

New Strategies in Personalized Medicine for Solid Tumors: Molecular Markers and Clinical Trial Designs

Table 2.

Genetic aberrations as putative predictive biomarkers for anticancer agents

Target/pathway	Aberration type in solid tumors	Disease examples	Putative or proven drugs	Examples for drugs in clinical development	References
<i>EGFR</i>	Mutation	Lung cancer	EGFR inhibitors	Erlotinib	(15, 16, 25, 26, 30)
	Amplification	GBM		Gefitinib	
				Afatinib	
				AZD9291	
<i>HER2 (ERB2)</i>	Mutation	Breast cancer	ERB2/ERB3 inhibitors	Lapatinib	(4, 5)
	Amplification	Gastric cancer		Neratinib	
		Lung cancer		Trastuzumab	
				Trastuzumab-emtansine	
<i>ALK</i>	Rearrangement	Lung cancer	ALK inhibitors	Crizotinib	(10, 22, 28, 29, 65, 66)
	Mutation	Neuroblastoma		Ceritinib	
		Colorectal cancer		Alectinib	
<i>RET</i>	Rearrangement	Thyroid cancer	RET inhibitors	Vandetanib	(19-21, 23)
	Mutation	Lung cancer		Carbozantinib	
<i>ROS1</i>	Rearrangement	Lung cancer	ROS1 inhibitors	Crizotinib	(18, 19)
<i>DDR2</i>	Mutation	Lung cancer	DDR2 inhibitors	Dasatinib	(67, 68)
				Nilotinib	
<i>FGFR1-4</i>	Amplification	Lung cancer	FGFR inhibitors	Ponatinib	(69, 70)
	Mutation	Gastric cancer		Dovitinib	
		Breast cancer		BGJ398	
		Bladder cancer		AZD4547	
<i>MET/HGF</i>	Mutation	Lung cancer	Met inhibitors	Onartuzumab	(71-73)
	Amplification	Gastric cancer		Crizotinib	
		Colorectal cancer		Foretinib	
		HCC		INC280	
		RCC			
<i>KIT</i>	Mutation	GIST	Kit inhibitors	Imatinib	(7, 8)
		Mastocytosis		Nilotinib	
		Melanoma		Sunitinib	
				Dasatinib	
				Ponatinib	
<i>PDGFRA and PDGFRB</i>	Mutation	GIST	PDGFR inhibitors	Imatinib	(8, 74)
	Translocation	Sarcoma		Sunitinib	
		GBM		Ponatinib	
		Leukemia			
		Dermatofibrosarcoma protuberans			
<i>KRAS, NRAS, HRAS (RAS-RAF-MEK)</i>	Mutation	Most cancers, including colorectal cancer, lung cancers	Mek inhibitors	Trametinib	(75)
				Selumetinib	
<i>BRAF (RAS-RAF-MEK)</i>	Mutation	Melanoma	Braf inhibitors	Vemurafenib	(75, 76)
		Colorectal cancer	Mek inhibitors	Dabrafenib	
		HCC		Trametinib	
				Selumetinib	
<i>PI3KCA (PTEN/PI3K /AKT/mTOR)</i>	Mutation	Multiple, including:	PI3K inhibitors	BKM-120	(77, 78)
	Amplification	Breast cancer	AKT inhibitors	BEZ235	
		Colorectal cancer, GBM		BYL719	
		Lung cancer		GDC0941	
		Endometrial		GDC0032	
				MLN1117	
			AKT inhibitors (see below)		
<i>PIK3R1 (PTEN/PI3K /AKT/mTOR)</i>	Mutation	Endometrial cancer	PI3K inhibitors	PI3K inhibitors (see above)	(78)
		Colorectal			

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<i>AKT1-3 (PTEN/PI3K/IAKT/mTOR)</i>	Mutation	Breast cancer	PI3K inhibitors	GDC0086	(⁷⁷⁻⁷⁹)
	Amplification	Colorectal cancer	AKT inhibitors	MK2206	
		Meningeal cancer		AZD5363	
		Urinary tract cancers		PI3K inhibitors (see above)	
		Endometrial cancer			
<i>PTEN (PTEN/PI3K/IAKT/mTOR)</i>	Deletion/Mutation	Most cancers, including breast cancer	PI3K inhibitors/ AKT inhibitors	PI3K and AKT inhibitors (see above)	(⁷⁷⁻⁸⁰)
		Lung cancer			
		Colorectal cancer			
<i>mTOR (PTEN/PI3K/IAKT/mTOR)</i>	Mutation	Endometrial cancer	mTOR inhibitors	Everolimus	(^{78, 81, 82})
		RCC		Temsirolimus	
		Colorectal cancer		MLN128	
		Lung cancer		AZD2014	
				GDC00980	
				BEZ235	
<i>TSC1/2 (PTEN/PI3K/IAKT/mTOR)</i>	Mutation	Tuberous sclerosis	mTOR inhibitors	mTOR inhibitors (see above)	(^{78, 83})
		Urinary tract cancers			
		Endometrial cancer			
		Cervical cancer			
		HCC/Colorectal cancer			
<i>LKB1 (PTEN/PI3K/IAKT/mTOR)</i>	Mutation	Cervical cancer	mTOR inhibitors	mTOR inhibitors (see above)	(⁷⁸)
		Small intestine cancer			
		Lung cancer			
		Skin cancer			
<i>SMO, PTCH1 (Hedgehog)</i>	Mutation	Basal cell carcinoma	Hedgehog inhibitors	Vismodegib	(^{84, 85})
		Medulloblastoma			
		Meningioma			
		Breast cancer			
<i>MDM2</i>	Amplification	GBM	MDM2 inhibitors/antagonists disrupting p53-MDM2 interaction	RG7388	(^{53, 54})
		Sarcoma			
<i>P53</i>	Mutation	Most tumors	P53 activators		(^{53, 54})
<i>NOTCH</i>	Mutation	Breast cancer	γ -secretase inhibitors	MK0752	(^{86, 87})
	Rearrangement	Lung cancer	ABs to notch receptors or ligands	PF03084014	
		Ovarian cancer		Demcizumab	
		GBM		OMP59R5	
		H&N cancer		OMP52M51	
			Enoticumab		
<i>CDKS</i>	Amplification	Sarcoma	CDK inhibitors	Flavopiridol	(⁸⁸)
	Mutation	Melanoma		Palbociclib	
	Rearrangement	GBM			
<i>CHK1/2</i>	Mutation	Multiple tumors, including those listed below: Colorectal cancer	CHK inhibitors	RG7741	(⁸⁸)
				LY2606368	
		Gastric cancer			
		Endometrial cancer			
		Breast cancer			
<i>AURKA (Aurora kinases)</i>	Amplification	Multiple tumors	Aurora kinase inhibitors	Alisertib	(^{88, 89})
<i>ATR</i>	Mutation	Gastric cancer	ATM inhibitors	No ATM inhibitors in clinical development	(^{88, 90})
	Deletion	Breast cancer	PARP inhibitors	PARP inhibitors (see below)	
		Endometrial cancer			
<i>ATM</i>	Mutation	Multiple tumors, including	ATR inhibitors	VX970	(^{88, 90})
	Deletion	Breast cancer	PARP inhibitors	PARP inhibitors (see below)	
<i>BRCA1/2</i>	Mutation	Breast cancer	PARP inhibitors	Olaparib	(^{91, 92})
		Ovarian cancer		Veliparib	
				Rucaparib	
				BMN673	

Abbreviations: GBM, glioblastoma multiforme; H&N cancer, head and neck cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.