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REVIEW

Trial Watch—Small molecules targeting the immunological tumor microenvironment for cancer therapy

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ABSTRACT

Progressing malignancies establish robust immunosuppressive networks that operate both systemically and locally. In particular, as tumors escape immunosurveillance, they recruit increasing amounts of myeloid and lymphoid cells that exert pronounced immunosuppressive effects. These cells not only prevent the natural recognition of growing neoplasms by the immune system, but also inhibit anticancer immune responses elicited by chemo-, radio- and immuno therapeutic interventions. Throughout the past decade, multiple strategies have been devised to counteract the accumulation or activation of tumor-infiltrating immunosuppressive cells for therapeutic purposes. Here, we review recent preclinical and clinical advances on the use of small molecules that target the immunological tumor microenvironment for cancer therapy. These agents include inhibitors of indoleamine 2,3-dioxigenase 1 (IDO1), prostaglandin E_2, and specific cytokine receptors, as well as modulators of intratumoral purinergic signaling and arginine metabolism.

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Introduction

Solid neoplastic lesions are not formed by cancer cells only, but contain elevated amounts of non-transformed cells, making up a highly interconnected system that encompasses malignant, endothelial, stromal and immunological components.[1-3] Thus, neoplastic lesions arise and evolve in the context of a physical and functional crosstalk with various populations of non-transformed cells, some of which *de facto* promote tumor progression and resistance to treatment.[4,5] Tumor-infiltrating myeloid and lymphoid cells play a particularly important role in this context.[3,6-11] Accumulating evidence indicates indeed that tumors can become clinically manifest only when the immunological mechanisms that are in place to recognize and eliminate potentially oncogenic cells (which are cumulatively referred to as natural anticancer immunosurveillance) fail.[12-15] Such a failure reflects the accumulation of genetic and/or epigenetic defects that ultimately renders (pre-)malignant cells undetectable by the immune system, or endows them with the capacity to block immune effector functions.[16-18] One of the main strategies whereby cancer cells maintain the immune system at bay consists in the establishment of robust immunosuppressive networks that operate both systemically (*i.e.*, in the circulation and lymphoid organs) and locally (*i.e.*, within the tumor microenvironment).[16,19-23]

Extensive tumor infiltration by immunosuppressive cells (and/or limited infiltration by immune effector cells with antitumor functions) support tumor progression as it inhibits natural immunosurveillance.[20,21] Accordingly, high intratumoral levels of particularly immunosuppressive cells like $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs) and so-called M2 tumor-associated macrophages (TAMs) have been attributed negative prognostic value in patients affected by a wide panel of solid neoplasms.[3,7,24,25] Moreover, the accumulation of immunosuppressive cells, rather than immune effector cells, within the tumor microenvironment limits the clinical benefits provided not only by anticancer immunotherapy, but also by various radio- and chemo therapeutic regimens.[3,7,24-26] Indeed, the long-term efficacy of radio- and chemotherapy appears to rely, at least in part, on the (re-)instatement of

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anticancer immunosurveillance.[27-32] In line with this notion, elevated intratumoral levels of Tregs, M2 TAMs and other immunosuppressive cells have been shown to predict dismal therapeutic outcome in multiple cohorts of individuals bearing solid malignancies.[3,7,24,27] Taken together, these observations provide a strong rationale to the development of clinically implementable strategies aimed at reverting immunosuppression within the tumor microenvironment, a wave of investigation that has been intensively pursued throughout the past decade, both preclinically and clinically.[33,34]

As it stands, a number of approaches is available to counteract immunosuppressive systems established within the tumor microenvironment for therapeutic purposes.[35-38] Schematically, we can classify these strategies into four major (not mutually-exclusive) groups, based on their main mechanism of action: (1) direct immunostimulatory agents (*i.e.*, interventions that mediate immunostimulatory effects by acting on immune effectors); (2) indirect immunostimulatory interventions (*i.e.*, interventions that mediate immunostimulatory effects by operating on immunosuppressive cells); (3) enriching/depleting agents (*i.e.*, interventions that exert immunostimulatory activity by influencing the recruitment of tumor-infiltrating immune cells); and (4) repolarizing interventions (*i.e.*, interventions that exert immunostimulatory activity by converting immunosuppressive cells into immune effectors). Thus, enriching/depleting and repolarizing agents *de facto* alter the relative composition of the tumor infiltrate, whereas immunostimulatory interventions (at least initially) fail to do so, but only alter its activation state.

Prominent examples of direct immunostimulatory agents include Toll-like receptor (TLR) agonists, which potently activate dendritic cells (DCs) and other antigen-presenting cells (APCs) to prime tumor-targeting adaptive immune responses,[34,39,40] immunostimulatory cytokines such as granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-15,[41] as well as a wide panel of monoclonal antibodies (mAbs) that operate as agonists of activatory receptors expressed on $CD8^+$ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, like tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, best known as CD137), TNFRSF4 (best known as OX40), or TNFRSF18 (best known as GITR).[42-45] This said, the molecules that are best known for their direct immunostimulatory effects are so-called "checkpoint blockers," *i.e.*, mAbs that antagonize immunosuppressive receptors expressed by activated CTLs like cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PDCD1, best known as PD-1) or their ligands, like CD274 (best known as PD-L1) and programmed cell death 1 ligand 2 (PDCD1LG2, best known as PD-L2).[36,46,47] No less than three checkpoint blockers are nowadays approved by the US Food and Drug Administration (FDA) and other regulatory agencies worldwide for use in cancer patients, including one CTLA4-specific molecule (ipilimumab) and two PD-1-targeting agents (nivolumab and pembrolizumab).[46-48] Good examples of indirect immunostimulatory agents are provided by mAbs that neutralize potent immunosuppressive cytokines, including transforming growth factor β 1 (TGFB1) and vascular endothelial growth factor A (VEGFA).[44,49,50] Various chemotherapeutic agents, especially when used according to a metronomic schedule, have been shown to promote tumor infiltration by immune effector cells or to limit the recruitment of immunosuppressive cells to the tumor microenvironment.[27,30] For example, this applies to doxorubicin and oxaliplatin, which kill cancer cells in a way that promotes the recruitment of DCs and CTLs coupled to the elicitation of tumor-targeting immune responses,[51,52] as well as to cyclophosphamide and gemcitabine,[53] both of which limit tumor infiltration by Tregs.[54,55] Finally, some agents like IL-21 have been associated with the capacity to promote a functional shift of TAMs from a prominently immunosuppressive (M2) to a mainly immunostimulatory and tumoricidal (M1) state.[56]

Of note, several of these molecules do not operate according to a single mechanism of action, but exert multipronged immunostimulatory effects. For example, cyclophosphamide not only depletes Tregs from the tumor environment, but also resembles doxorubicin and oxaliplatin in their ability to trigger so-called "immunogenic cell death" (ICD), hence promoting tumor infiltration by DCs and CTLs.[52,57-60] Along similar lines, VEGFA-targeting mAbs such as the FDA-approved agent bevacizumab[50] prevent VEGFA-dependent T-cell exhaustion and stimulate the normalization of the tumor vasculature, which favors tumor infiltration by immune effector cells.[49,61]

We have discussed recent progress on tumor-targeting mAbs, immunostimulatory mAbs, immunostimulatory cytokines, TLR agonists, ICD inducers, and their ability to target the immunological tumor microenvironment in recent articles of the Trial Watch series. Here, we present preclinical and clinical advances on small molecules that may be harnessed to boost natural or therapy-elicited immune responses as they act on the tumor infiltrate.

