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Supplementary information

Trends in oncology drug innovation in China

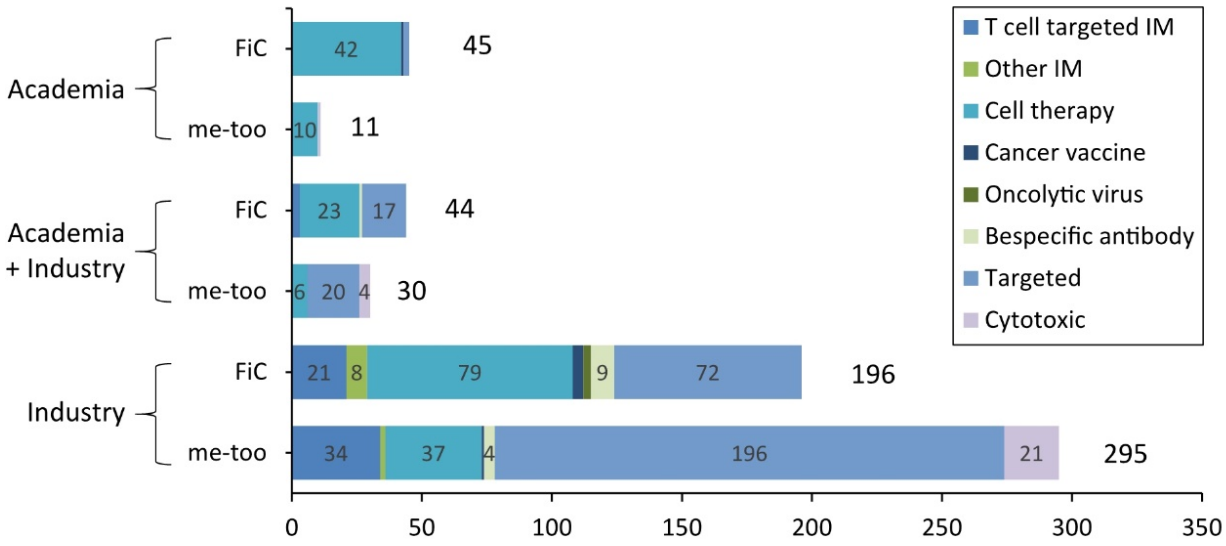
In the format provided by the authors

Data and analysis

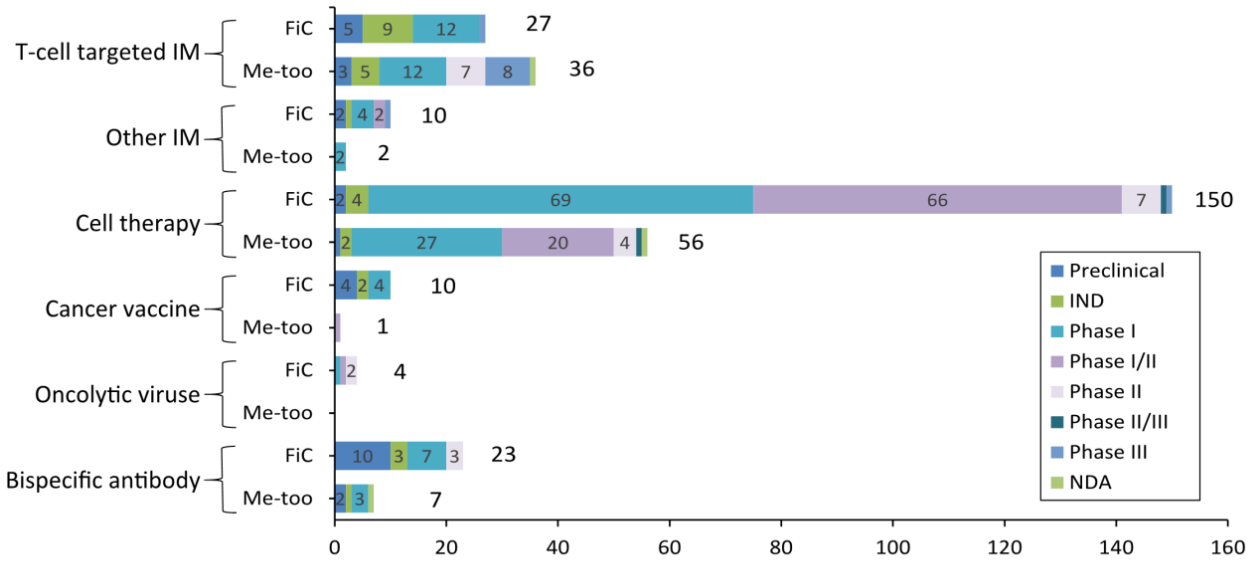
The data on China's domestic novel anticancer pipelines were collected from the Pharmcube database (one of the most authoritative platforms of drug information in China), curated from over 57 sources, including Chinese NMPA's Registration and Information Disclosure Platform for Drug Clinical Studies, Chinese Clinical Trial Register (ChiCTR), ClinicalTrials.gov clinical trial registries, scientific conferences, company press releases, published reports, investor presentations, and other sources. Drugs were included in our analysis with the following eligibility criteria: 1) investigational therapeutic agents for treating patients with cancer, excluding generic drugs or biosimilars; 2) were discovered *de novo* in China, or in-licensed to China; 3) had entered clinical development phase in China or any other countries; and 4) not yet received marketing authorization in China at the cut-off point of January, 2020. The current landscape of anticancer treatments has not changed much in 2020 owing to clinical trial disruption by COVID-19. Data were manually verified and further categorized by Tsinghua Clinical Research Institute (TCRI) and Pharmcube with parameters of drug target, drug type, innovation type, development stage in China and abroad, indications, and location of origin. Some product information might not be publicly disclosed, which might skew the classification of individual products. The total of 821 drug candidates included 18 agents for which development no longer seems to be active; however, the presence or not of these agents does not affect the trends discussed in the article.

With regard to drug type, cancer therapies were classified into cytotoxic, targeted, or immuno-oncology (IO) therapy based on the different mechanisms of action (MoA). "Others" indicated targets and MoA that were not disclosed or could not be classified into the above groups. Furthermore, IO therapies were sub-grouped into six categories[1]: 1) T cell-targeted immunomodulators, 2) other immunomodulators 3) cell therapies, 4) cancer vaccines, 5) oncolytic virus, 6) bispecific antibodies (T-cell-oriented). Innovation type included two groups: first-in-class and me-too, according to their targets and MoA. Products with the same targets and similar mechanisms of action to already-approved drug classes were defined as me-too, while first-in-class denoted the novel targets (targets for which there are not yet approved drugs in any drug classes) or novel MoA regardless of indications. "Others" included agents which were unamenable to classification into the above two categories owing to lack of adequate information. The origins of drugs were divided into two types: discovered in-house in China or in-licensed to China.

