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OVERVIEW OF MOLECULAR TARGETED THERAPY IN CANCER

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ABSTRACT

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Systemic therapy of cancer by cytotoxic agents is the cornerstone of cancer treatment. But now, these agents are being supplemented by a new generation of drugs that recognize specific targets in or on the cancer cells. These targeted agents can be classified broadly into monoclonal antibodies, signal pathway inhibitors and those targeting genetic abnormalities. Gene therapy and immunotherapy are the latest weapons in the arsenal that have been introduced and studies are ongoing. Although there as been an explosion in the armamentarium against cancer as far as targeted therapy in concerned, we need to further intensify our efforts as the era of 'personalised medicine' dawns on us and the concept of quality of life becomes more relevant in a developing country like ours.

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INTRODUCTION

Systemic therapy of cancer by cytotoxic agents is the cornerstone of cancer treatment. But now, these agents are being supplemented by a new generation of drugs that recognize specific targets in or on the cancer cells. These newer generation drugs not only fight cancer "smartly" but with fewer side effects as they tend to be more specific. For this reason, it is a promising therapy for the 3^{rd} millennium⁽¹⁾. Traditional cytotoxic chemotherapy works primarily through the inhibition of cell division. In addition to cancer cells, other rapidly dividing cells (e.g. hair, gastrointestinal epithelium, bone marrow etc.) are affected by these drugs. These molecular drugs are in their infancy; however, they hold promise of more effective therapies with fewer side effects. Several targeted drugs are already approved by the US Food and Drug Administration (FDA) for use in malignancies, and several more are in various phases of clinical developments⁽²⁾. The conventional anticancer agents used as systemic agents not only kill the rapidly proliferating cancer cells but they also lethal to all fast proliferating tissues in the body. The conventional therapy is going to stay for a longer period of time, however, it is deemed to be supplemented by targeted therapies⁽³⁾.

These targeted agents can be classified broadly into monoclonal antibodies, signal pathway inhibitors and those targeting genetic abnormalities.

*Corresponding author: Sahil Gupta King George's Medical University Below is a brief description of targeted agents that have been approved by the USFDA for use in the treatment of cancer during the last several years.

Monoclonal Antibodies- They are immunoglobulin structures designed to target specific antigens found on the cell surface, such as transmembrane receptors or extracellular growth factors for attack. In some cases, monoclonal antibodies are conjugated to radio-isotopes or toxins to allow specific delivery of these cytotoxic agents to the intended cancer cell target. Monoclonal antibodies end with the stem "-mab" (monoclonal antibody). Monoclonal antibodies have an additional subsystem designating the source of the compound e.g., "-ximab" for chimeric human-mouse antibodies, "-zumab" for humanized mouse antibodies, and "-mumab" for fully human antibodies⁽⁴⁾.

Small Molecules/Signal Pathway Inhibitors - Small molecules are usually designed to interfere with the enzymatic activity of the target protein. They can penetrate the cell membrane to interact with targets inside a cancer cell. Small molecules end with the stem "-ib" (indicating that the agent has protein inhibitory properties).

Both monoclonal antibodies and small molecules contain an additional stem in the middle of the name describing the molecule's target; examples for monoclonal antibodies include "-ci-" for a circulatory system target and "-tu-" for a tumor target, while examples for small molecules include "-tin-" for tyrosine kinase inhibitors and "-zom-" for proteasome inhibitors. At the beginning of the generic name there is a prefix that is unique for each agent ⁽⁴⁾.



Gene Therapy - Gene therapy implies any procedure intended to treator alleviate a disease by genetically modifying the cell of a patient either by blocking the expression of the oncogene or by replacing the missing or defective tumor suppressor gene. The material to be transferred into patientcells may be genes, gene segments, or oligonucleotides. Gene therapy can be broadly broken down into three categoriesimmunotherapy, oncolytic virotherapy and gene transfer ⁽⁵⁾. We have enlisted and briefly described the above mentioned modalities with the agents that have been approved by the USFDA during the past several years.

Table 1	1
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Drug	Target	Indication	Vear of approval
Ado-trastuzumah emtansine (Kadeyla)	HFR2 (FRB-B2/neu)	Breast cancer (HER2+)	2013
Alemtuzumah (Campath)	CD52	Breast cancer (HER2+)	2013
MentuZuniao (Campati)	6052	Urothalial assainoma	2001
Atezolizumab (Tecentriq)	PD-L1		2016
Deliminaria (Demlerate)	DAFE	Ivon-sman cen lung cancer	2011
Bellinumab (Belliysta)	БАГГ	Convised concerns	2011
		• Cervical cancer	2014
		Colorectal cancer	2013
		• Fallopian tube cancer	2014
Bevacizumab (Avastin)	VEGE ligand	Glioblastoma	2009
	(Dor inguid	 Non-small cell lung cancer 	2006
		Ovarian cancer	2014
		Peritoneal cancer	2014
		Renal cell carcinoma	2009
Prontuzimah vadatin (Adaptric)	CD20	 Hodgkin lymphoma 	2011
BrentuxInnab vedotini (Adced18)	CD30	 Anaplastic large cell lymphoma 	2011
Canakinumab (Ilaris)	H 10	 Juvenile idiopathic arthritis 	2016
	IL-IP	 Cryopyrin-associated periodic syndromes 	2016
Cetuximab (Erbitux)		• Colorectal cancer (KRAS wild type)	2004
	EGFR (HER1/ERB-B1)	• Squamous cell cancer of the head and neck	2004
Daratumumab (Darzalex)	CD38	Multiple myeloma	2015
Durataniana (Darbaren)	0200	Giant cell tumor of the bone	2013
		Bone metastasis	2013
Denosumab (Xgeva)	RANKL	 Done inclustasis Increase hone mass in patients on AI/ADT 	2010
		 Increase bone mass in patients on Al/AD1 Bostmanonausal woman with ostaoporosis at high risk of fracture 	2011
Disuturingh (Uniturin)	DACALNT1 (CD2)	Postinenopausai women with osteoporosis at high fisk of fracture	2010
Dinutuximab (Unituxin)	SLAME7	• Paediatric neuroblastoma	2015
Elotuzumab (Empliciti)	SLAMF/	Multiple myeloma	2015
	(CSI/CD319/CRACC)		2010
Gemtuzumab ozagamycin (pfizer)	CD33	• AML	2010
Ibritumomab tiuxetan (Zevalin)	CD20	Non-Hodgkin's lymphoma	2002
Ipilimumab (Yervoy)	CILA-4	• Melanoma	2011
Necitumumab (Portrazza)	EGFR (HER1/ERBB1)	Squamous non-small cell lung cancer	2015
		Hodgkin lymphoma	2016
Nivolumah (Ondivo)		Melanoma	2014
(Optivo)	PD-1	 Non-small cell lung cancer 	2015
		Renal cell carcinoma	2015
		Head and neck cancer	2016
Obienturnench (Correct)	CD20	Chronic lymphocytic leukaemia	2013
Obinutuzuniao (Gazyva)	CD20	Follicular lymphoma	2016
Ofatumumab (Arzerra, HuMax-CD20)	CD20	Chronic lymphocytic leukaemia	2016
Olaratumab (Lartruvo)	PDGFRa	Soft tissue sarcoma	2016
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	• Colorectal cancer (KRAS wild type)	2006
		Melanoma	2014
Pembrolizumab (Keytruda)	PD-1	• Non-small cell lung cancer (PD-L1+)	2015
	121	Head and neck squamous cell carcinoma	2016
Pertuzumah (Perieta)	HER2 (ERBR2/neu)	 Breast cancer (HER2+) 	2013
r crtuzuniao (r crjeta)	merce (ERDD2/neu)	Colorectal cancer	2015
Ramucirumah (Cyramza)		Gastric cancer or Gastroesonbageal junction (GEI)	2015
Kanuchumab (Cyramza)	VEGFR2	Gastile callel of Gastilesophageal junction (GEJ)	2014
		• Non small call lung concer	2014
		Non-Shah cen lung cancer Non-Hodelrin's lymphome	1007
		• Non-Hodgkin's lymphoma	1997
Kituximad (Kituxan, Madthera)	CD20	Chronic Tymphocytic leukemia Discussed autoritie	2010
		• Kneumatoid arthritis	2006
	 .	Granulomatosis with polyangiitis	2011
Siltuximab (Sylvant)	IL-6	MulticentricCastleman's disease	2014
Tocilizumah (Actemra)	IL-6R	Rheumatoid arthritis	2010
i semilarias (rictonia)	12 010	 Juvenile idiopathic arthritis 	2011
Trastuzumah (Herceptin)	HER2 (ERBR2/neu)	• Breast cancer (HER2+)	2006
masuzamao (mercepum)	(LKDD2/IICu)	 Gastric cancer (HER2+) 	2010

Effort has also been made to include agents that hold promise in major clinical trials.

Monoclonal Antibodies

This year marks the 30th anniversary of the Food and Drug Administration approval of the first mAb for human use.Few of the surface antigens present on the malignant cells and not on the surrounding normal cells are the excellent target for the specific antibodies to act. These tumor associated antigens are the ideal targets. The fragment antigen binding (Fab) of a monoclonal antibody, which recognizes and binds to antigens, is responsible for the highly specific targeting that is possible with such therapies. The mAbs exert their anti-neoplastic effects through a multiplicity of mechanisms: by engaging host immune functions to attack the target cell; or by binding either to receptors or ligands, thereby blocking crucial cancer cell processes. Other mechanism includes a lethal payload carrier, such as a radioisotope or toxin, to the target cell (i.e., conjugated mAbs). Because their protein structure is digested by gastrointestinal fluids, mAbs are administered intravenously. In addition, they are not subject to significant drug interactions because they do not undergo hepatic metabolism⁽⁴⁾.