IDO1 inhibitors

IDO1 catalyzes the initial, rate-limiting step of the so-called "kynurenine pathway," the biochemical cascade that transforms the essential amino acid *L*-tryptophan (Trp) into *L*-kynurenine (Kyn).[62-64] Two additional enzymes can catalyze the same reaction in humans, namely, indoleamine 2,3-dioxigenase 2 (IDO2), and tryptophan 2,3-dioxigenase (TDO2).[62,63] Nonetheless, IDO1 plays a quantitatively superior role in this context and initiates the kynurenine pathway in a majority of settings.[62,63] Besides being constitutively expressed by some tissues, IDO1 can be synthesized in an inducible manner by specific subsets of DCs, macrophages and immature monocytes,[65-71] and it was originally viewed as an active component of the innate immune response to microbial stimuli.[72] More recently, however, it turned out that IDO1 has a key function in the establishment and maintenance of peripheral tolerance as it exerts major immunosuppressive effects.[62,63,73] The immunosuppressive activity of IDO1 has first been ascribed to its ability to limit the microenvironmental availability of Trp while favoring the accumulation of Kyn, 3-hydroxykynurenine and 3-hydroxyanthranilic acid.[72,74-76] However, several other, less-direct mechanisms may account for the robust immunosuppressive effects of IDO1-expressing cells.[66,77-86] Irrespective of the precise mechanisms whereby IDO1 mediates

immunosuppressive effects, targeting IDO1 by pharmacological, genetic and immunological means has been associated with therapeutic effects in several distinct rodent models of carcinogenesis, and such effects were invariably accompanied by the (re)elicitation of tumor-targeting immune responses.[87] Today, several pharmacological inhibitors of IDO1 are available, some of which have also entered clinical evaluation.[88] Interestingly, the FDA-approved agent imatinib appears to limit IDO1 expression in the tumor microenvironment as a consequence of KIT inhibition.[89] However, imatinib is currently employed for its ability to directly inhibit oncogenic BCR-ABL1 fusion proteins, KIT and platelet-derived growth factor receptor, β polypeptide (PDGFRB), rather than for its immunostimulatory functions (and hence will not be discussed in further detail here).[90-92] TDO2 inhibitors are also being developed, although for the moment only in preclinical settings.[93,94]

The competitive inhibition of IDO1 (and IDO2) with 1-methyltryptophan (a chiral mixture of 1-methyl-*D*-tryptophan and 1-methyl-*L*-tryptophan) as well as genetic interventions specific for IDO1 reportedly re(activate) therapeutically relevant immune responses in rodent tumor models,[22,87] especially when employed in combination with chemotherapy or checkpoint blockers.[62,95-99] Since *in vivo* 1-methyl-*D*-tryptophan (also known as indoximod or NLG8189) has a superior immunostimulatory activity as compared to its *L*-counterpart,[96,100,101] the former has already entered clinical development.[87] The first results from such a wave of investigation, however, have become available only recently.[102-105] In particular, indoximod was well tolerated in two Phase I trials, one involving 27 patients with metastatic solid tumors, who received indoximod in combination with docetaxel-based chemotherapy,[102] and one enrolling 12 adult subjects with recurrent refractory malignant brain tumors, who were treated with indoximod plus the alkylating agent temozolomide (NCT02052648).[104,106] Preliminary findings from a Phase I/II trial testing indoximod in support of DC-based vaccination targeting tumor protein 53 (TP53, best known as p53) epitopes in 44 subjects with metastatic solid tumors (NCT01042535) have also been released, although the study is still registered as "Active, not recruiting."[105] Of 41 subjects who were evaluable, 37 (90.24%) experienced treatment-related side effects of any degree, while 14 (31.15%) were affected by Grade 3 or higher toxicities. However, 6 weeks after the completion of treatment, no study participants out of 30 who were evaluable in this sense exhibited objective responses (source www.clinicaltrials.gov). Official sources list nine additional studies aimed at assessing the immunostimulatory effects of indoximod in cancer patients. Five of these trials, including NCT01560923 (a Phase II study investigating the clinical profile of indoximod in prostate carcinoma patients receiving cellular immunotherapy with sipuleucel-T),[107] NCT01792050 (a Phase II trial assessing the safety and efficacy of indoximod plus docetaxel-based chemotherapy in women with metastatic breast carcinoma),[108] NCT02073123 (a Phase I/II study testing indoximod combined with ipilimumab in Stage III/IV melanoma patients),[109] NCT02077881 (a Phase I/II trial investigating the clinical profile of indoximod plus gemcitabine- and paclitaxel-based chemotherapy in subjects with metastatic pancreatic carcinoma), and NCT02502708 (a Phase I study assessing the safety and efficacy of indoximod plus temozolomide and radiation therapy in pediatric patients with primary brain tumors) are currently recruiting participants. Moreover, NCT02460367 (a Phase II trial testing indoximod combined with a cancer cell-based vaccine and docetaxel in subjects with advanced, previously treated non-small cell lung carcinoma, NSCLC) is listed as "Not yet recruiting." NCT00739609 (a Phase I study investigating the maximum tolerated dose of indoximod in subjects with relapsed or refractory solid tumors has been terminated owing to lack of enrollment. To the best of our knowledge, the results of NCT00567931 and NCT01191216 (two Phase I trials testing indoximod as standalone immunotherapeutic intervention or combined with docetaxel in patients with unresectable advanced solid tumors or breast carcinoma, respectively)[103] have not yet been released, even though both studies are listed as "Completed" (Table 1) (source www.clinicaltrials.gov).