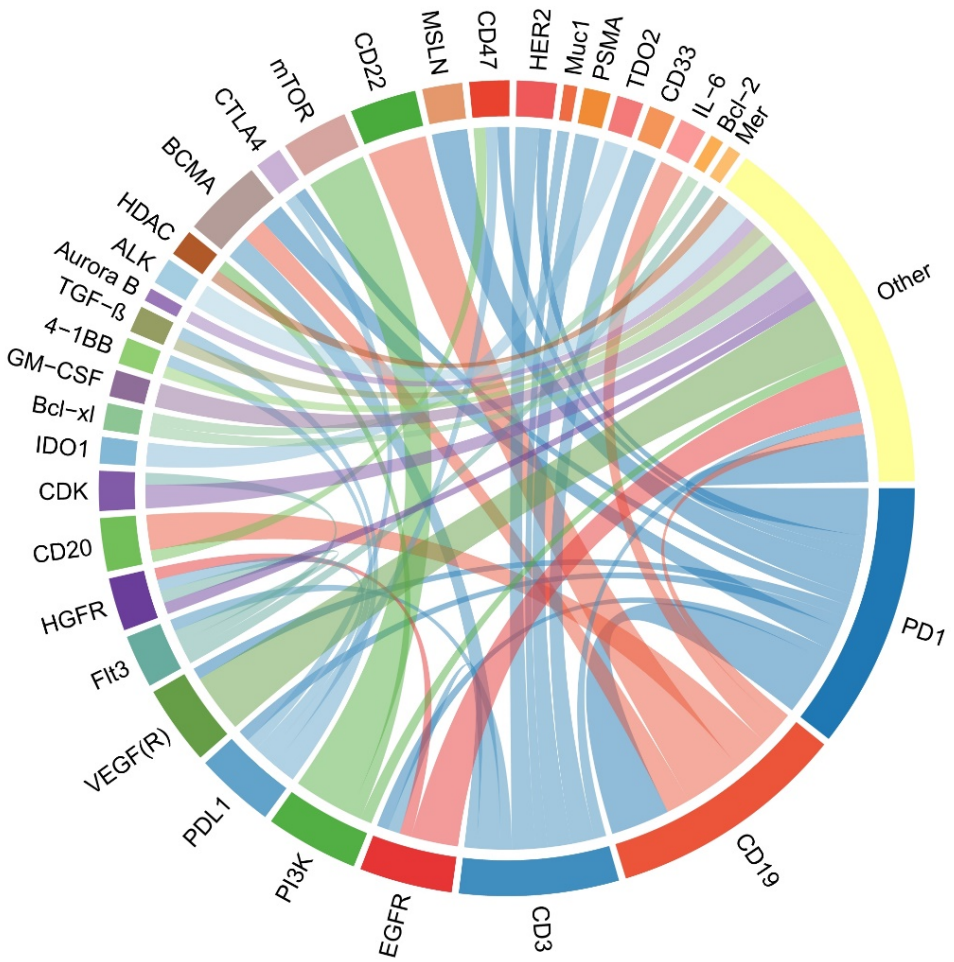
1. Tang, J., Shalabi, A. & Hubbard-Lucey, V. M. Comprehensive analysis of the clinical immuno-oncology landscape. *Ann Oncol* **29**, 84-91, doi:10.1093/annonc/mdx755 (2018).