Table 2

DRUG	TARGET	POSSIBLE	TRIAL
	CDA	INDICATION	
3F8 Abagayamah	GD2	Detection and treatment of neuroblastoma	Phase 2 Clinical Trials
Adagovolliad	EpCAM CD326	Tumor cells (prostate, breast cancers)	Phase 2 Clinical Trials
Anatumomah mafenatox	Glycoprotein 5T4	Non-small cell lung cancer	Phase 2 Clinical Trials
Apolizumab (HulDIO, REMITOGEN TM SMART TM)	HLA-DR β	Non-Hodgkin lymphoma, Chronic lymphocytic leukemia	Phase 2 Clinical Trials
Bavituximab	Phosphatidylserine	Cancer, viral infections	Phase 2 Clinical Trials
Bivatuzumab mertansine	CD44 v6	Squamous cell carcinoma	Phase 2 Clinical Trials
Cantuzumab mertansine (huC242-DMl, SB408075)	Mucin CanAg	Colorectal tumor, Pancreatic cancers	Phase 2 Clinical Trials
Citatuzumab bogatox VB6-845	TACSTD1	Ovarian cancer, solid tumors	Pre clinical trials
Cixutumumab	IGF-1 receptor	Solid tumors	Phase 1 Clinical Trials
Clivatuzumabtetraxetan yttrium (Y-90)	MUC1	Pancreatic cancer	Phase 2 Clinical Trials
Conatumumab (AMG-655)	TNFRSF10B, TRAIL-R2	Solid tumors	Clinical trials
	(CD262)	Non Hodgkin's lymphome and hematological	Chinical thats
Dacetuzumab (SGN 40)	CD40	malignancies	Clinical trials
Daratumumab	CD38	Multiple myeloma	Clinical trials
Ecromeximab (KW28/1)	GD3 ganglioside	melanoma	Phase II trials
Eisiimomad (B-E8)		Lympnoma/Myeloma	Pre clinical trials
Enumaxomad (Rexomun®) Eteraturumah MEDI 522 (Abagrin® or Vitavin)	Integrin av 63	Several type of concers	Phase 2 Clinical Trials
Earlatuzumah (MOPAh 002)	EP a	Overien concers	Dhogo 2 trials
Figitumumah (CP 751871)	ICE 1 recentor	Various types of cancers	Dhase 2 clinical trials
Galiximah (IDEC 114)	CD ⁸⁰	B cell lymphoma, Non-Hodgkin's lymphoma,	Phase 2 clinical trials
Gaixinao (IDEC-114)	CD80	Psoriasis	Thase 2 chinear thats
Girentuximab (Rencarex®cG250, WX-G250)	Carbonic anhydrase 9 (CA-LX, MN, G250)	Renal cell carcinoma	Phase 2 clinical trials
Glembatumumab vedotin(CR011,CDX-011)	GPNMB (transmembrane glycoprotein NMB)	Cancer cells expressing NMB: melanoma, breast cancer	Phase 2 clinical trials
Inotuzumab ozogamicin (CMC-544)	CD22	Diffuse large B cell lymphoma, Non-Hodgkin lymphoma	Phase 2 clinical trials
Iratumumab (MDX-060)	CD30	CD30-positive lymphoma including Hodgkin's	Phase 2 clinical trials
Labetuzumab (hMN14, CEACIDE™)	CEA	Colorectal tumor	Phase 2 clinical trials
Lexatumumab (ETR2-ST01)	TRAIL-R2 (AP02)	Tumors	Preclinical trials
Lintuzumab	CD33	AML	Preclinical trials
Lucatumumab	CD40	Cancer like multiple myeloma, non-Hodgkin's or	Phase 2 clinical trials
Lumiliainal (IDEC 152 DEES)	0210	Hodgkin's lymphoma	
Luminximat (IDEC-152,P3E8)	CD23	Chronic lymphocytic leukaemia, Allergic asthma	Phase 2 clinical trials
Mapatumumab	TRAIL-receptor (death receptor 4)	Several tumors	Preclinical trials
Mitumomab (BEC2)	GD3 ganglioside	Melanoma and Small cell lung carcinoma	Phase 3 clinical trials
Naptumomab estafenatox (ABR-217620, ANYARA, TTS CD3)	TPBG (trophoblast glycoprotein, 5T4)	Several tumors	Phase 2 clinical trials
Necitumumab (IMC-11F8)	EGFR	Several tumors	Phase 2 clinical trials
Olaratumab (IMC-3G3)	PDGF-Ra	Solid tumors	Phase 1 clinical trials
Oportuzumab monatox. (PROXINIUM [™] VICINIUM [™]	EpCAM, and others	Several tumors	Phase 3 clinical trials
Oregovomab (OVAREX®)	MUC16, CA-125	Ovarian tumors	Phase 2 clinical trials
Pritumumab	Vimentin	Brain cancer	Phase 2 clinical trials
Robatumumab (SCH 717454)	CD221	Colon sarcoma, Blood cancers	Phase 2 clinical trials
Tigatuzumab (CS-1008)	TRAIL-R2 OrDR5	Several tumors (colorectal, pancreas, ovary)	Phase 2 clinical trials
Ticilimumab (CP-675,206)	CD 152 (CTLA-4)	Melanoma/small cell lung cancer/prostate cancer	Phase 3 clinical trials
Veltuzumab	CD20	Non-Hodgkin's lymphoma	Phase 2 clinical trials
Volociximab	Integrin a5 ^{β1}	Solid tumors	Phase 2 clinical trials
Zalutumumab (HuMax-EGFR)	EGFR	squamous cen carcinoma resistant to chemotherapy	Phase 3 clinical trials

Several monoclonal antibodies have been approved for the treatment of neoplastic diseases.(Table-1)

A number of monoclonal antibodies are in the clinical trials which may supplement our armamentarium against cancer. A short list of these agents under trial is as follows-(Table-2)

Signal Pathway Inhibitors / Small Molecules

The normal cell growth and replication is a very complicated and organised process. DNA contains the code which is transcripted into m-RNA and this is further translated into proteins, including growth factors that bind to receptors of the same cell or surrounding or distant cell. This binding activates signalling pathways that relay information back to the nucleus, activates mechanisms responsible for cell division and proliferation. The main difference between malignant and normal cells is that malignant cells can proliferate indefinitely and have lost the normal signals that are responsible for apoptosis.

These abnormalities are targeted by these agents to inhibit cell proliferation, induce apoptosis or both. However, the basic flaw that undermines this approach is that very few malignancies are due to a single abnormality and most cancer cells sustain several mutations before turning malignant. This makes most malignancies in individual unique in nature, and thereby one approach doesn't fit all.

Generally, signal pathway inhibitors were administered orally because they are not degraded in the gastrointestinal tract. Furthermore, they are manufactured by chemical. Process that is less expensive than the bioengineering required for monoclonal Antibodies. They achieve less specific targeting than do monoclonal antibodies, as is evident in the multitargeting nature of the kinase inhibitors such asimatinib, dasatinib, sorafenib, and sunitinib. Unlike monoclonal Antibodies, most signal pathway inhibitors are metabolized by cytochrome P450 enzymes (CYP450), which could result in interactions with the potent inhibitors of CYP450 such as warfarin, macrolide antibiotics, azole antifungals, certain anticonvulsants, protease inhibitors, etc. Whereas monoclonal Antibodies have half-lives ranging from days to weeks (and are therefore usually administered once every one to four weeks), most signal pathway inhibitors have short half-lives (few hours) and require daily dosing⁽⁴⁾.

These agents can be broadly classified into

Protein Tyrosine Kinase Inhibitors (TKIs)- Protein Tyrosine Kinases are transmembrane or cytosolic enzymes that bind to its receptors leading to activation of downstream signalling pathways. These include growth factors, differentiation factors & hormones. More than 100 protein tyrosine kinases have been identified, including.

- a. Epidermal Growth Factor Receptor (EGFR/Erb B/HER 1-4)
- b. Platelet Derived Growth Factor Receptor (PDGFR)
- c. Vascular Endothelial Growth Factor Receptor
- (VEGFR) d Cutosolia Abalson (Abl) Turosina Kinasa
- d. Cytosolic Abelson (Abl) Tyrosine Kinase
- e. Other include
 - JAK2/mTOR/MEK/ALK/BTK/KIT/PI3K/RET etc.

Proteasome Inhibitors- Proteasome is a multi-enzyme complex that is responsible for the degradation of proteins that regulate cell cycle progression.

Blocking Intracellular Pathways- Downstream signalling pathways within the cancer cells can also be inhibited. Examples include Ras, Raf pathways etc.

Molecules Targeting Epigenome- Human gene expression patterns are controlled and coordinated by the activity of a diverse array of epigenetic regulators, including histone methyltransferases, acetyltransferases, and chromatin remodelers. Deregulation of these epigenetic pathways can lead to genome-wide changes in gene expression, with serious disease consequences. Currently the only epigenetically directed therapies in clinical practice are inhibitors of DNA methyltransferases and histone deacetylases (HDAC).

Poly(ADP-Ribose) (PARP) Inhibitors - Cancer cells may harbour defects in DNA repair pathways leading to genomic instability. This can foster tumorigenesis but also provide a weakness that can be exploited therapeutically. Tumors with compromised ability to repair double-strand DNA breaks by homologous recombination, including those with defects in the *BRCA1* and *BRCA2* genes, are highly sensitive to blockade of the repair of DNA single-strand breaks, via the inhibition of the enzyme poly(ADP-ribose) (PARP). This provides the basis for a *synthetic lethal* approach to cancer therapy, which is showing considerable promise in the clinic.