Similar to indoximod, epacadostat (also known INCB024360) and NLG919 (also known as GDC-0919) efficiently inhibit IDO1 (and less so IDO2), resulting in the restoration of therapeutically relevant anticancer immunity in rodent tumor models.[110-113] Clinical data from a Phase I trial testing the safety, tolerability, pharmacokinetics and pharmacodynamics of standalone epacadostat in subjects with advanced malignancies (NCT01195311) and from a Phase I/II study investigating the clinical profile of epacadostat plus ipilimumab in patients with unresectable or metastatic melanoma (NCT01604889) suggest that this IDO1 inhibitor is relatively well tolerated and exerts clinical activity, at least to some degree.[114-116] Official sources list 12 additional studies aimed at testing the immunostimulatory effects of epacadostat in oncological indications. Eight of these trials, including NCT01961115 (a Phase II study testing epacadostat in support of a multipeptide vaccine in subjects with unresectable or advanced melanoma), NCT02042430 (a trial investigating the safety and efficacy of epacadostat as standalone immunotherapeutic intervention in women with reproductive tract tumors), NCT02118285 (a Phase I study assessing the clinical profile of epacadostat plus adoptively transferred NK cells in patients affected by reproductive tract neoplasms), NCT02166905 (a Phase I/II trial testing epacadostat in combination with a DC-targeted variant of NY-ESO-1 and a TLR3 agonist in women with malignancies of the reproductive system), NCT02178722 (a Phase I/II study investigating the safety and efficacy of epacadostat plus pembrolizumab in subjects with advanced solid tumors), NCT02298153 (a Phase I trial assessing the clinical activity of epacadostat in combination with an experimental checkpoint-blocking mAb in NSCLC patients), NCT02318277 (a Phase I/II study testing epacadostat plus an experimental checkpoint blocker in subjects with advanced solid tumors), and NCT02559492 (a Phase I trial investigating the safety and efficacy of epacadostat combined with a Janus kinase 1 (JAK1) inhibitor in individuals affected by advanced solid tumors) are currently recruiting participants, while NCT02575807 (a Phase II study assessing the therapeutic profile of epacadostat combined with a mesothelin-expressing bacterial vector in women with chemoresistant malignancies of the reproductive tract) is now listed as "Not yet recruiting." NCT01982487 (a Phase I/II trial assessing the ability of epacadostat to boost the efficacy of a NY-ESO-1-targeting recombinant vaccine in women with cancers of the reproductive tract) has been withdrawn prior to enrollment for undisclosed reasons. To the best of our knowledge, the results

Table 1. Clinical trials recently started to assess the safety and efficacy of small molecules targeting the tumor microenvironment for oncological applications*.

Molecule	Indication(s)	Phase	Status	Notes	Ref.
IDO1 inhibitors					
Epacadostat	MDS	II	Completed	As standalone immunotherapeutic agent	NCT01822691
	Melanoma	I/II	Not recruiting	In combination with ipilimumab	NCT01604889
	Melanoma	II	Recruiting	Combined with a peptide-based vaccine	NCT01961115
	NSCLC	I	Recruiting	In combination with atezolizumab	NCT02298153
	RTCs	I	Recruiting	Combined with a adoptively transferred NK cells	NCT02118285
	RTCs	I/II	Withdrawn	Combined with a recombinant vaccine	NCT01982487
	RTCs	I/II	Recruiting	Combined with DC-targeted vaccine and polyI:C	NCT02166905
	RTCs	II	Not yet recruiting	Combined with a mesothelin-expressing bacterial vaccine	NCT02575807
	RTCs	II	Completed	As standalone immunotherapeutic agent	NCT01685255
	RTCs	n.a.	Recruiting	As standalone immunotherapeutic agent	NCT02042430
	Solid tumors	I	Completed	As standalone immunotherapeutic agent	NCT01195311
	Solid tumors	I	Recruiting	Combined with pembrolizumab	NCT02178722
	Solid tumors	I	Recruiting	Combined with a JAK1 inhibitor	NCT02559492
	Solid tumors	I/II	Recruiting	In combination with MEDI4736	NCT02318277
Indoximod	Brain tumors	I	Recruiting	Combined with temozolomide and radiotherapy	NCT02502708
	Brain tumors	I/II	Recruiting	Combined with temozolomide and bevacizumab	NCT02052648
	Breast carcinoma	I	Completed	Combined with docetaxel-based chemotherapy	NCT01191216
	Breast carcinoma	II	Recruiting	Combined with paclitaxel or docetaxel	NCT01792050
	Melanoma	I/II	Recruiting	In combination with ipilimumab	NCT02073123
	NSCLC	I	Not yet recruiting	Combined with a cancer cell-based vaccine and docetaxel	NCT02460367
	Pancreatic carcinoma	I/II	Recruiting	Combined with gemciteeeeeeeeeeeeeeeeeeeabine and paclitaxel	NCT02077881
	Prostate carcinoma	II	Recruiting	Combined with sipuleucel-T	NCT01560923
	Solid tumors	I	Terminated	As standalone immunotherapeutic agent	NCT00739609
	Solid tumors	I	Completed	As standalone immunotherapeutic agent	NCT00567931
	Solid tumors	I/II	Active, not recruiting	Combined with DC-based vaccination	NCT01042535
NLG919	Solid tumors	I	Recruiting	As standalone immunotherapeutic agent	NCT02048709
	Solid tumors	I	Recruiting	In combination with atezolizumab	NCT02471846
PGE_2 inhibitors					
Aspirin	Breast carcinoma	I	Unknown	Combined with neoadjuvant metronomic cyclophosphamide and methotrexate	NCT01612247
	Ovarian carcinoma	I	Completed	Combined with multimodal immunotherapy	NCT01312376
	RTCs	0	Recruiting	Combined with DC-based vaccination	NCT01132014
Celecoxib	CRC	n.a.	Withdrawn	As standalone immunotherapeutic agent	NCT01284504
	CRC	I/II	Recruiting	Combined with IFN-α2b and polyI:C	NCT01545141
	CRC	II	Not yet recruiting	Combined with IFN-α2b, polyI:C and DC-based vaccination	NCT02615574
	CRC	IV	Completed	As standalone immunotherapeutic agent	NCT00473980
	HCC	I	Completed	In combination with sequential viral vaccination	NCT00081848
	HNC	I/II	Recruiting	As standalone immunotherapeutic agent or combined with 1,25-dihydroxyvitamin D3	NCT00953849
	HNC	II	Unknown	Combined with genetically-modified DC-based vaccine	NCT00589186
	Melanoma	I/II	Completed	Combined with metronomic cyclophosphamide, IL-2 and autologous DC-based vaccination	NCT00197912
	Neuroblastoma	II	Recruiting	Combined with metronomic chemotherapy	NCT02641314
	NSCLC	I	Completed	As standalone immunotherapeutic agent	NCT00104767
	NSCLC	I	Completed	Combined with DC-based vaccination	NCT00442754
	NSCLC	I	Withdrawn	As standalone immunotherapeutic agent	NCT00108186
	Ovarian carcinoma	I/II	Recruiting	Combined with intensive chemoimmunotherapy plus intranodal DC-based vaccination	NCT02432378
	Peritoneal cancers	I/II	Recruiting	Combined with IFN-α2b, polyI:C and a DC vaccine	NCT02151448
	Solid tumors	I	Completed	In combination with decitabine	NCT00037817
	Solid tumors	I	Completed	Combined with allogeneic cancer cell vaccine	NCT01143545
	Solid tumors	I	Completed	Combined with allogeneic cancer cell vaccine plus metronomic cyclophosphamide	NCT01313429
	Solid tumors	I	Suspended	Combined with cancer cell vaccine plus ISCOMATRIX™	NCT01258868
	Solid tumors	I	Suspended	Combined with cancer cell vaccine plus ISCOMATRIX™ and cyclophosphamide	NCT01341496
Celecoxib	Solid tumors	I/II	Suspended	Combined with allogeneic cancer cell vaccine plus metronomic cyclophosphamide	NCT02054104

