

In the format provided by the authors and unedited.

Harnessing innate immunity in cancer therapy

Olivier Demaria¹, Stéphanie Cornen¹, Marc Daëron^{2,3}, Yannis Morel¹, Ruslan Medzhitov⁴ & Eric Vivier^{1,2,5*}

¹Innate Pharma, Marseille, France. ²Aix Marseille Université, INSERM, CNRS, Centre d'Immunologie de Marseille-Luminy, Marseille, France. ³Institut Pasteur, Paris, France. ⁴Howard Hughes Medical Institute and Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA. ⁵Service d'Immunologie, Marseille Immunopole, Hôpital de la Timone, Assistance Publique-Hôpitaux de Marseille, Marseille, France. *e-mail: vivier@ciml.univ-mrs.fr

Supplementary table 1. Current clinical landscape of drugs targeting innate immunity

A selection of active clinical programs targeting innate immunity in cancer therapy is presented. The table is organized according to four modes of action: A) Capitalizing on antimicrobial immunity for tumor control; B) Induction and amplification of the innate immune response; C) Promotion of the effector responses of innate immunity; D) Relieving immune suppression at the tumor bed. Abbreviations: A, approved; 2019, IND planned in 2019, * see box3; [§] programs stopped in phase 3 but still active in phase 1 and 2 trials.