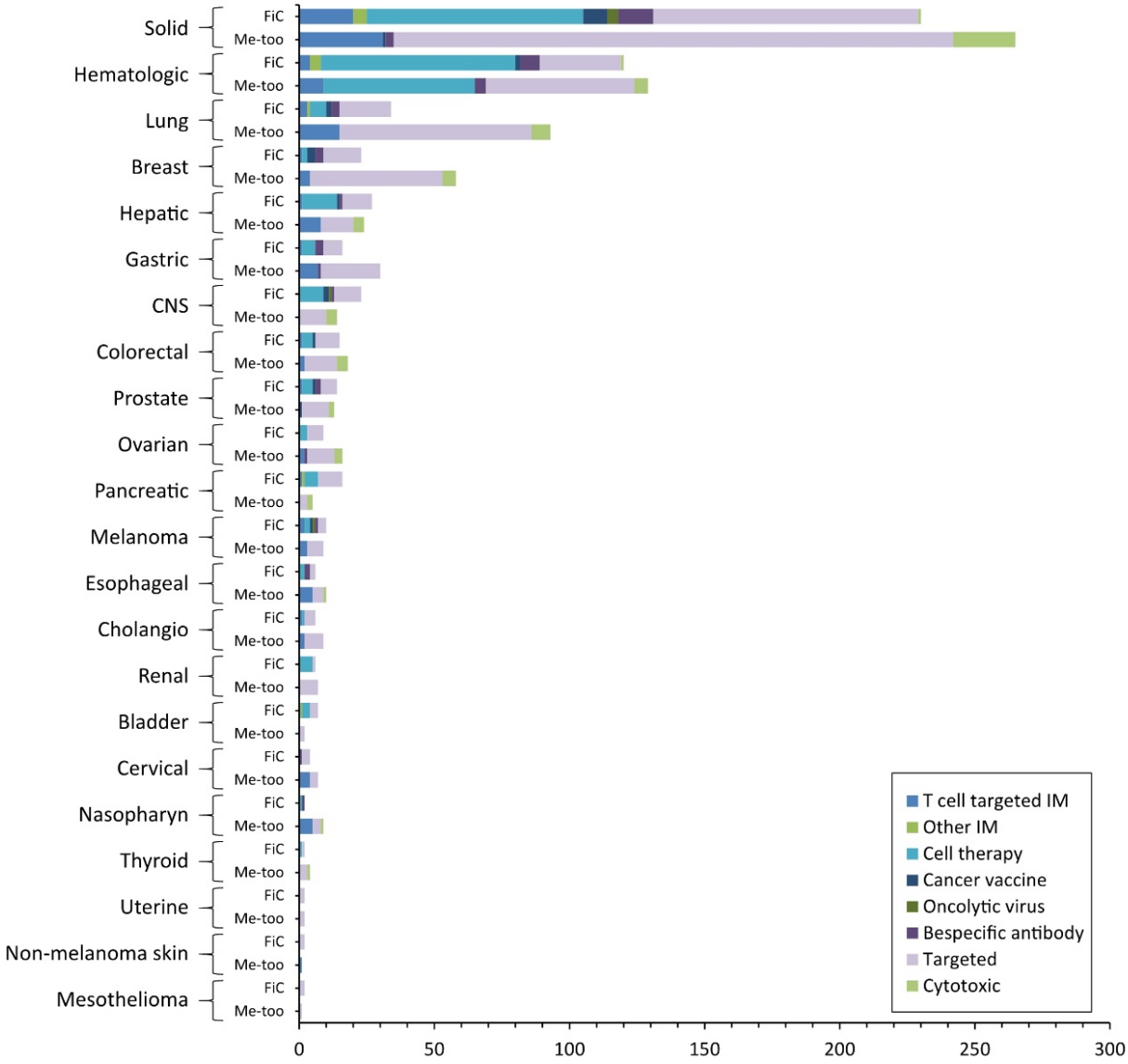
Supplementary Figure 1 | In-house anticancer agents discovered by academia, industry or in collaboration (academia + industry). FiC, first-in-class; IM, immunomodulators.