Table 1. (*Continued*).

Molecule	Indication(s)	Phase	Status	Notes	Ref.
PF-04418948	Healthy volunteers	I	Completed	As standalone agent	NCT01002963
Cytokine receptor inhibitors					
LY2510924	Renal cell carcinoma	II	Active, not recruiting	In combination with sunitinib	NCT01391130
	SCLC	II	Active, not recruiting	Combined with carboplatin and etoposide	NCT01439568
Maraviroc	CRC	I	Completed	As standalone immunotherapeutic agent	NCT01736813
MSX-122	Solid tumors	I	Suspended	As standalone immunotherapeutic agent	NCT00591682
PF4136309	Pancreatic carcinoma	I	Active, not recruiting	Combined with the FOLFIRINOX regimen	NCT01413022
Plerixafor	Glioma	I	Recruiting	In combination with bevacizumab	NCT01339039
	Glioma Glioblastoma	I/II	Recruiting	Combined with temozolomide and radiotherapy	NCT01977677
	Solid tumors	I	Recruiting	As standalone immunotherapeutic agent	NCT02179970
PLX3397	Breast carcinoma	I/II	Recruiting	In combination with eribulin	NCT01596751
	Breast carcinoma	II	Recruiting	Combined with paclitaxel-based chemotherapy	NCT01042379
	Glioblastoma	I/II	Active, not recruiting	Combined with temozolomide and radiotherapy	NCT01790503
	Glioblastoma	II	Completed	As standalone immunotherapeutic agent	NCT01349036
	Melanoma	I	Terminated	In combination with vemurafenib	NCT01826448
	Prostate carcinoma	I	Recruiting	Combined with radiation and androgen ablation	NCT02472275
	Prostate carcinoma	II	Completed	As standalone immunotherapeutic agent	NCT01499043
	Solid tumors	I	Recruiting	Combined with paclitaxel-based chemotherapy	NCT01525602
	Solid tumors	I/II	Recruiting	In combination with pembrolizumab	NCT02452424
POL6326	Breast carcinoma	I	Recruiting	In combination with eribulin	NCT01837095
Kinase inhibitors					
BMS-777607	Solid tumors	I	Active, not recruiting	As standalone immunotherapeutic intervention	NCT01721148
	Solid tumors	I/II	Completed	As standalone immunotherapeutic intervention	NCT00605618
Galunisertib	Breast carcinoma	II	Recruiting	Combined with radiation therapy	NCT02538471
	Glioblastoma	II	Active, not recruiting	In combination with lomustine	NCT01582269
	Glioma	I	Active, not recruiting	In combination with lomustine	NCT01682187
	Glioma	I/II	Active, not recruiting	Combined with temozolomide and radiotherapy	NCT01220271
	HCC	I/II	Recruiting	In combination with sorafenib	NCT01246986
	HCC	I/II	Recruiting	In combination with sorafenib	NCT02178358
	HCC	I/II	Recruiting	In combination with sorafenib	NCT02240433
	Healthy volunteers	I	Completed	As standalone agent	NCT01746004
	Healthy volunteers	I	Completed	As standalone agent	NCT01965808
	MDS	II/III	Active, not recruiting	As standalone immunotherapeutic agent	NCT02008318
	Pancreatic carcinoma	I	Recruiting	In combination with nivolumab	NCT02154646
	Pancreatic carcinoma	I/II	Active, not recruiting	Combined with gemcitabine-based chemotherapy	NCT01373164
	Prostate carcinoma	II	Not yet recruiting	Combined with androgen-receptor antagonist	NCT02452008
	Solid tumors	I	Completed	As standalone immunotherapeutic agent	NCT01722825
	Solid tumors	I	Recruiting	As standalone immunotherapeutic intervention	NCT02304419
	Solid tumors	I/II	Recruiting	In combination with nivolumab	NCT02423343
TEW-7197	Solid tumors	I	Recruiting	As standalone immunotherapeutic intervention	NCT02160106
Modulators or arginine metabolism					
Tadalafil	HNSCC	I/II	Not yet recruiting	Combined with peptide-based vaccination	NCT02544880
	HNSCC	II	Completed	As standalone immunotherapeutic intervention	NCT00843635
	HNSCC	II	Completed	As standalone immunotherapeutic intervention	NCT00894413
	HNSCC	II	Recruiting	As standalone immunotherapeutic intervention	NCT01697800
	MM	I	Terminated	Combined with lenalidomide and dexamethasone	NCT01374217
	MM	II	Recruiting	Combined with lenalidomide as maintenance therapy	NCT01858558
	Pancreatic carcinoma	I	Unknown	Combined with a peptide-based vaccine and irradiation	NCT01342224
	Pancreatic carcinoma	I	Active, not recruiting	Combined with gemcitabine and radiotherapy	NCT01903083

Abbreviations: CRC, colorectal carcinoma; DC, dendritic cell; FOLFIRINOX, folinic acid + 5-fluorouracil + irinotecan + oxaliplatin; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; IFN, interferon; IL, interleukin; JAK1, Janus kinase 1; MDS, myelodysplastic syndrome; mAb, monoclonal antibody; MM, multiple myeloma; n.a., not available; NK, natural killer; NSCLC, non-small cell lung carcinoma; RTC, reproductive tract cancer; polyI:C, polyinosinic:polycytidylic acid; SCLC, small cell lung carcinoma; TLR, Toll-like receptor. *initiated before 2016, January 1st; excluding studies assessing the immunostimulatory profile of tumor-targeting mAbs, immunostimulatory mAbs, immunostimulatory cytokines, TLR agonists, and immunogenic chemotherapies, which are discussed in other articles of the Trial Watch series.