Target	Multispecific	Drug	Clinical trial active phase in oncology	Developer	Format
A. Capitalizing on antimicrobial immunity for tumor control					
TLR7	TLR7x8	Imiquimod	A	3M Pharmaceuticals	Small molecule
		Resiquimod	A	Spirig Pharma, Galderma	Small molecule
		NKTR-262	1,2	Nektar Therapeutics	Small molecule
	HER2xTLR7	LHC165	1	Novartis	Small molecule
		NJH395	1	Novartis	HER2 targeting antibody adjuvant conjugate
		DSP-0509	1	Boston Biomedical	Small molecule
TLR9		IMO-2125 /Tiltsotolimod	3	Idera Pharmaceuticals	Small molecule (DNA based)
		MGN1703/Lefitolimod	3	Mologen AG	Small molecule (DNA based)
		SD-101	2	Dynavax	Small molecule (DNA based)
		CMP-001	2	Checkmate Pharmaceuticals	Small molecule (DNA based)
		AST-008	1,2	Excicure	Small molecule (DNA based)
STING		MIW815 /ADU-S100	2	Aduro Biotech, Novartis	Small molecule
		MK-1454	1	Merck	Small molecule
			1	BMS, IFM Therapeutics	Small molecule
TLR4		G100	2	Immune Design	Small molecule (glucopyranosyl lipid A-stable-emulsion)
		GSK1795091	1	GSK	Small molecule
TLR8		VTX-2337/ Motolimod	1,2	Celgene, VentiRx Pharmaceuticals	Small molecule
		DN1508052	1	Shangai Denovo Pharmatech	Small molecule
RIG-I		MK-4621/RGT100	1,2	Merck, Rigontec	Small molecule (ssRNA)
	TLRxRIG-I	CV8102	1,2	CureVac	Small molecule (Synthetic RNA oligonucleotide)
NLRP3		BMS-986299	1	BMS, IFM Therapeutics	NLRP3 agonist
B. Induction and amplification of the immune response					
APC activation, expansion and/or differentiation					
GM-CSF		talimogene laherparepvec	A	Amgen	Engineered oncolytic virus with GM-CSF gene
FLT3L		CDX-301	2	Celldex	Recombinant FLT3L
CD40		APX005M	2	Apexigen	Agonist IgG1 mAb
		Selicrelumab/RG7876	1,2	Roche	Agonist IgG2 mAb
		ABBV-927	1	Abbvie	Agonistic mAb
		ADC-1013/JNJ-64457107	1	Alligator Bioscience, Janssen Research & Development	Agonist IgG1 mAb
	CD40xTAA	CDX-1140	1	Celldex	Agonist IgG2 mAb
		SEA-CD40	1	Seattle Genetics	Non-fucosylated, humanized IgG1 mAb
		ABBV-428	1	Abbvie	Bispecific CD40, TAA
		MEDI5083	1	AstraZeneca	CD40L-Fc fusion protein
		NG350A	1	PsiOxus Therapeutics	Oncolytic adenoviral vector. NG-350A virus bears genes coding for an
					agonist anti-CD40 monoclonal mAb
Costimulatory signals					
4-1BB	Utomilumab	2	MorphoSys, Pfizer	Ligand-blocking IgG2 mAb	
	Urelumab	2	BMS, Ono Pharmaceutical	Non-ligand-blocking IgG4 mAb	
	ADG106	1	Adagene	Ligand-blocking agonistic IgG4 mAb	
	4-1BBLx FAP	CTX-471	1	Compass Therapeutics	Agonistic IgG4 mAb
		RG7827	1	Roche	mAb-like structure with one arm binding to FAP and the other arm carrying the signalling molecule 4-1BBL
	4-1BBxPD-L1	ES101/INBRX-105	1	Elpiscience Biopharmaceuticals, InhibRx	Bispecific 4-1BB x PD-L1
4-1BBxPD-L1	MCLA-145	1	Merus, Incyte	Bispecific 4-1BB x PD-L1	
	4-1BBxHER2	PRS-343	1	Pieris Pharmaceuticals	Bispecific 4-1BB x HER2
OX40	PF-04518600	2	Pfizer	Agonist IgG2 mAb	
	INCAAGN1949	1,2	Agenus, Xoma, Incyte	Agonist IgG1 mAb	
	BMS-986178	1,2	BMS	Agonist IgG1 mAb	
	IBI101	1	Innovent Biologics	Agonist mAb	
	GSK3174998	1	GSK	Agonist IgG1 mAb	
	ABBV-368	1	Abbvie	Agonist IgG1 mAb	
	OX40xCTLA4	ATOR-1015	1	Alligator Bioscience	Bispecific OX40 x CTLA-4
ICOS	Vopratelimab/JTX-2011	2	Jounce Therapeutics	Agonist mAb	
	GSK3359609	2	GSK	Agonist mAb	
	BMS-986226	1,2	BMS	Agonist mAb	
	ICOSxPD-1	XmAb23104	1	Xencor	Bispecific mAb
CD27		Varilumab	2	Celldex	Agonist IgG1 mAb
GITR	INCAAGN1876	1,2	Agenus, Xoma, Incyte	Agonist IgG1 mAb	
	TRX518	1,2	Leap Therapeutics	Agonist aglycosylated IgG1 mAb	
	BMS-986156	1,2	BMS	IgG1 mAb	
	MK-4166	1	Merck	Agonist IgG1 mAb	
	GWN323	1	Novartis	Agonist IgG1 mAb	
	PTZ-522/ASP 1951	1	Astellas Pharma	Tetravalent mAb	
Interferons					
IFN-α2a		Roferon-A	A	Roche	Interferon alfa-2a
IFN-α2b		Intron A	A	Merck	Interferon alfa-2b
Cytokine-mediated effector cell proliferation and activation					
IL-2		Aldesleukine	A	Novartis	Recombinant Human IL-2
		Bempegaldesleukin/NKTR-214	3	Nektar Therapeutics, BMS	CD122-biased PEGylated IL-2
	IL-2xfibronectin + TNFxfibronectin	Daromun	3	Philogen	Combination of the immunocytokines L19IL2 (Darleukin) and L19TNF (Fibromun)
		RO6874281/RG7461	2	Roche	Engineered IL-2 variant conjugated to anti-FAP mAb
	IL-2xFAP	Darleukin	2	Philogen	Fusion protein consisting of mAb L19 and of human IL-2
	IL-2xfibronectin	Teleukin/F16IL2	1,2	Philogen	Fusion protein consisting of mAb F16 and of human IL-2
	IL-2xtenascin-C	THOR-707	1,2	Synthorx	CD122-biased PEGylated IL-2
		ALK4230	1	Alkermes	Engineered fusion protein comprised of a circularly permuted interleukin-2 (IL-2) and IL-2 Receptor (IL-2R) α
IL-10		Pegilodecakin/LY3500518/ AMO010	3	ARMO Biosciences, Eli Lilly and Company	PEGylated recombinant IL-10