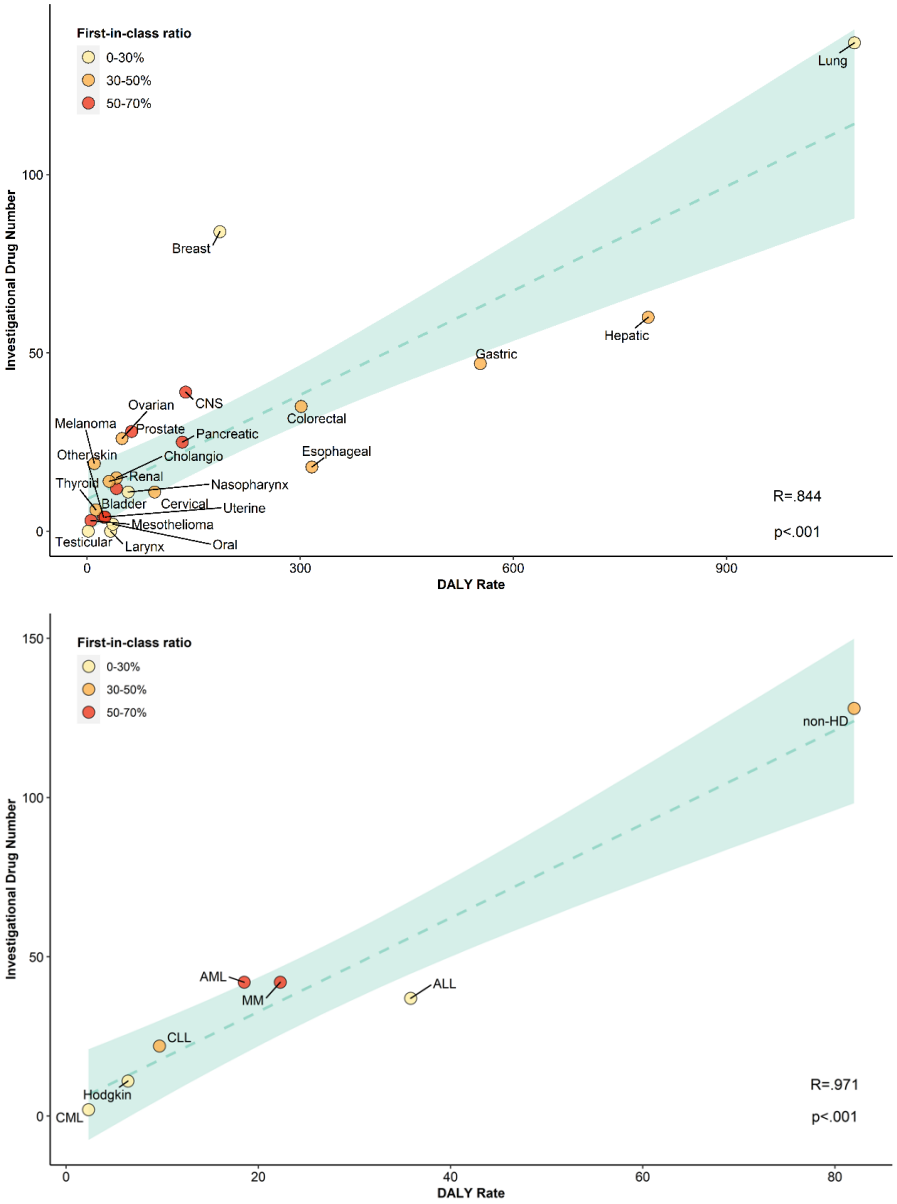
Supplementary Figure 2 | Overview of 326 IO investigational agents by drug class and innovation type. 11 IO products unamenable to classification were excluded, given the lack of adequate information. FiC, first-in-class; IM, immunomodulators.



Supplementary Figure 3 | Target combinations for first-in-class multi-target agents. For drugs with three targets, two targets are listed together and separated by a "|" symbol.



Supplementary Figure 4 | Overview of investigational cancer therapies by different cancer types. FiC, first-in-class; IM, immunomodulators.



Supplementary Figure 5 | Association of the number of investigational new drugs with disability-adjusted life years (DALY) across 23 solid tumours (A) and seven haematological cancers (B). A higher investigational agent number was generally associated with a higher DALY rate. DALY rate indicates the DALY per 100,000 population in China for individual cancer types, calculated using data from the Global Burden of Disease (GBD) 2017 database (http://ghdx.healthdata.org/gbd-results-tool). The colour indicates the proportion of first-in-class candidates for each cancer type. The dashed line with shadow represents the 95% confidence interval of the linear fit. Pearson coefficient (R) and p-value are shown on the lower right corner. CNS, brain and nervous system cancer; oral, lip and oral cavity cancer; other skin, non-melanoma skin cancer; ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; CLL, chronic lymphoid leukemia; CML, chronic myeloid leukemia; MM, multiple myeloma; non-HD, Non-Hodgkin lymphoma.