Miscellaneous Agents

Following is a comprehensive list of small molecules approved by USFDA for use in treatment in cancer. (Table-3)

Many of these agents are in various phases of clinical trials. Important of them are enlisted below-

Over the last few decades, the success of small molecule cancer drugs over conventional chemotherapy has been clearly demonstrated. The main focus of molecularly targeted therapy using small molecule inhibitors have been the pathways that are usually deregulated in cancer, thus inhibiting cancer cell survival and proliferation. Majority of the inhibitors that have been developed and currently in clinical use target the kinases, which include the receptor molecules as well as downstream regulators. With the exception of proteasome inhibitor bortezomib, small molecule inhibitors of MMPs and those targeting apoptosis have albeit been extensively studied, but are yet to be approved for clinical use. Identifying specific genes/proteins, and understanding the mechanism(s) underlying the progression of each cancer will help design novel strategies to further improve the efficacy of current drugs and possibly identification of novel agents. The advantages of using a combination of different agents that inhibit several pathways or use of small molecule inhibitors in combination with radiation therapy can also be explored. In this regard, combination therapies using small molecule drugs and monoclonal Antibodies have been exploited and are emerging to be a promising anti-cancer strategy.

The rate at which new drugs are discovered and developed is frustratingly slow, with an increasing failure rate of most drugs at the clinical level. It is therefore of utmost importance to address the limitations of these drugs so as to reduce the delay in approval of these drugs for clinical use.