IL-15	ALT-803	2	Altor bioscience	IL-15 superagonist complex consisting of an IL-15 mutant (IL-15N72D)
	NIZ985	1	Novartis	bound to an IL-15 receptor α /IgG1 Fc fusion protein
	XmAb24306	2019	Xencor	Recombinant Human NIZ985 ((hetIL-15) (IL15/sIL-15Ra))
	NKTR-255	2019	Nektar Therapeutics	Fusing IL15 with reduced potency/IL15R α and heterodimer Fc Polymer-conjugated human IL-15
IL-12	IT-pIL12-EP	2	OncoSec Medical	Intratumoral plasmid IL-12 electroporation
	IL-12xnecrotic DNA M9241/NHS-IL12	1	Merck	Two IL-12 heterodimers fused to the NHS76 mAb
C. Promotion of the effector responses of innate immunity				
Broad spectrum immune checkpoint inhibitors				
LAG-3	Relatlimab/BMS-986016	2,3	BMS	IgG4 mAb
	MK-4280	2	Merck	IgG4 mAb
	LAG525	2	Novartis	IgG4 mAb
	Eftilagimod alpha/IMP321	2	Immutep	LAG-3Ig fusion protein
	BI 754111	2	Boehringer Ingelheim	IgG4 mAb
	INCAGN02385	1	Agenus, Xoma, Incyte	Fc-engineered IgG1k mAb
	Sym022	1	Symphogen, Servier	Fc-inert human monoclonal mAb
	TSR-033	1	Tesaro, GSK	IgG4 mAb
	REGN3767	1	Regeneron Pharmaceuticals	mAb
	LAG-3xCTLA4	1	Xencor	LAG-3, CTLA-4
	LAG-3xPD-1	1	MacroGenics	IgG4k bispecific DART [®] molecule, to bind PD-1 and LAG-3
	LAG-3xPD-L1	1	F-Star, Merck	Bispecific antagonist simultaneously targeting LAG-3 and PD-L1
NKG2A	Monalizumab	2	AstraZeneca, Innate Pharma	IgG4 mAb
TIGIT	Tiragolumab/RG6058	2	Roche	mAb
	BMS-986207	1,2	BMS, Ono Pharmaceutical	mAb
	AB154	1	Arcus Biosciences	mAb
	OMP-313M32/Etigitimab	1	OncoMed Pharmaceuticals	mAb
	ASP8374	1	Astellas Pharma	mAb
TIM-3	TSR-022	2	Tesaro, GSK	mAb
	MBG453	2	Novartis Pharmaceuticals	mAb
	BMS-986258	1,2	BMS, Five Prime Therapeutics	mAb
	BGB-A425	1,2	BeiGene	IgG1-variant mAb
	Sym023	1	Symphogen, Servier	mAb
	LY3321367	1	Eli Lilly and Company	IgG1 mAb (Fc null)
	INCAGN02390	1	Agenus, Xoma, Incyte	IgG1 mAb (aglycosylated, N297A)
	TIM-3xPD-1	1	Roche	PD1-TIM3 biMAb
	TIM-3xPD-L1	1	Eli Lilly and Company	Bispecific mAb PD-1 x TIM-3
VISTA	VISTAxPD-L1	1	Curis, Aurigene	Small molecule VISTA and PD-L1 antagonist
CD32b	BI-1206	2	BiInvent International	mAb
PVRIG	COM701	1	Compugen	mAb
CD47	Hu5F9-G4	1,2	Forty Seven	IgG4 mAb
	TTI-621	1	Trillium Therapeutics	CD47-binding domain of human SIRP α linked to the Fc region of human IgG1
	IBI188	1	Innovent Biologics	IgG4 mAb
	AO-176	1	Arch Oncology	IgG2 mAb
	TTI-622	1	Trillium Therapeutics	CD47-binding domain of human SIRP α linked to the Fc region of human IgG4
	CC-90002	1	Celgene	mAb
	SRF231	1	Surface Oncology	mAb
	SHR-1603	1	Jiangsu Hengrui Medicine Co	mAb
	CD47xCD19	1	Novimmune,TG Therapeutics	Bispecific CD47 x CD19
	TG-1801	1	ALX Oncology	Fusion protein comprised of an engineered high affinity CD47 binding domain of SIRP α linked to an inactive Fc region
	ALX148	1		
SIRP α	CC-95251	1	Celgene	mAb
	BI 765063	1	Boehringer Ingelheim, OSE Immunotherapeutics	mAb
LILRB2	MK-4830	1	Merck, Agenus	mAb
D. Relieving immune suppression at the tumor bed				
Immunosuppressive factors				
IDO	BMS-986205	3 ^S	BMS	Small molecule
	Epacadostat	3* ^S	Incyte	Small molecule
	Indoximod	2	NewLink Genetics	Small molecule
				Immune modulatory vaccine containing a single IDO-derived peptide sequence
	IO102	1,2	IO Biotech	
	NLG802	1	NewLink Genetics	Small molecule prodrug of indoximod
	LY3381916	1	Eli Lilly and Company	Small molecule
	KHK2455	1	Kyowa Hakko Kirin Pharma	Small molecule
	IDO1xTDO2	1	Shangai Denovo Pharmatech	Small molecule
	TDOxIDO1	1	Hengrui Therapeutics	Small molecule inhibitor
TGF- β	TGF- β xPD-L1	2	Merck, GSK	Bifunctional fusion protein
		2	Eli Lilly and Company	Small molecule inhibitor
	TEW-7197/Vactosertib	1,2	MedPacto	Small molecule inhibitor of TGF- β receptor type 1
	SAR439459	1	Sanofi	mAb
	TGF- β xPD-L1	1	Jiangsu HengRui Medicine	Bispecific Fusion Protein
	SHR-1701	1	Formation Biologics	Small molecule inhibitor isoform-selective TGF- β 1 and- β 3
	AVID200	1		mAb
	NIS793	1	Novartis	
	LY3200882	1	Eli Lilly and Company	Small molecule inhibitor of TGF- β receptor type 1
	PF-06952229	1	Pfizer	Small molecule inhibitor of TGF- β receptor type 1
A2AR	NIR178/PBF-509	2	Novartis, Palobiofarma	Small molecule A2AR antagonist
	CPI-444	2	Corvus Pharmaceuticals	Small molecule A2AR antagonist
	AZD4635	1,2	AstraZeneca, Heptares Therapeutics	Small molecule A2AR antagonist
	EOS100850	1	ITeas Therapeutics	Small molecule A2AR antagonist
	A2ARx A2BR	1	Arcus Biosciences	Small molecule Dual A2AR/A2BR antagonist
				Small molecule Dual Adenosine A2a receptor antagonist /
CD73	A2ARxPDE-10	1	Palobiofarma	Phosphodiesterase 10 inhibitor
	Oleclumab	2	AstraZeneca	mAb
	BMS-986179	1,2	BMS	mAb
	AB680	1	Arcus Biosciences	Small molecule CD73 inhibitor
	CPI-006	1	Corvus Pharmaceuticals	mAb
	NZV930/SRF373	1	Surface Oncology, Novartis	mAb
CD39			I-Mab Biopharma, Traccon Pharmaceuticals	
	TJ004309/TJD5	1		mAb
	TTX-030	1	Abbvie, Tizona Therapeutics	mAb
	IPH5201	2019	AstraZeneca, Innate Pharma	mAb
Arginase	INC8001158/CB-1158	1,2	Calithera Biosciences, Incyte	Small molecule inhibitor
EP4 (PGE2 receptor)	ONO-4578	1	BMS, Ono Pharmaceutical	Small molecule PGE2 receptor 4 (EP 4) antagonist