Supplementary Table 1 | Target summary of first-in-class and me-too agents

First-in-class agents					
T cell-targeted IM	**27**	PD1|MSLN|CTLA4	1	vimentin	1
PD(L)1	4	CXCR5|EGFR	1	procaspase 3	1
TIM3	3	CD7	1	p53	1
LAG3	3	MG7-Ag	1	ARK5|CDK4|CDK6	1
IDO1|TDO2	2	ROR2	1	Bcl-2	1
TIGIT	2	Axl	1	ERα	1
4-1BB	2	syndecan-1	1	MST1R|HGFR, c-Met	1
OX40	2	EBV	1	EZH2	1
IDO1	2	FUT3, Lewis Y	1	Chk1	1
BTLA	1	BSG	1	FAK	1
GM-CSF|CD80	1	FRα	1	STAT3	1
CTLA4	1	**Cancer vaccine**	**10**	FAS	1
CD276	1	NY-ESO-1	2	uPA	1
4-1BB|FAP	1	EGFR	2	FasL	1
MHC class II	1	GM-CSF|CD40L, CD154	1	MDM2	1
CD40	1	HER2	1	FGFR	1
Other IM	**10**	survivin	1	CDK9|CDK7	1
IL-15R	2	VEGF(R)	1	Flt3|Bcr-Abl|EGFR	1
CD47	2	Muc1	1	PAK4|NAMPT	1
Muc1	1	HER3	1	Flt3|CDK	1
MSLN	1	**Oncolytic virus**	**4**	PLK1|PI3K	1
CD73	1	CSF-2R, CD116	2	Flt3|FGFR	1
CD22	1	CD|UPRT	1	PYK2|FAK|ALK	1
IL-15	1	CD116	1	Flt3|Mer	1
IL-15/IL-15R	1	**Bispecific Antibody**	**23**	TK	1
Cell therapy	**150**	HER2|CD3	2	GJA1	1
BCMA	14	CD33|CD3	2	Trk|VEGFR|Axl|HGFR|Mer|RET|DDR	1
PD(L)1	8	BCMA|CD3	2	BRD4	1
CD22	8	PSMA|CD3	2	VEGFR|PDGFR|CSF-1R|Aurora B	1
IL-3Rα, CD123	7	PD1|HER2	1	HDAC|PI3K	1
NA	7	PDL1|CD47	1	CD43	1
Muc1	7	PD1|PDL1	1	BSG	1
GPC3	6	CD20|CD47	1	MetAP2	1
MSLN	5	CD3|Flt3	1	CD	1
HER2	5	DLL3|CD3	1	CDK9	1
CD19|CD22	5	PD1|LAG3	1	CD19	1
EGFR	5	CD3|EGFRvIII	1	opioid receptor	1
PD1|CD19	5	PD1|VEGF-A	1	HGFR, c-Met|EGFR	1
CD33	5	PDL1|TGF-β	1	PAI-1	1
CD20	4	PDL1|CTLA4	1	αvβ3|αvβ5 integrin	1
CD19	3	4-1BB|PDL1	1	CEA	1
CD30	3	PD1|CTLA4	1	A3R	1
CD20|CD19	3	Muc1|CD3	1	PLK1	1
disialoganglioside GD2	3	PD1|CD47	1	Aurora A|Aurora B	1
PD1|MSLN	3	**Targeted**	**134**	PORCN	1
PSMA	3	NA	8	IFNγ	1
CEA	2	TRAILR	5	CLDN18.2	1
IL-6|CD19	2	PI3K|mTOR	5	IGF-1R	1
EpCAM	2	Akt	4	ROS1|FAK|ALK	1
BCMA|PD1	2	HER2	4	IL-7R	1
BCMA|CD19	2	MAPK	3	COX-2|TGF-β1	1
CLDN18.2	2	ALK	3	IRE1	1
AFP	2	TACSTD2, TROP2	3	TLR8	1