Table 3

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Ablemanni (Mereman) Alechini (Mereman) Ashimi (Mereman) A			•	Squamous cell cancer lung Renal cell carcinoma	1000
ALK (b) (A) (b) (b) (b) (b) (b) (CFR (12) > Non-staff (c) (monotone) (b) (c) (c) (c) (c) (c) (c) (c) (c) (c) (c	Aldesleukin (Proleukin)	1L-2	•	Melanoma	1998
Asiabilit (bips) beliance it (bips) beliance	Alectinib (Alecensa)	ALK	0	Non-small cell lung cancer (with ALK fusion)	2015
Interaction (Velocity) IDAC 0 Perspensive (Velocity) 2014 Bootzahls (Beaulf) ABL 0000 Coharanish (Charrey (Cohare) PLIS. KT, MET, NET, WEGPR2 Metalle synophic accor 2013 (Ideating) PLIS. KT, MET, NET, WEGPR2 Metalle synophic accor 2013 (Ideating) PLIS. KT, MET, NET, WEGPR2 Metalle synophic accor 2014 (Ideating) Protocore Mainfel synophic accor 2015 (Ideating) NERA Mainfel synophic accor 2016 (Ideating) NERA NERA 2016 <td>Axitinib (Inlyta)</td> <td>KIT, PDGFRβ, VEGFR1/2/3</td> <td>0</td> <td>Renal cell carcinoma</td> <td>2011</td>	Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	0	Renal cell carcinoma	2011
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Bostable (Bealth) ABL • Chronic mydragenos lednain (Philadelphia chromosome positive) 2013 Cortanic Conversion Protecome Modality chronic acre 2014 Carling Carlingtonin (Synthia) Protecome Modality chronic acre 2015 Cortanic Kolkanis MAK Modality chronic acres 2015 Danariah (Spryoth) AIL MER (Beand Carling) 2013 Danariah (Spryoth) AIL Martine Carling acres (Win Relation) 2013 Danariah (Spryoth) AIL Martine Carling acres (Win Relation) 2016 Edotabi Clarcon EOR (HERLERBE) Parcentac ingin neuromalocine turar 2016 Edotabi Clarcon martine cingin neuromalocine turar 2016 Cortaine (Resal) EOR (HERLERBE) Parcentac ingin neuromalocine turar 2016 Cortaine (Resal) EOR (HERLERBE) Neuronic ingin neuromalocine turar 2016 Cortaine (Resal) EOR (HERLERBE) Neuronic ingin neuromalocine turar 2016 Cortaine (Insus) EOR (HERLERBEN) Neuronic ingingin neuronalocine turar </td <td></td> <td></td> <td>•</td> <td>Mantle cell lymphoma</td> <td>2006</td>			•	Mantle cell lymphoma	2006
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Jane Barran (Benjar) Patensone Patensone (Barran (Benjar)	Cabozantinib (Cabometyx	FLT3, KIT, MET, RET, VEGFR2	•	Medullary thyroid cancer	2012
Laronne Kynness Colminatis (Groutin) ALK MET, ROSI Casonin (Kalkon) ALK MET, ROSI Database (Collis) ARK MET, ROSI Effort (Firster) BRAF VOID mataton) Database (Collis) ARK MET, ROSI Effort (Firster) BRAF VOID mataton) Database (Collis) ARK MET, ROSI Effort (Firster) ARK MET, ROSI Firster) ARK MET, ROSI Effort (Firster) ARK MET, ROSI Firster) ARK MET, ROSI Effort (Firster) ARK MET, ROSI Firster) ARK MET, ROSI Firster) ARK MET, ROSI Firster, Collision (Collis) ARK MET, ROSI Firster) ARK MET,	[tablet], Cometriq [capsule])	D	•	Renal cell carcinoma	2016
Columna (Controls) MIR Instanta (Controls) Alley Controls (Controls) ALX, MET, ROSI Non-small cell lung cancer (with ALX fusion of ROSI) 201 Datafasion (Controls) ABL Controls (Malari) 2013 Datafasion (Controls) ABL Control in proceeding and the statement (Maladelpin chromosome positive) 2064 Datafasion (Controls) ABL Control in proceeding and the statement (Maladelpin chromosome positive) 2064 Elociab Clavera) EGER (HER/LEERIN) Non-small cell lung cancer (with IGIR exon 19 deletions or exon 21 2014 Elociab Clavera) EGER (HER/LEERIN) Non-small cell lung cancer (with IGIR exon 19 deletions or exon 21 2016 Elociab Clavera) marcrais (raigin neurondocrine turnor 2016 Controls (With IGIR exon 19 deletions or exon 21 2012 Elociab Clavera) EGER (HER/LEERIN) Non-small cell lung cancer (with IGIR exon 19 deletions or exon 21 2012 Controls (With IGIR exon 19 deletions or exon 21 2012 2012 2014 Marcal cell carcinom 2014 2014 2014 Marcal cell (With Internologic motion) 2015 2014 2014 Marcal cell (With Internologic motion) 2014 2014 2014 Marcal cell (With Internologic motion) 2014 2014 2	Caritinih (Zukadia)			Numpre myeloma	2015
Constant (Contrac) ILLX ILLX <td< td=""><td>Cohimatinih (Cotallic)</td><td>ALK</td><td></td><td>Malanama (with PBAE V600E or V600K mutation)</td><td>2014</td></td<>	Cohimatinih (Cotallic)	ALK		Malanama (with PBAE V600E or V600K mutation)	2014
Chronis (Vallari) ALK. MET, ROSI Intermetation agence (for non-constrained) 2011 Dabradient (Tailur) REAF Melianov (in REAF 2000 matching) 2013 Dassinis (Sprycel) AlL Chronis myelogenous selecting (Philadelphin chronisonopositiv) 2007 Edotinis (Tarceva) FGER (HERLIERBRI) Auto (in the constraint of the prophositiv) 2007 Edotinis (Afinitor) mTOR Pasteratio (rigin accore (whe KIFR even 19 deletions or exon 21 2014 Evendinis (Afinitor) mTOR Constraint of the prophositiv (inclure) mercore doring in encomedoring turnor 2015 Evendinis (Afinitor) mTOR Constraint of the prophositiv (inclure) mercore doring in encomedoring turnor 2011 Evendinis (Afinitor) mTOR FGER (HERLIERBRI) Menter of the DFR exon 19 deletions or exon 21 2012 Matching (Creation) mercore doring in encomedoring turnor 2013 Branish (Interwica) FGER (HERLIERBRI) Menter of the DFR exon 19 deletions or exon 21 2014 Matching (Leward) PTIK Chronis (tympborins) 2013 Matching (Leward) PTIK Chronis (tympborins) 2014 Matching (Leward) PTIK Chronis (tympborins) 2014 Matching (Leward) PTIK Chronis (tympborins) 2014 Lapartini (Ty	coolinetino (cotenie)	MER		Non-small cell lung cancer (with ALK fusion or ROS1 gene alteration)	2015
Inductants (Unitalian) IBAF Melanous (with IBAF Vector mataion) 2001 Dasainb (Spryech) ABL Christer inceptiquenes in hermiter (Philadelphila chromosome positive) 2004 Extentis (Tarcwa) FGPR (IER.IF.R.BR1) Antel symphotistic televini (Philadelphila chromosome positive) 2004 shell unit of (Link) (Carcwa) FGPR (IER.IF.R.BR1) Image: Carcwa (Carcwa) 2004 shell unit of (Link) (Carcwa) FGPR (IER.IF.R.BR1) Image: Carcwa (Carcwa) 2004 Secondines (Afmior) FGPR (IER.IF.R.BR1) Image: Carcwa (Carcwa) 2004 Secondines (Afmior) FGPR (IER.IF.R.BR1) Image: Carcwa (Carcwa (Crizotinib (Xalkori)	ALK, MET, ROS1	•	Non-small cell lung cancer (with AEK lusion of KOST gene attention)	2011
Destinit (Sprycel) ABI. Chronic myclogrous lockenin (Philadelphia chronosone positiv) 2007 Erlorinb (Tarceva) EGR (HERL/ERBB1) Nos-snall cell ung cacer (with EGR exen 19 deletions or exon 21 2008 Parteratic camer Parteratic camer Parteratic camer 2016 Parteratic camer Parteration (Parteration (Parteraticamon (Part	Dabrafenib (Tafinlar)	BRAF	•	Melanoma (with BRAF V600 mutation)	2013
Dashmo (Spicer) And Ande (spiphofische leukeria (Philadelphia chromosone-positive) 2004 Electuib (Taceva) EGR (HER/FERB1) Non-secture (Philadelphia chromosone-positive) 2014 mbstrution (LSSM) mutations) 2014 barron (Afminor) mTOR 2014 Certaina (Afminor) mTOR 2014 Certaina (Afminor) mTOR 2014 Certaina (Afminor) mTOR 2014 Certaina (Afminor) EGR (HER/FERB1) Non-sectable subpendyrul giant cell arrox-(torm associated with the sectars) (Philadelphia chromosone-cell subpendyrul giant cell arrox-(torm associated with the sectars) (Philadelphia chromosone-cell subpendyrul giant cell arrox-(torm associated with the sectars) (Philadelphia chromosone-cell subpendyrul giant cell arrox-(torm associated with the sectars) (Philadelphia chromosone-cell subpendyrul giant cell arrox-(torm associated with the sectars) (Philadelphia chromosone-cell sectars) (Philadelphia chromoso		ADI	•	Chronic myelogenous leukemia (Philadelphia chromosome positive)	2007
Ensuine Characesay EGFR (HERL/ERB J) • Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 204 Evendimux (Afinitor) * Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 2015 Evendimux (Afinitor) * Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 2016 Evendimux (Afinitor) * Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 2016 Gefrinin (hesos) EGFR (HERL/ERB J) * Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 2015 Busuinab (Indravica) EGFR (HERL/ERB J) Non-smill cell lung cancer (with EGFR en 19 deletions or exon 21 2015 Instainb (Indravica) EGFR (HERL/ERB J) Non-smill even lung cancer (with EGFR en 19 deletions or exon 21 2015 Instainb (Indravica) EGFR (HERL/ERB J) Non-smill even lung cancer (with EGFR en 19 deletions or exon 21 2015 Instainb (Indravica) EGFR (HERL/ERB J) Non-small even lung cancer (with EGFR en 19 deletions or exon 21 2015 Instainb (Indravica) FIT Non-small even lung cancer (with EGFR en 19 deletions or exon 21 2015 Instainb (Indravica) FIT State anore (HERL) 2016 Instainb (Indravica) Portessome State anore (HERL) 2016 Instainb (Indravica) Portessome State anore (HERL) 2016 Instainb (I	Dasatinib (Sprycel)	ABL	•	Acute lymphoblastic leukemia (Philadelphia chromosomepositive)	2006
Internation (Larkerson) EGFR (HERL/ERBB1) substitution (LSSR) mataions) Parterencic center Parterencic center 2011 Parterencic center Controlistential, erb ange center center 2016 Parterencic center Controlistential, erb ange center center 2017 Ceffrinib (hessa) EGFR (HERL/ERBB1) EGFR (HERL/ERBB1) 2012 Parterencic center ce	Enlactine in (Tananana)		•	Non-small cell lung cancer (with EGFR exon 19 deletions or exon 21	2004
Function of the second of the secon	Eriounib (Tarceva)	EGFR (HER1/ERBB1)		substitution (L858R) mutations)	
Percelians (Afinitor) mTOR Plancentic origin enromedocrine tumor 001 Percelians (Afinitor) mTOR Plancentic origin enromedocrine tumor 002 Percelians (Afinitor) mTOR Plancentic origin enromedocrine tumor 003 Percelians (Lessa) EGFR (HER.LERBBI) Plancentic origin enromedocrine tumor 003 Press (Lester (HE +, HER2)) Plancentic (Math ell) phyloposite leakenis or cono 21 013 Press (Lester (HE +, HER2)) Plancentic (Math ell) phyloposite leakenis or cono 21 013 Press (Lester (HE +, HER2)) Plancentic (LESSR) mutations 014 Plancentic (Lesse) Plancentic (LESSR) mutations 014 Plancentic (LESSR) Plancentic (LESSR) Plancentic (LESSR) Plancentic (LESSR) Plancentic (LESSR) Plancentic (LESSR) Plancent			•	Pancreatic cancer	2005
			•	Pancreatic origin neuroendocrine tumor	2011
