) + Endocrine therapy	HR+/HER2- breast cancer	Phases I and I/II
Buparlisib (BKM120) + Endocrine therapy	HR+/HER2- breast cancer	Phase I
Copanlisib (BAY 80-6946) + Endocrine therapy	HR+/HER2- breast cancer	Phase I/II
CYH33 + Endocrine therapy	HR+/HER2- PIK3CA-mutant breast cancer	Phase I
Inavolisib (GDC-0077) + Endocrine therapy	HR+/HER2- PIK3CA-mutant breast cancer	Phase II/III
Pictilisib +/- Endocrine therapy	HR+/HER2- PIK3CA-mutant breast cancer PIK3CA-mutant solid tumors	Phase I
Taselisib +/- Endocrine therapy	HR+/HER2- PIK3CA-mutant breast cancer PIK3CA-mutant solid tumors	Phase I
PI3K/mTOR dual inhibitors		
Gedatolisib (PF-05212384) +/- Endocrine therapy	Squamous cell lung cancer HNSCC Pancreatic cancer Breast cancer Solid tumors	Phase I
LY3023414 +/- Endocrine therapy	NSCLC Pancreatic cancer HR+ breast cancer	Phases I and II
Proteasome inhibitors		
Bortezomib	Mantle cell lymphoma	Phase I
Bortezomib + Dexamethasone	Multiple myeloma	Phase II
SHP2 inhibitors		
TNO155	Solid tumors	Phase I
VEGF inhibitors		
Bevacizumab	GBM with <i>CDKN2A/B</i> loss or <i>CDK4/6</i> amplification	Phase I
VEGFR2 inhibitors		
Ramucirumab	Esophageal/gastroesophageal junction cancer NSCLC Solid tumors	Phases I and I/II

AR, androgen receptor; BTK, Bruton's tyrosine kinase; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated protein kinase 1/2; FGFR, fibroblast growth factor receptor; GBM, glioblastoma multiforme; HAT, histone acetyltransferase; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; HIF-2 α , hypoxia-inducible factor-2 α ; HNSCC, head and neck

squamous cell carcinoma; HPV, human papillomavirus; HR, hormone receptor; IGF1/2, insulin-like growth factor 1/2; IGF1R, insulin-like growth factor 1 receptor; NSCLC, non-small cell lung cancer; PARP, poly (ADP-ribose) polymerase; RTK, receptor tyrosine kinase; SCLC, small cell lung cancer; SHP2, Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2; TNBC, triple-negative breast cancer; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.