of NCT01685255 (a Phase II study comparing the clinical activity of epacadostat to that of tamoxifen in women with biochemically-recurrent malignancies of the reproductive tract that achieved complete remission on first-line chemotherapy) and NCT01822691 (a Phase II study testing epacadostat as standalone immunotherapeutic agent in patients with myelodysplastic syndromes) have not been released yet, even though all these studies are listed as "Completed." Finally, NCT02048709 (a Phase I trial assessing the safety and efficacy of NLG919 as standalone therapeutic intervention in subjects with advanced solid tumors) and NCT02471846 (a Phase I study investigating the clinical profile of NLG919 plus an experimental checkpoint-blocking antibody in individuals with locally advanced or metastatic solid tumors) are currently recruiting participants (Table 1) (source www.clinicaltrials.gov).

Various other chemical inhibitors of IDO1 have been developed and tested for their immunostimulatory effects in preclinical settings, including methylthiohydantoin tryptophan,[95,117] brassinin and derivatives,[118,119] annulin B and derivatives,[120,121] exiguamine A and derivatives,[122,123] and INCB023843.[110] However, the clinical development of these molecules appear to stand at an impasse (source www.clinicaltrials.gov). Along similar lines, the TDO2-specific inhibitor LM10 has been shown to mediate therapeutically relevant immunostimulatory effects in mice with TDO2-expressing tumors.[124] However, the actual relevance of TDO2 for tumor-driven immunosuppression in patients has not yet been confirmed, and (at least for the moment) LM10 has not entered clinical development (source www.clinicaltrials.gov).

Modulators of purinergic tumor metabolism

Purinergic signaling plays a fundamental role in the elicitation of tumor-targeting immune responses.[52,58,125] Indeed, dying cancer cells actively secrete ATP (especially if they are undergoing ICD),[126,127] and acute elevations in extracellular ATP levels have a dual immunostimulatory effect. First, by activating purinergic receptor P2Y, G-protein coupled, 2 (P2RY2), they mediate robust chemotactic functions and recruit APCs and their precursors to site of cancer cell death.[128] Second, by acting on purinergic receptor P2X, ligand gated ion channel, 7 (P2RX7), they favor the activation of APCs and boost their ability to cross-prime an adaptive immune response specific for dead cell-associated antigens.[129] Moreover, extracellular ATP is normally degraded by the sequential activity of two enzymes, namely, ectonucleoside triphosphate diphosphohydrolase 1 (ENTPD1, best known as CD39) and 5′-nucleotidase, ecto (NT5E, best known as CD73).[130] In particular, CD39 converts ATP into ADP and AMP, whereas CD73 transforms AMP into adenosine.[130,131] Importantly, while extracellular ATP has immunostimulatory effects, extracellular adenosine (and less so AMP) exerts major immunosuppressive functions as it binds adenosine A2a receptor (ADORA2A) and adenosine A2b receptor (ADORA2B).[132] ADORA2A limits the ability of NK cells and CTLs to mediate interferon (IFN)γ-dependent cytotoxicity,[133,134] promotes CTL anergy,[135] and stimulates the immunosuppressive functions of Tregs and M2 TAMs.[133,136-138] ADORA2B promotes the recruitment and activation of a heterogeneous populations of relatively immature and potently immunosuppressive myeloid cells cumulatively referred to as myeloid-derived suppressor cells (MDSCs),[139,140] and stimulates DCs to express various immunosuppressive molecules including IL-6, IL-10, TGFB1 and IDO1.[141] Last, but not least, both ADORA2A and ADORA2B have direct effects on malignant cells, stimulating their survival and proliferation.[142] Of note, chronic elevations in extracellular ATP levels may also mediate immunosuppressive (rather than immunostimulatory) effects.[143] In particular, chronically high concentrations of extracellular ATP have been shown to promote the development of semi-mature, dysfunctional DCs by signaling via purinergic receptor P2Y, G-protein coupled, 11 (P2RY11),[144] and to stimulate the activity of MDSCs.[143] Taken together, these observations provide a robust rationale to the development of strategies that target the purinergic system within neoplastic lesions for the potentiation of chemo-, radio- or immuno therapy-driven anticancer immune responses.[52,58,145] Two major approaches are being pursued with this objective: (1) blocking the extracellular conversion of ATP into adenosine, and (2) modulating purinergic receptor signaling.

Inhibitors of extracellular ATP degradation

Multiple small molecules that limit the conversion of extracellular ATP into adenosine by inhibiting CD39 or CD73 are currently available for investigational purposes.[146] Molecules that inhibit CD39 (with variable degree of selectivity) include N^6,N^6-diethyl-D-β-γ-dibromomethylene-ATP (ARL-67176), 1-amino-2-sulfo-4-(2-naphthylamino)anthraquinone, suramin, polyoxotungstate (POM-1), reactive blue 2, pyridoxal phosphate-6-azophenyl-2′,4′-disulfonic acid (PPADS), as well as 8-thiobutyl-ATP and derivatives (8-thiobutyl-ADP and 8-thiobutyl-AMP).[147,148] CD73 inhibitors encompass α-β-methylene-ADP (AMPCP or APCP) and various derivatives (*i.e.*, PSB-12441, PSB-12425, and PSB-12379).[149-151] The pharmacological inhibition of CD39 and/or CD73 has been shown to promote therapeutically relevant tumor-targeting immune responses in several rodent models of oncogenesis and tumor progression.[147,152-163] None of these agents, however, has yet entered clinical evaluation for its immunostimulatory activity (source www.clinicaltrials.gov). Indeed, while suramin has been tested as standalone therapeutic interventions or in combination with other treatments modalities in more than 15 clinical trials performed over the past 2 decades, all these studies tested suramin for its ability to operate as broad-spectrum antagonists of P2Y receptors expressed malignant cells and to neutralize some soluble growth factors including various members of the fibroblast growth factor (FGF) family.[164-168] Of note, the results of these trials suggest that non-cytotoxic doses of suramin are well-tolerated by cancer patients, but generally fail to improve the clinical activity of chemotherapy.[164-168]

Modulators of purinergic receptors

Besides suramin and PPADS, both of which operate as broad-spectrum P2Y receptor antagonists, a few specific inhibitors of P2RY11, ADORA2A and ADORA2B are currently available.[37]