PD1|CTLA4|EGFR	1	EGFR	3	JAK	1
SLAMF7, CS1	1	IAP	3	Bcl-xl|Bcl-2	1
PD1|Muc1|CTLA4	1	BET	2	KRAS G12C	1
gp100	1	GnRHR	2	TrxR1	1
NY-ESO-1	1	PKCβ	2	KSP	1
CD19|HPK1	1	endostatin	2	VEGFR|FGFR1|CSF-1R	1
EphA2	1	mTOR	2	KSP|VEGF	1
CD276	1	HGFR, c-Met	2	VEGFR2|CSF-1R|FGFR	1
ROBO1	1	CD20	2	LSD1	1
HGFR, c-Met|PDL1	1	DR5	2	Bcl-xl|Bcl-2|Mcl-1	1
TSHR	1	PTPN11, SHP2	2	CD30	1
Hsp70	1	EP4	2	Hsp90	1
CD38	1	TNFR	2	**Cytotoxic**	**1**
IL-12|EGFR	1	Mcl-1	2	**HDAC|DNA**	**1**
PD1|EGFR	1	HER3	2		
CLL-1|IL-3Rα, CD123	1	HPV	2		
Me-too agents					
T cell-targeted IM	**36**	ROS1|ALK	4	Hedgehog signaling pathway|mTOR	1
PD(L)1	32	VEGFR2|HGFR, c-Met	4	RET	1
CTLA4	3	IDH	4	Trk|ROS1	1
CSF-1R	1	NA	4	Axl|HGFR, c-Met	1
Other IM	**2**	ER	3	Bcl-2	1
CD37	2	SMO	3	Axl|VEGFR2|Flt3	1
Cell therapy	**56**	XPO1	3	VEGFR|RET|EGFR	1
CD19	56	androgen receptor	3	ROS1|HGFR, c-Met|ALK	1
Cancer vaccine	**1**	JAK	3	VEGFR|SCFR, c-Kit|PDGFR	1
GM-CSF|PAP	1	CRBN	3	mTORC	1
Bispecific Antibody	**7**	HGFR, c-Met|ALK	2	VEGFR2|FGFR	1
CD19|CD3	4	A2aR	2	Muc16	1
CD3|EpCAM	3	SCFR, c-Kit|PDGFRα	2	Na/K-ATPase	1
Targeted	**268**	proteasome	2	Src kinase	1
EGFR	44	VEGFR|FGFR	2	Wnt signaling pathway	1
HER2	25	BRAF	2	Syk	1
HER2|EGFR	14	Flt3	2	TLR3	1
VEGF(R)	13	Bcr-Abl	2	RNR	1
CDK	12	TLR7	1	CYP17A1	1
FGFR	10	VEGFR|SCFR, c-Kit|PDGFR|Flt3	1	**Cytotoxic**	**34**
PI3K	9	VEGFR|PDGFR|FGFR	1	MT	10
BTK	9	P-gp	1	Top I	7
HGFR, c-Met	9	VEGFR2|PDGFR|PI3K|EGFR	1	DNA	5
PARP	8	CXCR4	1	NA	4
CD20	7	CD38	1	Top II	3
VEGFR|PDGFR	6	CD52	1	human DNA polymerase	3
HDAC	6	VEGFR|RET|PDGFRβ|Raf kinase	1	TYMS	1
RANKL	5	Raf kinase	1	RNR	1
MEK	5	VEGFR2|FGFR1|PDGFRβ	1		
ALK	5	Cyp	1		