Suppressive cell recruitment, depletion and polarization				
IL-1 β	Canakinumab	3	Novartis	IgG1 mAb
IL-1 α	Bermekimab	3 ^S	Xbiotech	IgG1 mAb
CCR2/CCR5	BMS-813160	2	BMS	Small molecule dual CCR2/CCR5 chemokine antagonist
STAT3	AZD9150	2	AstraZeneca	Oligonucleotide antisense molecule
PI3K γ	IP1-549	2	Infinity Pharmaceuticals	Small molecule selective PI3K γ inhibitor
CSF-1R	Cabiralizumab/FPA008	2	Five Prime Therapeutics, BMS	mAb
	JNJ-40346527	2	Johnson & Johnson	Small molecule
	AMG820	1,2	Amgen	mAb
	MCS110/lacnotuzumab	1,2	Novartis	mAb
	BLZ945	1,2	Novartis	Small molecule
	IMC-CS4/LY3022855	1	Eli Lilly and Company	IgG1 mAb
	ARRY-382	1	Array BioPharma	Small molecule
CXCR2	AZD5069	1,2	AstraZeneca	Small molecule inhibitor
C5aR1	IPH5401	1	Innate Pharma	IgG1 mAb (Fc silent)
ApoE	RGX-104	1	Rgenix	Small molecule