So far, the P2RY11-selective antagonist NF340 has only been employed to confirm the implication of P2RY11 in IL-8 secretion and in the acquisition of a dysfunctional, immunosuppressive phenotype by DCs exposed to ischemia/reperfusion.[144,169] It will therefore be interesting to see whether NF340 can also limit the P2RY11-dependent accumulation of semi-mature DCs that may accompany some instances of tumor progression. Two experimental ADORA2A antagonists, namely ZM241365,[163] and SCH58261,[153,154,170,171] have been shown to exert therapeutically relevant immunostimulatory effects in tumor-bearing mice, but these molecules have not yet entered clinical evaluation (source www.clinicaltrials.gov). Two other small-molecule inhibitors of ADORA2A, namely, preladenant (also known as SCH420814) and istradefylline (also known as KW-6002), have been extensively tested in the clinic as therapeutic options for Parkinson disease,[172-174] but not as anticancer agents or immunostimulatory molecules (source www.clinicaltrials.gov). Although Phase III clinical data demonstrated that preladenant is well tolerated by patients with Parkinson disease, there was no therapeutic activity,[174,175] and the development of preladenant has been discontinued.[37] Conversely, istradefylline demonstrated a good safety profile and modest efficacy, and this was sufficient for obtaining regulatory approval in Japan.[176] It will be important to investigate whether preladenant or istradefylline may exert clinically relevant immunostimulatory effects in cancer patients receiving chemo-, radio- or immuno therapeutic regimens. The ADORA2B-selective antagonists PSB603 and PSB1115 have been shown to limit immunosuppression and neoangiogenesis mediated by Tregs and MDSCs in a murine melanoma model,[177-179] but have not yet entered clinical development (source www.clinicaltrials.gov). Others ADORA2B inhibitors like CVT-6883 and GS-6201 are being developed for the treatment of non-oncological, inflammatory conditions, like inflammatory bowel disease and chronic obstructive pulmonary disease.[180,181] Preliminary clinical data indicate that CVT-6883 is well tolerated.[182] To the best of our knowledge, however, whether CVT-6883 or GS-6201 can improve the efficacy of anticancer therapy has not yet been investigated.

PGE_2 inhibitors

Especially under hypoxic conditions, several tumors overexpress prostaglandin-endoperoxide synthase 2 (PTGS2, best known as COX2),[183] which catalyzes the first and rate-limiting step of the biochemical cascade that converts arachidonic acid into prostaglandins, prostacyclin and thromboxane A2.[184] Sustained elevations in local prostaglandin E_2 (PGE_2) levels not only have a direct mitogenic activity on malignant cells,[185,186] but also mediate multipronged immunosuppressive effects by acting on tumor-infiltrating immune cells as well as on the tumor vasculature.[187-191] The principal responsible of the immunosuppressive activity of PGE_2 are prostaglandin E receptor 2 (PTGER2, best known as EP_2) and prostaglandin E receptor 4 (PTGER4, best known as EP_4).[184] Indeed, EP_2 and/or EP_4 robustly inhibit the cytotoxic activity of NK cells and CTLs,[192-195] suppress the ability of M1 TAMs to secrete tumoricidal molecules like IFNγ and tumor necrosis factor (TNF),[193] activate Tregs,[196] promote the accumulation of MDSCs[194,197-199] and their capacity to secrete TGFB1,[194,200] limit inflammasome activation in macrophage,[201,202] and stimulate endothelial cells to express Fas ligand (FASLG), hence impeding tumor infiltration by immune effector cells.[188] Intriguingly, PGE_2 is also overproduced in the course of apoptotic cell death,[203,204] owing to the caspase-3-dependent activation of phospholipase A2, group VI (PLA2G6).[185] This reinforces the notion that the precise cell death mechanisms activated by chemo- or radio therapy have a major impact on the consequent elicitation of a tumor-targeting immune response.[205] Irrespective of this aspect, two approaches have been pursued to limit the immunosuppressive activity of PGE_2: (1) inhibiting PGE_2 synthesis, and (2) antagonizing EP_2 and EP_4.

Inhibitors of PGE_2 synthesis

A wide panel of COX2 inhibitor (with various degree of selectivity) is currently approved by the US FDA and equivalent agencies worldwide for use as non-steroidal anti-inflammatory agents, including (but not limited to) acetylsalicylic acid (best known as aspirin) and celecoxib (source www.fda.gov/Drugs/default.htm). Aspirin is a relatively non-selective COX1 and COX2 inhibitor commonly available over the counter for the treatment of pain, fever and inflammation.[184] Low-dose aspirin is often prescribed as maintenance therapy to patients surviving myocardial infarction and other ischemic events, owing to its capacity to inhibit platelet aggregation.[206] Prolonged aspirin intake has also been associated with a reduced incidence of colorectal cancer, an on-target effect presumably linked to the oncogenic effects of chronic inflammation in large intestine as well as to phosphoinositide-3-kinase (PI3K) signaling (which is directly connected to EP_2 and EP_4).[207,208] Celecoxib is a COX2-specific inhibitor, available on prescription for the treatment of various inflammatory disorders associated with pain including osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.[209] Aspirin as well as celecoxib have been shown to favor the (re-)establishment of an immunostimulatory tumor microenvironment,[188,210-218] hence limiting natural tumor progression or improving the therapeutic effects of various treatments. Taken together with the well-established safety profile of aspirin and celecoxib, these findings prompted an intense wave of investigation aimed at elucidating the ability of COX2 inhibitors to provide clinical benefits to cancer patients. Official sources list indeed 95 and 202 studies aimed at assessing the therapeutic profile of aspirin and celecoxib, respectively, in cancer patients. Only a minority of these trials, however, specifically focused/focuses on the immunostimulatory potential of aspirin (three studies) and celecoxib (21 studies) (source www.clinicaltrials.gov). In particular, the ability of aspirin to mediate clinically relevant immunostimulatory effects has been/is being assessed in (1) breast carcinoma patients, who are treated with aspirin plus neoadjuvant metronomic cyclophosphamide and methotrexate (NCT01612247: Phase I, status "Unknown");[219,220] (2) women with ovarian carcinoma, who received aspirin in the context of a multimodal immunotherapeutic regimen (NCT01312376: Phase I, status "Completed"); and (3) subjects with reproductive tract neoplasms, receiving aspirin plus bevacizumab and metronomic cyclophosphamide in support of DC-based vaccination (NCT01132014: Phase 0, status