Supplementary Table 2 | Full names and acronyms of targets

Acronym	Full name	Acronym	Full name
A2aR	adenosine A2A receptor	**IL-15R**	interleukin-15 receptor
A3R	adenosine A3 receptor	**IL-3Rα, CD123**	interleukin-3 receptor alpha
AFP	alpha-fetoprotein	**IL-7R**	interleukin-7 receptor
Akt	protein kinase B	**IRE1**	inositol-requiring enzyme 1
ALK	anaplastic lymphoma kinase	**JAK**	Janus kinase
Axl	AXL receptor tyrosine kinase	**KSP**	kinesin spindle protein
Bcl-2	B-cell lymphoma 2	**LAG3**	lymphocyte-activation gene 3
BCMA	B-cell maturation antigen	**LSD1**	lysine-specific demethylase 1
BET	bromo- and extra-terminal domain	**MAPK**	MAP kinase
BRD4	bromodomain-containing protein 4	**Mcl-1**	myeloid leukemia cell differentiation protein
BSG	basigin	**MDM2**	murine double minute 2
BTK	Bruton's tyrosine kinase	**MEK**	MAP kinase kinase
BTLA	B and T lymphocyte attenuator	**MetAP2**	methionine aminopeptidase 2
CD	cytidine deaminase	**MG7-Ag**	MG7-Ag
CD116	GM-CSF receptor	**MSLN**	mesothelin
CDK	cyclin-dependent kinase	**MT**	microtubule
CEA	carcinoembryonic antigen	**mTOR**	mammalian target of rapamycin
Chk1	checkpoint kinase 1	**mTORC**	mammalian target of rapamycin complex
CLDN18.2	claudin-18.2	**Muc1**	mucin 1
CRBN	cereblon	**Muc16**	mucin 16
CSF-1R	CSF-1 receptor	**Na/K-ATPase**	sodium-potassium adenosine triphosphatase
CTLA4	cytotoxic T-lymphocyte-associated protein 4	**P-gp**	P-glycoprotein
CXCR4	CXC chemokine receptor 4	**PAI-1**	plasminogen activator inhibitor 1
Cyp	cyclophilin	**PARP**	poly ADP ribose polymerase
CYP17A1	cytochrome P450 17A1	**PD(L)1**	programmed death-(ligand) 1
DR5	death receptor 5	**PI3K**	phosphoinositide 3-kinase
EBV	Epstein-Barr virus	**PKCβ**	protein kinase C beta
EGFR	epidermal growth factor receptor	**PLK1**	polo-like kinase 1
EP4	PGE2 receptor 4	**PORCN**	porcupine homolog
EpCAM	epithelial cell adhesion molecule	**PSMA**	prostate-specific membrane antigen
EphA2	ephrin receptor A2	**PTPN11**	tyrosine-protein phosphatase non-receptor type 11
ER	estrogen receptor	**RANKL**	receptor activator of nuclear factor kappa-B ligand
EZH2	enhancer of zeste homolog 2	**RNR**	ribonucleotide reductase
FAK	focal adhesion kinase	**ROBO1**	roundabout homolog 1
FAS	fatty acid synthase	**ROR2**	receptor tyrosine kinase-like orphan receptor 2
FasL	Fas ligand	**SLAMF7**	SLAM family member 7
FGFR	fibroblast growth factor receptor	**SMO**	smoothened
Flt3	Fms-like tyrosine kinase 3	**STAT3**	signal transducer and activator of transcription 3
FRα	folate receptor alpha	**Syk**	spleen tyrosine kinase

FUT3	fucosyltransferase III	**TACSTD2**	tumor-associated calcium signal transducer 2
GJA1	gap junction α1	**TIGIT**	T cell immunoreceptor with Ig and ITIM domains
GnRHR	GnRH receptor	**TIM3**	T-cell immunoglobulin and mucin domain 3
gp100	glycoprotein 100	**TK**	thymidine kinase
GPC3	glypican-3	**TLR3**	Toll-like receptor 3
HDAC	histone deacetylase 2|histone deacetylase 1	**TLR7**	Toll-like receptor 7
HER2	human epidermal growth factor receptor 2	**TLR8**	Toll-like receptor 8
HER3	human epidermal growth factor receptor 3	**TNFR**	tumor necrosis factor receptor
HGFR	hepatocyte growth factor receptor	**Top I**	topoisomerase I
HPV	human papillomavirus	**Top II**	topoisomerase II
Hsp70	heat shock protein 70	**TRAILR**	TRAIL receptor
Hsp90	heat shock protein 90	**TrxR1**	thioredoxin reductase 1
IAP	inhibitor of apoptosis protein	**TSHR**	TSH receptor
IDH	isocitrate dehydrogenase	**TYMS**	thymidylate synthase
IDO1	indoleamine 2,3-dioxygenase	**uPA**	urokinase
IFNγ	interferon γ	**VEGF(R)**	vascular endothelial growth factor (receptor)
IGF-1R	IGF-1 receptor	**XPO1**	exportin 1
IL-15	interleukin 15		