Evenolisms (Affinitor) mTOR • Renal cell carcinoma 2009 Protections (Affinitor) mTOR • Renal cell carcinoma 2012 • Benutine (Insersa) EGRE (HER.I/ER.BB1) • Renal cell carcinoma 2013 Brutine (Insersa) EGRE (HER.I/ER.BB1) • Renal cell carcinoma 2013 Brutine (Insersa) BTK • Chronic (Prophocytic Insternia 2014 Aldelaisish (Zydelig) PUKA • Chronic (Prophocytic Insternia 2014 Aldelaisish (Zydelig) PUKA • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic (Prophocytic Insternia 2014 • Chronic Insternia 2014 • Chronic Insternia 2014 • Chronic Insternia 2014 • Layatini (Calara) • Dermatofibroarcom protubernas 2016 • Layatini (Calara) • Dermatofibroarcom protubernas 2016 • Layatini (Vistern) • Dermatofibroarcom protubernas 2014 • Datatini (Visternia) • Dermatofibroarcoma protubernas 2014 <			•	Gastrointestinal, or lung origin neuroendocrine tumor	2011
Gefinish (hessa) EGFR (HER/FEBB1) Nonreschabe subpersynal gain cell astroytom associated with sports above the post of	Everolimus (Afinitor)	mTOR	•	Renal cell carcinoma	2009
Gefininb (hessa) EGR (HER./ER.BB1) Interact cancer (MR+, HER.2-) Interact cancer (MR+, HER.2			•	Nonresectable subependymal giant cell astrocytoma associated with	2012
Gefinitb (hessa) EGFR (HER/ERBB) Ans-snall cell lange cancer (with EGFR exon 19 delations or exon 21 substitution (LSSSR) mattaines 2015 Bruninb (inbruvica) BTK Charlen prophone 2015 Idelalisb (Zydelig) BTK Charlen prophone 2016 Idelalisb (Glevec) FWL Charlen prophone 2017 Intainab (Glevec) KT, PDGFR, ABL Charlen prophone 2017 Intainab (Glevec) KT, PDGFR, ABL Charlen prophone 2016 Intainab (Glevec) KT, PDGFR, ABL Charlen prophone 2016 Intainab (Glevec) KT, PDGFR, ABL Charlen prophone 2016 Intainab (Glevec) Potescome Multiple hematologin programs including Philadelphin chromosome- positive ALL and CML 2016 Intainab (Lawina) Potescome Multiple hydeona 2016 Intainab (Lawina) VEGFR2 Fenal cell carcinoma 2016 Intainab (Lawina) VEGFR2 Potescome Multiple hydeona 2016 Intainab (Lawina) VEGFR2 Portain and Potescome 2016 Intainab (Lawina) VEGFR2 Potaina carcer (with BCA mutation) 2016 Intainab (Lawina) VEGFR2 Potaina carcer (with BCA mutation) 2016 Intainab (Lawina) ABL Chronic my				Tuberous scierosis	2012
Gefninb (hess) EGFR (HERL/ERBB1) Provisinal Letting Status (Mail Letting Control Letting Status (Mail Letting Sta				Non small call lung concer (with ECEP even 10 deletions or even 21	
Brutinb (Inbruvica) BTK Martle cell (prophorma Chronic (prophorytic texternia Waldenstrom wancorg obborytic (texternia Waldenstrom wancorg obborytic (texternia Coltronic (Fignelia) PDK5 Folicicata B-cell non-Hodgiki (prophorma Coltronic (Tri) Folicicata B-cell non-Hodgiki (prophorma Coltronic (Tri) Brunili (Gleevec) KTT, PDGFR, ABL Coltronic (Tri) Brunini (Nilaro) Proteasome Multiple Hommo (KIT -) Breast cancer (HERZ) Breast cancer (HER	Gefitinib (Iressa)	EGFR (HER1/ERBB1)	•	substitution (L858R) mutations	2015
nmining (mining) BTK Chronic lymphocytic lynchesmia 2014 Malestard Science 2014 2014 Idelalish (Zydelig) PBKS Chronic lymphocytic lymphoma 2014 Imatinib (Glevvec) KTI, PDGFR, ABL Control kymphoma 2016 Inatinib (Glevvec) KTI, PDGFR, ABL Different Control KTI+ 2017 Inatinib (Ninlaro) Portasome Multigle Myelona 2015 Lapatinib (Ninlaro) Portasome Multigle Myelona 2015 Lapatinib (Tykerb) HER2 (ERBB2/neu), EGFR (HER1/ERBB1) Press cancer (HER2-) 2013 Olipatin (Lawing) ABL Chronic symphosize leaking (Philadelphia chromosome positive CDM) 2015 Olipatin (Lawing) ABL Chronic symphosize leaking (Philadelphia chromosome positive CDM) 2016 Olipatin (Lawing) ABL Chronic symphosize leaking (Philadelphia chromosome positive CDM) 2016 Pabohinosat (FaryAdk) HDAC Multigle Myelona 2015 Palbocicib (Innace) CDK4, CDK6 Breast cancer (Vih BER7 T790M mutation) 2016 Pabohinosat (FaryAdk) HDAC Multigle Myelona 2017 Parotanib (Iclusig) ABL, FGFR1-3, FLT3, VEGFR1/23 Colmonic symphositic (Ielexinin (Philadelphia chromosome positive) 2016 Parotanib (Icl			•	Mantle cell lymphoma	2013
	Ibrutinib (Imbruvica)	BTK	•	Chronic lymphocytic leukemia	2014
bdelalisb (Zydelig) PBK5 Chronic lymphocytic lymphozona 2014 PBK5 Follicular B-cell non-Holgkin lymphoma 2014 Imatinib (Gleevec) RTT, PDGFR, ABL Gl stromal lymphocytic lymphozona 2012 Imatinib (Gleevec) RTT, PDGFR, ABL Gl stromal lymphocytic lymphozona 2015 Izapatinib (Tykerb) HER2 (ERBB2/nou), EGFR (HERL/ERBB1) Breast cancer (HER 2-) 2015 Izapatinib (Lervima) VEGFR2 Renal cell carcinoma 2016 Noltinib (Tasigna) ABL Chronic myelogenous lenvina (With BCR Tr00M mutation) 2015 Noltinib (Tasigna) ABL Chronic myelogenous lenvina (With BCR Tr00M mutation) 2016 Panobinostat (Farydak) HDAC Mutafiel Myeloma 2016 Panobinostat (Farydak) HDAC Senta sent (Rer, HER2-) 2016 Panobinostat (Farydak) HDAC Mutafiel Myeloma 2016 Panobinostat (Farydak) HDAC Senta sent (Rer, HER2-) 2012 Ponatinib (klusign) ABL, FGFR1-3, FLT3, VEGFR2 Chronic myelogenous lenkinia 2012 Regorafenib (Sitvarga) ABL, FGFR1-3, FLT3, VEGFR2 Chronic myelogenous lenkinia 2012 Regorafenib (Sitvarga) JAK1/2 Sental sental carcinoma 2012 Regorafenib (Sitvarga) J			•	Waldenstrom'smacroglobulinemia	2015
Instantion (Lynering) PIBK6 + Follicular B-cell non-Hodgkin lymphoma 2014 Instainb (Gleevec) KTT, PDGFR, ABL Control tumor (KT+) 2014 Instainb (Gleevec) KTT, PDGFR, ABL Control tumor (KT+) 2014 Izazomib (Ninlaro) Porteasome Multiple hematologic malignancies including Philadelphia chromosome- positive ALL and CML 2015 Lanvatinb (Learvina) VEGFR (HER1/ERBB) Breast cancer (HER2+) 2013 Olaparb (Lynparza) PARP Ovaria cancer (with BCA' nutation) 2014 Olaparb (Lynparza) PARP Ovaria cancer (HER2+) 2013 Pabociclib (Brance) CDK4, CDK6 Presst cancer (HER2+) 2016 Pabociclib (Brance) CDK4, CDK6 Presst cancer (ER+, HER2-) 2016 Pabociclib (Brance) CDK4, CDK6 Presst cancer (ER+, HER2-) 2016 Pabociclib (Brance) CDK4, CDK6 Presst cancer (ER+, HER2-) 2016 Pabociclib (Brance) CDK4, CDK6 Presst cancer (ER+, HER2-) 2016 Paropanib (Vorient) VEGFR, PDGFR, KTT Renal cell carcinoma 2012 Ponatinb (Lausig) ABL, FGFR1-3, FLT3, VEGFR2 Concort mayle opponib 2012 Resortenent (Stivarga) HDAC Concort cancer 2012 Resortenent (Stivarga)	Idelalisib (Zydelig)		•	Chronic lymphocytic leukemia	2014
Instinib (Gleevec) KIT, PDGFR, ABL Coll strong trutherans 2014 Instinib (Gleevec) KIT, PDGFR, ABL Of strong trutherans 2016 Iszomib (Ninlaro) Porteasome 2016 2015 Lenvatinib (Tayisgn) ABL Envating (Lenvinna) 2016 Object (Linggin) ABL Othorine myelogenous leakenia (Philadelphia chromosome positive 2013 Object (Linggin) ABL Othorine myelogenous leakenia (Philadelphia chromosome positive 2013 Object (Linggin) ABL Othorine myelogenous leakenia (Philadelphia chromosome positive 2013 Osimertinib (Tagrisgn) EGFR Othorine myelogenous leakenia (Philadelphia chromosome positive 2016 Panobinostat (Farydak) HDAC Breast cancer (RFR, HEZ-2) 2016 Paropanib (Vorient) VEGFR, PDGFR, KIT Real cell carcinoma 2012 Regoratenib (Stivarga) ABL, FGFR1-3, FLT3, VEGFR2 Controit envelogenous leakenia 2012 Regoratenib (Stivarga) HDAC Othorine myelogenous 2013 Regoratenib (Stivarga) MILA Othorine m	Idefailsib (Zydefig)	ΡΙ3Κδ	•	Follicular B-cell non-Hodgkin lymphoma	2014
Inatinib (Glevec) KIT, PDGFR, ABL Gl stromal turnor (KT+) 201 Dermatofbrosarcoma protuberans 2016 Vermatofbrosarcoma protuberans 2016 Lazomib (Nilaro) Proteasome Multiple hematofbrosarcoma protuberans 2016 Lapatinb (Tykerb) HER2 (ERBB2/nou.), EGFR (HER1/ERBB1) 9 Fersat cancer (HER2+) 2016 Lenvatinb (Laviruna) VEGFR2 8 Renal cell carcinoma 2016 Nilotiub (Tasigna) ABL Chronic myelogenous leukemia (Philadelphia chromosome positive 2013 Olaparib (Lynparza) PARP Ovarian cancer (with EGFR T790M mutation) 2015 Parbocichib (Tagrisso) EGR Non-small cell lung cancer (with EGFR T790M mutation) 2015 Parbocichib (Iranze) CDK4, CDK6 9 reast cancer (HER2+) 2016 Parbocichib (Iranze) CDK4, CDK6 9 reast cancer (HER2+) 2016 Parbocichib (Iranze) VEGFR, PDGFR, KIT 8 Renal cell carcinoma 2012 Parbocichib (Iranze) ABL, FGFR1-3, FLT3, VEGFR1/2 Concretal cancer 2012 Ponatinib (Lynparz) ABL, FGFR1, RAF, RET, VEGFR1/2/3 Concretal cancer 2012 Regorafenib (Stivarga) KIT, PDGFR, RAF, RET, VEGFR1/2/3 Concretal cancer 2012 Ruxolitinib (Jakafi) JAK1/2 Polycythemiave			•	Small lymphocytic lymphoma	2014
Intainib (Glevec)KTT, PDGFR, ABLDermatofbroarcome protuberansDore and CMLIzazomib (Ninlaro)ProteasomeMultiple Myeloma2015Lapatinib (Tykerb)HER2 (ERBB2/neu), EGFR (HER1/ERBB1)Herad CML2013Lenvatinib (Lavivna)VEGFR2Renal cell carcinoma2016Nilotinib (Lavivna)VEGFR2Renal cell carcinoma2016Nilotinib (Tasigna)ABLChronic myelogenous leuemia (Philadelphia chromosome positive2013Olaparib (Lyaparza)PARPOvaria cancer (with BGCA mutation)2014Osimertinib (Tagriso)EGFRNons-mall cell lung cancer (with EGFR T790M mutation)2015Panobinostat (Farydak)HDACNons-mall cell lung cancer (with EGFR T790M mutation)2016Pazopanib (Vorrient)VEGFR, PDGFR, KITRenal cell carcinoma2010Paropanib (Vorrient)VEGFR, PDGFR, KITSoft issue sarcoma2012Ponatinib (Lusig)ABL, FGFR1-3, FLT3, VEGFR2Cloroctal cancer2013Regorafenib (Stivarga)KIT, PDGFRB, RAF, RET, VEGFR1/2/3Cloroctal cancer2014Ruxolitinib (Jakafi)JAK1/2Myelofbrosis2014Sorialegib (Odomzo)Smoothened(SMO)Baal cell carcinoma2015Sorafenib (Neavar)VEGFR, PDGFR, KIT, RAFPeripheral T-cell lymphoma2015Sorafenib (Neavar)VEGFR, PDGFR, KIT, RAFHepatocellufar carcinoma2015Sorafenib (Neavar)MTORRenal cell carcinoma2015Transitolimas (Trisel)mTORRenal cell carcinoma201			•	GI stromal tumor (KIT+)	2012
 Multiple Manilogic malignancies including Philadelphia chromosome- positive ALL and CML Lazomih (Ninlaro) Proteasome Multiple Myeloma 2015 Lapatinib (Tykerb) HER2 (ERBE2/nou), EGFR (HER1/ERBB1) Breast cancer (HER2+) Renal cell carcinoma 2016 Thyroid cancer Chronic myelogenous leukenia (Philadelphia chromosome positive 2013 Olaparib (Lynparza) PARP Ovarian cancer (Wth BKCA mutation) 2015 Palbociclib (brance) CDK4, CDK6 Breast cancer (Wth BKCA mutation) 2015 Palbociclib (brance) CDK4, CDK6 Breast cancer (Wth BKCA mutation) 2016 Parobinos (Tesylogenous leukenia (Philadelphia chromosome positive 2016 Parobinos (Tesylogenous leukenia 2012 Panobinos (Tesylogenous leukenia 2012 Parobinos (Tesylogenous leukenia 2012 Ponatinib (klusig) ABL, FGFR1-3, FLT3, VEGFR2 Chronic myelogenous leukenia 2012 Acute lympholyastic leukenia (Philadelphia chromosome positive) 2012 Acute lymphoma 2013 Acute lymphoma 2014 Polycythemiavera 2015 Polycythemiavera 2014 Polycythemiavera 2015 Polycythemiavera 2014 Polycythemiavera 2015 Polycythemiavera 201	Imatinib (Gleevec)	KIT, PDGFR, ABL	•	Dermatofibrosarcoma protuberans	2012