"Recruiting"). To the best of our knowledge, the results of NCT01312376 have not been released yet (Table 1) (source www.clinicaltrials.gov). Moreover, the immunostimulatory potential of celecoxib has been/is being investigated in (1) colorectal cancer patients, receiving celecoxib either as standalone pre-operative intervention (NCT01284504: Phase n.a., status "Withdrawn;" NCT00473980: Phase IV, status "Completed"), or in the context of a chemokine-modulatory regimen involving IFN-α2b and an experimental TLR agonist given alone (NCT01545141: Phase I/II, status "Recruiting") or in support to DC-based vaccination (NCT02615574: Phase II, status "not yet recruiting); (2) subjects with NSCLC, who were treated with celecoxib as standalone immunotherapeutic intervention (NCT00104767: Phase I, status "Completed;" NCT00108186: Phase I, status "Withdrawn") or in support of DC-vaccination (NCT00442754: Phase I, status "Completed"); (3) patients with oral or nasopharyngeal neoplasms, who received celecoxib alone (NCT00953849: Phase I/II, Status "Recruiting"), combined with 1,25-dihydroxyvitamin D3 (NCT00953849: Phase I/II, Status "Recruiting"), or as an adjuvant to a genetically modified DC-based vaccine (NCT00589186: Phase II, Status "Unknown"); (4) individuals with hepatocellular carcinoma, receiving celecoxib in support of a sequential strategy of virus-based anticancer vaccination (NCT00081848: Phase I, status "Completed");[221,222] (5) melanoma patients, who received celecoxib plus metronomic cyclophosphamide and IL-2 as adjuvant to autologous DC-based vaccination (NCT00197912: Phase I/II, status "Completed");[223] (6) children and adolescents with recurrent or progressive high-risk neuroblastoma, who are treated with celecoxib in the context of multimodal metronomic chemotherapy (NCT02641314: Phase II, status "Recruiting"); and (7) women with ovarian carcinoma, receiving celecoxib in the context of intensive locoregional chemoimmunotherapy plus intranodal DC-based vaccination (NCT02432378: Phase I/II, status "Recruiting") (Table 1) (source www.clinicaltrials.gov). In addition, the immunostimulatory activity of celecoxib has been/is being evaluated in several cohorts of patients with locally advanced or metastatic solid neoplasms, receiving celecoxib (1) together with metronomic cyclophosphamide and/or the particulate adjuvant commonly known as ISCOMATRIX™ in support of vaccination with autologous or heterologous cancer cell lysates (NCT01143545: Phase I, status "Completed;" NCT01258868: Phase I, status "Suspended;" NCT01313429: Phase I, status "Completed;" NCT01341496: Phase I, status "Suspended;" NCT02054104: Phase I/II, status "Suspended"); (2) in the context of a chemokine-modulatory regimen involving IFN-α2b and an experimental TLR agonist in support to DC-based vaccination (NCT02151448: Phase I/II, status "Recruiting"); and (3) combined with the epigenetic modifier decitabine (NCT00037817: Phase I, status "Completed") (Table 1) (source www.clinicaltrials.gov). Both NCT00108186 and NCT01284504 were withdrawn owing to low accrual rate. NCT01258868, NCT01341496 and NCT02054104 suspended enrollment for undisclosed reasons. Preliminary findings from NCT00081848 suggest that celecoxib does not cause unexpected side effects in cancer patients.[221,222] Moreover, the results of NCT00197912 suggest that celecoxib plus metronomic cyclophosphamide may considerable improve the efficacy of DC-based vaccination, although no decrease in tumor-infiltrating Tregs was detected in this setting.[223] To the best of our knowledge, the findings of NCT00037817, NCT00104767, NCT00442754, NCT00473980, NCT00953849, NCT01143545, and NCT01313429 have not yet been disclosed (source www.clinicaltrials.gov).

Pge_2 receptor antagonists

Various small-molecule antagonists of EP_2 and EP_4 are currently available, including the EP_2-specific inhibitor PF-04418948,[224,225] and the EP_4-specific agents RQ-15986,[200,217] AH 23848,[198,226] and BGC201531.[227] The safety of PF-04418948 has been tested in a single clinical trial enrolling healthy volunteers (NCT01002963), but the development of PF-04418948 has subsequently been discontinued.[37] In murine models of breast carcinoma, RQ-15986 has been shown to protect NK cells from PGE_2-dependent immunosuppression,[200] and to inhibit tumor-infiltration by immunosuppressive macrophages,[217] resulting in limited tumor growth and reduced metastatic dissemination. AH 23848 has been demonstrated to resemble RQ-15986 in its capacity to protect NK cells from immunosuppression,[226] and to inhibit the ability of MDSCs to infiltrate neoplastic lesions upon the downregulation of chemokine (C–X–C motif) receptor 4 (CXCR4).[198] To the best of our knowledge, neither RQ-15986 nor AH 23848 has been tested in the clinic so far (source www.clinicaltrials.gov). Finally, BGC20-1531 has never been investigated for its immunostimulatory activity, but preliminary clinical data indicate that it is well tolerated by healthy subjects.[227] Preclinical experiments testing whether BGC20-1531 mediates therapeutically relevant immunostimulatory activity in rodent tumor models are urgently awaited.

Cytokine receptor inhibitors

The establishment of an immunostimulatory *versus* immunosuppressive immune infiltrate is determined by several factors, among which cytokine signaling has a prominent role.[228-231] Indeed, cytokines and chemokines not only guide the recruitment of immunostimulatory *versus* immunosuppressive cells to the tumor microenvironment, but also influence the local acquisition of immunostimulatory *versus* immunosuppressive functions.[228-231] One strategy to suppress immunosuppressive cytokine signaling consists in the administration of neutralizing mAbs, like the TGFB1-targeting molecule fresolimumab,[232-234] or mAbs that operate as receptor antagonists, like the CXCR4-specific molecule BMS-936564.[235] Cytokine receptors, however, are common G protein-coupled receptors and hence can be also be targeted with small molecules that operate as antagonists.[145,236,237]