Lazomb (Ninlaro)ProteasomeUltiple Myeloma2015Lapatinb (Tykerb)HER2 (ERBB2/neu), EGFR (HER1/ERBB1)Freast cancer (HER2+)2013Lenvatinb (Lenvinn)VEGFR2Freast cancer (HER2+)2015Nilotinb (Tasigna)ABLChronic myolegonus leukenia (Philadelphia chromosome positive2013Olaparib (Lynparza)PARPOvarian cancer (with BKCA mutation)2014Osimertinib (Tagrisso)EGFRNon-small Cell lung cancer (with BCGR T790M mutation)2015Pablocicil (brance)CDK4, CDK6Breast cancer (Est, HER2-)2016Panobinostat (Farydak)HDACMultiple Myeloma2012Paropanib (Votrient)VEGFR, PDGFR, KITSoft itsue sarcoma2012Ponatinib (klusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukenia2012Ponatinib (klusig)ABL, FGFR1-3, FLT3, VEGFR2Colorectal cancer2013Romidepsin (Istodax)HDACCute lymphoblastic leukemia (Philadelphia chromosome positive)2012Romidepsin (Istodax)HDACCute lymphobna2013Romidepsin (Istodax)HDACCute lymphobna2014Sonidegib (Odomzo)Smoothened(SMO)East calc carcinoma2015Temsirolimas (Torise)mTORRenal cell carcinoma2013Temsirolimas (Torise)MTORRenal cell carcinoma2013Temsirolimas (Torise)MTORRenal cell carcinoma2013Temsirolimas (Caroise)EGFR (HER1/FRBR), RT, VEGFR2Melanoma (with BRAF V600 mutation)2014Va		, - ,	•	Multiple hematologic malignancies including Philadelphia chromosome-	2001
Lazomb (Nniaro)Protessome• Muttple Myeloma2015Lapatinb (Tykerb)HER2 (ERBB2/neu), EGFR (HER/ERBB1)Breast cancer (HER2+)2013Lenvatinib (Lenvima)VEGFR2• Renal cell carcinoma2016Nilotinib (Tasigna)ABL• Chronic myelogenous leukemia (Philadelphia chromosome positive2013Olaparb (Lynparza)PARP• Ovariar cancer (with BRCA mutation)2014Osimetrihi (Tagrisso)EGFR• Non-small cell lung cancer (with CFR T790M mutation)2015Palbocicihi (brance)CDK4, CDK6• Breast cancer (KH+, HER2-)2016Panobinostat (Farydak)HDAC• Multiple Myeloma2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2• Chronic myelogenous leukemia2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2• Chronic myelogenous leukemia2012Regorafenib (Stivarga)HDAC• DAC• Cutanours2013Ronidepsin (Istodax)HDAC• Ovariar cancer (M+ Imphohasi cleukemia (Philadelphia chromosome positive)2012Rasolitinib (Jakafi)JAK1/2• Ovariar cancer (M+ Imphohasi2016Sonidegib (Odomzo)Smoothened(SMO)• Basal cell carcinoma2013Sorafenib (Keavar)TGR• Moltrois2013Temsirolimus (Torisel)mTOR• Renal cell carcinoma2014Veeterkeib (Caper)JAK3• Renal cell carcinoma2015Temsirolimus (Caprise)mTOR• Renal cell carcinoma2013Venterkeib (Caper)BRAF• Melanoma (with BRAF V600 mutation) </td <td></td> <td>D</td> <td></td> <td>positive ALL and CML</td> <td>2015</td>		D		positive ALL and CML	2015
Lapathin (1yster) HER2 (LEBB2/ReU, EGFR (HER L/ERBB1) HER2 (LEBB2/ReU, EGFR (HER L/ERBB1)) HER2 (LERBB2/ReU, EGFR (HER L/ERBB1)) HER2 (LERBB2/ReU), EGFR (HER2/FR)) (2013) (2013) (2013) (2013) (2013) (2014)	Ixazomib (Ninlaro)	Proteasome	•	Multiple Myeloma	2015
Lenvatinib (Lenvina)VEGFR2Renal cell carcinoma2015Nilotinib (Tasigna)ABLThyroid cancer2013Olaparbi (Jynparza)PARPOvarian cancer (with BCA mutation)2014Osimertinib (Tagisso)EGFRNon-small cell lung cancer (with BCA mutation)2015Palbociclib (Brance)CDK4, CDK6Breast cancer (ER+, HER2-)2016Panobinostat (Farydak)HDACMultiple Myclona2012Pazopanib (Votrient)VEGFR, PDGFR, KITRenal cell carcinoma2012Ponatinib (Lelusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Ponatinib (Stivarga)KIT, PDGFR, RAF, RET, VEGFR1/2/3Colorectal cancer2012Regorafenib (Stivarga)HDACColorectal cancer2013Runditinib (Jakafi)JAK1/2Colorectal cancer2014Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2015Sorafenib (Neavar)VEGFR, PDGFR, KIT, RAFMyclofibrosis2011Sorafenib (Neavar)MTORRenal cell carcinoma2015Tranectinib (Mekinist)MTORRenal cell carcinoma2013Tranectinib (Kekinist)MEKMelanoma cancom2013VentorelasEGFR, PDGFR, KIT, RAFRenal cell carcinoma2014VentorelasEGFR, PDGFR, KIT, RAFNotifrosis2013Tranectinib (Mekinist)MTORRenal cell carcinoma2013Tranectinib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2014VentorelasEGFR (HE	Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	•	Breast cancer (HER2+)	2013
Nilotnib (Tasigna)ABLChronic myelogenous leukemia (Philadelphia chromosome positive)2013Olaparib (Lynapaza)PARPOvarian cancer (with BRCA mutation)2014Osimertinib (Tagrisso)EGFRNon-small cell lung cancer (with EGFR T790M mutation)2015Palbociclib (brance)CDK4, CDK6Breast cancer (ER+, HER2-)2016Panobinostat (Farydak)HDACMultiple Myeloma2012Pazopanib (Votrient)VEGFR, PDGFR, KITSoft issue sarcoma2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Ponatinib (Stivarga)KIT, PDGFR), RAF, RET, VEGFR1/2/3Colorectal cancer2013Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2013Rusolitinib (Jakafi)JAKL/2Colorectal cancer2014Soridegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2015Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2014Soridegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Temsirolimus (Torisel)mTORRenal cell carcinoma2013Temsirolimus (Torisel)MTORRenal cell carcinoma2013Tametinib (Mekinit)MEKMelanoma (with BRAF V600 mutation)2014Vandetanib (Caprelsa)EGFR (HER1/EBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Vandetanib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Venutrafenib (Calorata)BCL2Chronic ty	Lenvatinib (Lenvima)	VEGFR2		Thuroid cancer	2016
Oliqarib (Lynparza)PARPOvarian cancer (with BRCA mutation)2014Osimeritinb (Tagrisso)EGFRNon-small cell lung cancer (with EGFR T790M mutation)2015Palbociclib (Ibrance)CDK4, CDK6Breast cancer (with EGFR T790M mutation)2016Panobinosta (Farydak)HDACMultiple Myelona2019Pazopanib (Votrient)VEGFR, PDGFR, KITRenal cell carcinoma2009Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Ponatinib (Istivarga)KIT, PDGFR, RAF, RET, VEGFR1/2/3Colorectal cancer2013Regorafenib (Stivarga)KIT, PDGFR, RAF, RET, VEGFR1/2/3Colorectal cancer2011Rusolitinib (Jakafi)JAK1/2Colorectal cancer2011Sonidegib (Odomzo)Smoothened(SMO)Peripheral -cell lymphoma2013Sorafenib (Neavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Tensirolimus (Torisel)mTORRenal cell carcinoma2013Tensirolimus (Colarela, Venderka)JAK3Rheumatoid arthritis2013Venderable (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2013Tofactinib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Vendetable (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Vendetable (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Vendetable (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Mel	Nilotinih (Tasigna)	ABI		Chronic myelogenous leukemia (Philadelphia chromosome positive	2013
Ospan (1) Osimertinib (Tagrisso)EGFR EGFRNon-small cell lung cancer (with EGFR T790M mutation)2015Palbocicibi (brance)CDK4, CDK6Breast cancer (ER+, HER2-)2016Panobinostat (Farydak)HDACMultiple Wyeloma2009Paropanib (Votrient)VEGFR, PDGFR, KITRenal cell carcinoma2012Ponatinib (clusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic inyelogenous leukemia2012Ponatinib (klusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Regorafenib (Kivarga)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3Colorectal cancer2012Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2011Ruxolitinib (Jakafi)JAK1/2Operytheniavera2014Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2015Tensirolimus (Torisel)mTORRenal cell carcinoma2015Trametinib (Mexinst)MEKMelanoma (with BRAF V600 mutation)2012Ventorfenb (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2013Trametinib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2014Ventorfenb (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2011Ventorfenb (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2011Ventorfenb (Calurar)BRAFMelanoma (with BRAF V600 mutation)2011Ventorfenb (Calurar)BRAFMelanoma (with BRAF V600 mutation)2011 <td< td=""><td>Olaparib (Lynparza)</td><td>PARP</td><td></td><td>Ovarian cancer (with BRCA mutation)</td><td>2013</td></td<>	Olaparib (Lynparza)	PARP		Ovarian cancer (with BRCA mutation)	2013
Palbociclib (brance)CDK4, CDK6Breast cancer (BR, HER2-)2016Panobinostat (Farydak)HDACMultiple Myeloma2015Pazopanib (Votrient)VEGFR, PDGFR, KITRenal cell carcinoma2012Ponatinib (klusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Ponatinib (klusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Regorafenib (Stivarga)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3Colorectal cancer2012Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2011Ruxolitinib (Jakafi)JAK1/2Myelofibrosis2014Son sondegib (Odonzo)Smoothened(SMO)Basal cell carcinoma2015Tensirolimus (Torisel)mTORRenal cell carcinoma2013Tensirolimus (Torisel)mTORRenal cell carcinoma2013Tranetinib (Mekinis)MEKMelanoma (with BAF V600 mutation)2011Venderathib (Zelboraf)BRAFMelanoma (with BAF V600 mutation)2013Venderathib (Zelboraf)BRAFMelanoma (with BAF V600 mutation)2011Ventoclax (Venclexta)BRAFChronic lymphocytic leukemia (with 17p deletion)2011Ventoclax (Venclexta)BRAFChronic lymphocytic leukemia (with 17p deletion)2011Ventoclax (Venclexta)BCZChronic lymphocytic leukemia (with 17p deletion)2016Virmodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2012Ventoclax (Venclexta)BCAFChronic lymphocytic leukemia (with 17p deletion)<	Osimertinib (Tagrisso)	EGFR		Non-small cell lung cancer (with EGER T790M mutation)	2015
Panobinostat (Farydak)HDACMultiple Myeloma2015Pazopanib (Votrient)VEGFR, PDGFR, KITRenal cell carcinoma2009Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic myelogenous leukemia2012Regorafenib (Stivarga)KIT, PDGFR, RAF, RET, VEGFR1/2/3Colorectal cancer2013Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2016Ruxolitinib (Jakafi)JAK1/2Peripheral T-cell lymphoma2011Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Temsirolimus (Torisel)mTORRenal cell carcinoma2013Trametinib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2014Vemaratenib (Zeprelsa)EGFR (HERI/ERBBI), RET, VEGFR2Medullary thyroid cancer2013Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2014Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2014Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2011Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2014Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2014Vemaratenib (Zebroaf)BAAFMelanoma (with BRAF V600 mutation)2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma <t< td=""><td>Palbociclib (Ibrance)</td><td>CDK4, CDK6</td><td></td><td>Breast cancer (ER+, HER2-)</td><td>2016</td></t<>	Palbociclib (Ibrance)	CDK4, CDK6		Breast cancer (ER+, HER2-)	2016
Pazopanib (Votrient)VEGFR, PDGFR, KIT· Renal cell carcinoma2009Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2· Soft tissue sarcoma2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2· Chronic myelogenous leukemia2012Regorafenib (Stivarga)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3· Colorectal cancer2013Romidepsin (Istodax)HDAC· Cutaneous T-cell Jymphoma2009Ruxolitinib (Jakafi)JAK1/2· Poripheral T-cell Jymphoma2014Sonidegib (Odomzo)Smoothened(SMO)· Basal cell carcinoma2015Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAF· Renal cell carcinoma2015Temsirolimus (Torisel)mTOR· Renal cell carcinoma2013Tofacitinib (Xeljanz)JAK3· Rehematoid artritis2017Vemuratenib (Mekinist)MEK· Melanoma (with BRAF V600 mutation)2014Venuratenib (Zerlesa)EGFR (HER//ERBB1), RET, VEGFR2· Meldullary thyroid cancer2011Venuratenib (Zerlesa)EGFR (HER//FRBB1), RET, VEGFR2· Melanoma (with BRAF V600 mutation)2014Venuratenib (Zerlesa)EGFR (HER//FRBB1), RET, VEGFR2· Melanoma (with BRAF V600 mutation)2011Venuratenib (Zerleva)BCL2· Chronic lymphorytic leukemia (with 17p deletion)2016Vismodegib (Erivedge)PTCH, snoothened· Basal cell carcinoma2012Vorinostat (Zolinza)HDAC· Colorectal cancer2011Vernuratenib (Zelbara)BCL2· Chronic lymphorytic leukemia (with 17p deletion)2011 <td>Panobinostat (Farvdak)</td> <td>HDAC</td> <td></td> <td>Multiple Myeloma</td> <td>2015</td>	Panobinostat (Farvdak)	HDAC		Multiple Myeloma	2015
Pacopanib (Votrient)VEGR, PDGFR, KITSoft tissue sarcoma2012Ponatinib (Iclusig)ABL, FGFR1-3, FLT3, VEGFR2Chronic nyelogenous leukemia (Philadelphia chromosome positive)2012Regorafenib (Stivarga)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3Colorectal cancer2013Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2001Ruxolitinib (Jakafi)JAK1/2Myelofibrosis2011Ruxolitinib (Jakafi)JAK1/2Myelofibrosis2013Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Temsirolimus (Torisel)mTORRenal cell carcinoma2013Trametnib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2014Venetoclax (Venclexta)BCFR (HER1/EBBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Venetoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2014Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2015Venetoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2014Venetoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2012Vorinostat (Zolinza)HDACColorectal cancer2014Ventoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2016Vismodegib (Erivedge)PT			•	Renal cell carcinoma	2009
Ponatinib (clusig)ABL, FGFR1-3, FLT3, VEGFR2• Chronic myelogenous leukemia2012Regorafenib (Stivarga)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3• Colorectal cancer2013Romidepsin (Istodax)HDAC• Cutaneous T-cell Iymphoma2009Ruxolitinib (Jakafi)JAK1/2• Cutaneous T-cell Iymphoma2014Sonidegib (Odomzo)Smoothened(SMO)• Basal cell carcinoma2015Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAF• Polycythemiavera2015Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAF• Renal cell carcinoma2013Tofacitinib (Xeljanz)MTOR• Renal cell carcinoma2013Trametnib (Mekinist)MEK• Melanoma (with BRAF V600 mutation)2014Venetoclax (Venclexta)BRAF• Melanoma (with BRAF V600 mutation)2014Venetoclax (Venclexta)BCL2• Chronic (hymphocytic leukemia (with 17p deletion)2014Vismodegib (Erivedge)PTCH, Smoothened• Basal cell carcinoma2015Vismodegib (Erivedge)PTCH, Smoothened• Basal cell carcinoma2015Vismodegib (Erivedge)PTCH, Smoothened• Basal cell carcinoma2014Vismodegib (Erivedge)PTCH, Smoothened• Basal cell carcinoma2015Vismodegib (Erivedge)PTCH, Smoothened• Bas	Pazopanib (Votrient)	VEGFR, PDGFR, KIT	•	Soft tissue sarcoma	2012
Poliadilio (clusig)ABL, POPKL ² , PLIS, VEOPKLAcute lymphoblastic leukemia (Philadelphia chromosome positive)2012Regorafenib (Stivarga) Colorectal cancerColorectal cancer2013Romidepsin (Istodax) PomphoranHDACColorectal cancer2013Ruxolitinib (Jakafi) Sonidegib (Odomzo)JAK1/2Cutaneous T-cell lymphoma2011Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Temsirolimus (Torisel)mTORRenal cell carcinoma2013Trametinib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2012Vandtahib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Melanoma (with BRAF V600 mutation)2014Venetoclax (Venclexta)BAFMelanoma (with BRAF V600 mutation)2014Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2015Venetoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2016Vismodegib (Erivedge)PTGF, VEGFA/BCutaneous T-cell lymphoma2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2016Vorinostat (Zolinza)PIGF, VEGFA/BCutaneous T-cell lymphoma2016Vorinostat (Zolinza)PIGF, VEGFA/BCutaneous T-cell lymphoma2016	Denotinih (Jaluaia)	ADI ECEDI 2 ELT2 VECED2	•	Chronic myelogenous leukemia	2012
Regorafenib (Stivarga) Romidepsin (Istodax)KIT, PDGFRβ, RAF, RET, VEGFR1/2/3• Colorectal cancer2012Romidepsin (Istodax) HDACGastrointestinal stromal tumors2013Ruxolitinib (Jakafi) Akuf1/2Cutaneous T-cell lymphoma2001Ruxolitinib (Jakafi) JAK1/2Myelofibrosis2011Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2015Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFHepatocellular carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Termsirolimus (Torisel)mTORRenal cell carcinoma2013Trametinib (Meinist)MEKMelanoma (with BRAF V600 mutation)2014Vandetanib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Medullary thyroid cancer2013Venotoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2014Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2015Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2017Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2011Vorinostat (Zolinza)BCL2Chronic lymphocytic leukemia (with 17p deletion)2016Vorinostat (Zolinza)PIGF, VEGFA/BColorectal cancer2012	Foliatilito (tetusig)	ABL, FOFRI-5, FL15, VEOFR2	•	Acute lymphoblastic leukemia (Philadelphia chromosome positive)	2012
Romidepsin (Istodax) HDAC 2013 Ruxolitinib (Jakafi) HDAC 2009 Ruxolitinib (Jakafi) JAK1/2 Myelofibrosis 2011 Sonidegib (Odonzo) Smoothened(SMO) Basal cell carcinoma 2013 Sorafenib (Nexavar) VEGFR, PDGFR, KIT, RAF Renal cell carcinoma 2013 Temsirolimus (Torisel) mTOR Renal cell carcinoma 2013 Tofacitinib (Xeljanz) JAK3 Renal cell carcinoma 2013 Trametinib (Meknist) MEK Melanoma (with BRAF V600 mutation) 2013 Ventrafenib (Zelboraf) BRAF Melanoma (with BRAF V600 mutation) 2014 Ventrafenib (Zelboraf) BCL2 Chronic lymphocytic leukemia (with 17p deletion) 2011 Vismodegib (Erivedge) PTCH, Smoothened Basal cell carcinoma 2013 Vorinostat (Zolinza) BCL2 Chronic lymphocytic leukemia (with 17p deletion) 2011 Venetoclax (Venclexta) BCL2 Chronic lymphocytic leukemia (with 17p deletion) 2016 Vorinostat (Zolinza) PICF, VEGFA/B Colorectal cancer 2012	Regorafenib (Stivarga)	KIT DOCEDS DAE DET VEGED1/2/2	•	Colorectal cancer	2012
Romidepsin (Istodax)HDACCutaneous T-cell lymphoma2009Ruxolitinib (Jakafi)JAK1/2Peripheral T-cell lymphoma2011Ruxolitinib (Jakafi)JAK1/2Myelofibrosis2011Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2005Temsirolimus (Torisel)mTORRenal cell carcinoma2007Tofacitinib (Xeljanz)JAK3Renal cell carcinoma2011Vandetanib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Medullary thyroid cancer2011Vemurafenib (Zelboraf)BRAFMelanoma (with BRAF V600 mutation)2011Vismodgib (Erivedge)PTCH, Smoothened8asal cell carcinoma2011Vismodgib (Erivedge)PTCH, Smoothened6012011Vismodgib (Erivedge)PTCH, Smoothened6012012Vorinostat (Zolinza)HDACCutaneous T-cell lymphoma2012Vorinostat (Zolinza)PIGF, VEGFA/B600 corectal cancer2011Vismolegib (Erivedge)PTCH, Smoothened20122012Vorinostat (Zolinza)HDACCutaneous T-cell lymphoma2012Vorinostat (Zolinza)PIGF, VEGFA/B600 corectal cancer2012		KII, I DOI KP, KAI, KEI, VEOI KI/2/5	•	Gastrointestinal stromal tumors	2013
Ruxolitinib (Jakafi)JAK1/2Peripheral T-cell lymphoma2011Ruxolitinib (Jakafi)JAK1/2Myelofibrosis2011Sonidegib (Odomzo)Smoothened(SMO)Basal cell carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFHepatocellular carcinoma2013Sorafenib (Nexavar)VEGFR, PDGFR, KIT, RAFRenal cell carcinoma2013Temsirolimus (Torisel)mTORRenal cell carcinoma2005Trametinib (Xeljanz)JAK3Rheumatoid arthritis2012Trametinib (Mekinist)MEKMelanoma (with BRAF V600 mutation)2014Vandetanib (Caprelsa)EGFR (HER1/ERBB1), RET, VEGFR2Medullary thyroid cancer2011Venurafenib (Zelboraf)BRAFMelanoma (with BRAF V600 mutation)2011Ventoclax (Venclexta)BCL2Chronic lymphocytic leukemia (with 17p deletion)2016Vismodegib (Erivedge)PTCH, SmoothenedBasal cell carcinoma2012Vorinostat (Zolinza)HDACCutaneous T-cell lymphoma2012Vorinostat (Zolinza)PIGF, VEGFA/BColorectal cancer2012	Romidepsin (Istodax)	HDAC	•	Cutaneous T-cell lymphoma	2009
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With more than 60% of cancer deaths occurring in low and middle income countries, newer approaches are urgently warranted to identify and develop cost effective drugs. Future studies on small molecule cancer drugs should also focus on alternative strategies so as to develop newer drugs targeting novel pathways while striving to improve the efficacy of currently marketed drugs.

Gene Therapy

Gene therapy implies any procedure intended to treat or alleviate a disease by genetically modifying the cell of a patient either by blocking the expression of the oncogene or by replacing the missing or defective tumor suppressor gene⁽⁶⁾. The material to be transferred into patient cells may be genes, gene segments, or oligonucleotides. Gene therapy can be broadly broken down into three categoriesimmunotherapy, oncolytic virotherapy and gene transfer. It can be in vivo (intradermal injection of a metastatic nodule, or intra-vesical therapy for superficial bladder cancer) or ex vivo (transgene)⁽⁷⁾.

Target cells may be normal cells, cancerous cells, immune mediated cells, or pluripotent stem cells. Once the transgene enters a cancer cell, it may assist in its death or restore normal cellular functions, whereas for normal cells, the transgene can protect them from drug-induced toxicities, or activate an immune cell to get rid of the cancer cell. Gene and vectorbased molecular therapies for cancer comprise a wide range of

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treatment modalities to modify cancer cells, normal cells, and/or a tumor microenvironment $^{(8)}$.

The evolution from minority clone to lethal metastases follows branched evolution. Thus, tumors with high level of intratumor heterogeneity and genomic instability could be more likely to escape from targeted therapies such as gene therapy, unless such a branched evolution is taken into consideration. Hence, gene therapy is somewhat difficult to achieve, with limited success. Presently, most approaches are for monogenic gene therapy, tackling one or more critical gene defects. Selection of the appropriate mode of gene therapy is based on the assessment of the immune status, and determination of the molecular nature of a patient's disease. With the recent increases in knowledge of molecular biology of various medical disorders, a more advanced and comprehensive gene therapy approach will ultimately become available, with anticipated improved results⁽⁹⁾.

Gene transfer available* Phases II,III,IV ** Non-Viral Electroporation, nanoparticles, hydrodynamics, cationic liposomes, symbhetic viruses 18,1,0 Bacterial Escherichia coli, Salmonella, Clostridium, Listeria, CEQ508 6,0,0 viruses Adeno-Associated: Parvovirus 6,0,0 sSDNA viruses Adeno-Associated: Parvovirus 6,0,0 dsDNA viruses Adeno-Associated: Parvovirus 0NYX+015 11,3,0 dsDNA viruses Adenovirusses: Ad5-D24, CG870, Ad5-CD7, Krep, Recombinant H103, Gutless ONYX+015 11,3,0 dsDNA viruses Herpetic viruses: Herpes simplex-1, TVEC 42,10,0 8,2,0 dsRNA viruses Lentiviruses: HIV-1, H1V-2, Simia IV, Feline IV. 8,2,0 dsRNA viruses Lentiviruses: HIV-1, H1V-2, Simia IV, Feline IV. 8,2,0 dsRNA viruses Recoviruses 9,1,0 Immunondulation 11,3,0 11,3,0 Active immunotherapy Single Tumor cell surface antigen vaccine 41,3,0 Recombinant fow Jox virus, Combination (TRICOM) (Prostvac-VF vaccine). 219,29,2 Passive immunotherapy Antibodies against: Rituximab CD20 Protein on Jymphoma cells Rituximab CD20 Protein on Jymphoma cells Rituximab CD20 Protein on Jymphoma cells Brentuximab <t< th=""><th>Predominant action</th><th>Examples</th><th>Commercially</th><th>Clinical trials,</th></t<>	Predominant action	Examples	Commercially	Clinical trials,
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Table 4 List of GeneTherapies Under Evolution

*Commercially approved medications by FDA US as of July 1, 2014. ONYX-015 was previously approved by FDA China. **Clinical trials: Number of active clinical trials on gene therapy for cancer (Phases-II, -III, and -IV) as of July 1, 2014 (www.clinicaltrials.gov). Gene transfer is mediated by vectors (viral or bacterial), physical (gene gun, ultrasound, gene vaccination, electroporation) & chemical methods (cationic liposomes & synthetic viruses)⁽⁹⁾.

Immunotherapy in cancer can be classified into four major categories⁽¹⁰⁾. Active immunotherapy includes strategies that directly sensitize the host immune system to tumor-specific antigens, exemplified as cancer vaccines. Passive immunotherapy utilizes humanized or chimeric antibodies to specifically target tumor antigens without direct activation of the immune system. Adaptive immuno-therapy utilizes patients' immune cells, whether T-cells or dendritic cells, stimulated or manipulated ex vivo, then in-fused back, to better react against tumor antigens. Immune enhancement therapy aims to augment co-stimulatory molecules or block inhibitory molecules. Immune-based therapy may include one or more of the above approaches, either as distinct immunotherapy treatment, or in combination with other modalities of cancer therapy. This can be achieved by-

- 1. Autologous stimulated T-lymphocytes
- 2. Autologous activated T-lymphocytese.g.sipuleucel T
- 3. Genetically modified activated T-lymphocytes
- 4. Chimeric antigen receptor integrated into T-lymphocytes
- 5. Genetically modified dendritic cells
- 6. Genetically modified tumor cell vaccine
- 7. Single-antigen plasmid-based vaccine

Oncolytic viruses are therapeutically useful anticancer viruses that will selectively infect and damage cancerous tissues without causing harm to normal tissues.

Each virus has a specific cellular tropism that determines which tissues are preferentially infected, and hence, what disease is caused. Rabies virus, for example, damages neurons, hepatitis B virus damages hepatocytes, HIV damages helper T lymphocytes and influenza virus damages airway epithelium. Many, if not most, naturally occurring viruses have a preferential, although nonexclusive, tropism for tumors and tumor cells. This probably has more to do with tumor biology than with virus biology since most tumors have evolved not only to avoid immune detection or destruction, but also to resist apoptosis and translational suppression, which are the key responses used by normal cells to limit a virus infection. Oncolytic viruses can kill infected cancer cells in many different ways, ranging from direct virus-mediated cytotoxicity through a variety of cytotoxic immune effector mechanisms.

Gene Therapy Implementation

Once genetic materials are transferred into target cells and incorporated into nuclear genetic DNA, they may induce silencing, down-regulation, modification, or re-pair of the target cell genes. Depending on the intensity of the gene expression, it may lead to cell death and tumor necrosis (as with the suicide gene), or impaired cell growth with tumor regression (as with the silencing gene). Modification of the gene may improve the response from subsequent cancer therapy, such as chemotherapy, immunotherapy, or radiation. Repair of the target gene may help in preventing subsequent malignancy or cancer-related complications such as thrombosis. They may also be helpful in the future by preventing hereditary cancer syndromes.

CONCLUSION

Although there as been an explosion in the armamentarium against cancer as far as targeted therapy in concerned, we need to further intensify our efforts as the era of 'personalised medicine' dawns on us and the concept of quality of life becomes more relevant in a developing country like ours.

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