CXCR4 inhibitors

CXCR4 is main receptor for chemokine (C–X–C motif) ligand 12 (CXCL12), and the CXCL12–CXCR4 signaling axis appears to play a central role in the recruitment of immunosuppressive cells to the tumor microenvironment.[238,239] Several CXCR4 antagonists have been developed, some of which have already entered clinical evaluation.[240,241] Of note, part of this wave of

investigation has been driven by the fact that CXCR4 also operates as co-receptor for the entry of T-tropic HIV-1 strains into $CD4^+$ cells.[242-244] Moreover, various CXCR4 antagonists including plerixafor (also known as AMD3100 or JM3100 and commercialized under the trade name of Mozobil™), burixafor (also known as TG0054), LY2510924, and POL6326 and BKT140 (also known as BL-8040) have been developed (and are currently being tested in clinical settings) because of their ability to rapidly mobilize $CD34^+$ cells.[245] This has two major clinical applications: (1) the mobilization of healthy haematopoietic stem cells for collection and subsequent autologous or heterologous transplantation,[246,247] and (2) the disruption of beneficial interactions between haematopoietic cancer cells and their microenvironment, resulting in chemosensitization.[248,249] Nonetheless, official sources list no less than seven studies testing CXCR4 antagonists for their anticancer (as opposed as $CD34^+$ cell-mobilizing) effects. NCT01339039 (a Phase I trial assessing the clinical profile of plerixafor[250] plus bevacizumab in individuals with recurrent high-grade glioma), NCT01977677 (a Phase I/II study testing plerixafor plus temozolomide and radiation therapy in patients with newly diagnosed high-grade glioma), and NCT02179970 (a Phase I trial investigating the safety of continuous intravenous plerixafor in subjects with advanced pancreatic, ovarian and colorectal tumors) are currently recruiting participants. NCT01391130 (a Phase II study assessing the therapeutic profile of LY2510924[251] combined with the multi-target tyrosine kinase inhibitor sunitinib in patients with metastatic renal cell carcinoma) and NCT01439568 (a Phase II trial investigating the safety and activity of LY2510924 plus carboplatin and etoposide in subjects with extensive stage small cell lung carcinoma) are currently listed as "Active, not recruiting." Preliminary results from NCT01391130 indicate that the addition of LY2510924 to sunitinib-based chemotherapy is safe, but does not improve efficacy,[252] while early findings from NCT01439568 suggest that the clinical activity of LY2510924 may not involve immunological effects in this setting.[253,254] NCT00591682 (a Phase I study testing oral MSX122[255,256] in individuals with metastatic or locally advanced solid tumors) has suspended the recruitment of participants for undisclosed reasons. Finally, NCT01837095 (a Phase I trial evaluating the clinical profile of POL6326[241] plus eribulin in women with metastatic breast carcinoma) is currently recruiting participants (Table 1) (source www.clinicaltrials.gov).

Additional CXCR4 antagonists including CTCE9908, and POL5551 have been shown to limit neoplastic growth and/or metastatic dissemination in mice, in some instances coupled to reduced tumor infiltration by MDSCs or immunosuppressive TAMs.[257-263] To the best of our knowledge, however, none of these agents has entered clinical development yet (source www.clinicaltrials.gov).

CCR2 inhibitors

Similar to CXCR4 and CXCL12, chemokine (C–C motif) receptor 2 (CCR2) and its cognate ligand chemokine (C–C motif) ligand 2 (CCL2) have been implicated in tumor infiltration by immunosuppressive cells, notably M2 TAMs and MDSCs.[264-269] However, CCR2 has also been involved in the recruitment of $CD4^+$ T_H1 lymphocytes and DC precursors to the tumor bed, underlying the local activation of anticancer immunity.[270-273] Thus, even though targeting the CCL2-CCR2 axis may have context-dependent effects, several CCR2 inhibitors are currently being evaluated for their immunostimulatory activity, mostly in preclinical settings.[274] The majority of these molecules have indeed been tested clinically for the therapy of non-oncological conditions, but their development has come to an impasse.[274] This applies to AZD2423, which has been studied for the treatment of chronic obstructive pulmonary disease and neurotic pain;[275] BMS741672, which has been investigated for safety and efficacy in patients with diabetes or neurotic pain; BMS813160 and CCX140, which have been assessed as therapeutic measures in subjects experiencing diabetic kidney disease;[276-278] JNJ17166864, which has been tested as a treatment for allergic rhinitis; MK0812, which has been investigated as a therapy for multiple sclerosis, rheumatoid arthritis and Alzheimer disease;[279] as well as PF04634817, which has been intensively tested in subjects with diabetic kidney disease (source www.clinicaltrials.gov). Cenicriviroc, a mixed CCR2/CCR5 antagonist, is still being assessed for its activity against HIV-1 infection, primary sclerosing cholangitis, and hepatic disorders, but not as an immunostimulatory agent in cancer patients (source www.clinicaltrials.gov). Conversely, the safety and efficacy of PF4136309 (which mediated promising therapeutic activity in preclinical settings)[265] are being evaluated in subjects with borderline resectable and locally advanced pancreatic adenocarcinoma under the FOLFIRINOX chemotherapeutic regimen (folinic acid plus 5-fluorouracil plus irinotecan plus oxaliplatin), in the context of a Phase I clinical trial that is listed by official sources as "Active, not recruiting" (NCT01413022) (Table 1) (source www.clinicaltrials.gov).

CCR5 inhibitors

Chemokine (C–C motif) receptor 5 (CCR5) is expressed by a plethora of immune cells, including CTLs, $CD4^+$ T_H1 cells, monocytes, macrophages, MDSCs and Tregs, and is well known for its ability to operate a co-receptor for the entry of M-tropic HIV-1 strains into $CD4^+$ cells.[280,281] In addition, CCR5 has been implicated in the recruitment of Tregs and MDSCs to the tumor microenvironment.[282,283] A bunch of CCR5 antagonists have been developed so far, mostly for antiretroviral applications.[37,284] Some of these molecules, however, are also being evaluated as immunostimulatory agents for oncological indications, mostly in preclinical settings. In mice, maraviroc has been shown to limit diet-induced hepatocellular tumorigenesis,[285] to interrupt the metastatic dissemination of basal breast cancer cells,[286] and to impede the recruitment of immunosuppressive TAMs to triple-negative breast carcinomas.[90,287,288] An intense wave of investigation, which has not yet come to an and, evaluated the safety, tolerability and pharmacodynamics of maraviroc in healthy subjects, as well as its therapeutic activity in subjects affected by HIV-1 and associated complications (*e.g.*, Kaposi sarcoma, dementia).[289,290] More recently, maraviroc has been tested for its capacity to limit graft-*versus*-host disease in transplanted patients,[291,292] and

as a single immunotherapeutic intervention in subjects affected by advanced colorectal cancer patients with hepatic metastases (NCT01736813). To the best of our knowledge, the results of this Phase I trial (MARACON-001) have not yet been released, even though the study is listed as "Completed" by official sources (Table 1) (source www.clinicaltrials.gov). The safety and efficacy of additional CCR5 antagonists including INCB009471,[293] aplaviroc and vicriviroc have been assessed in multiple clinical studied enrolling HIV-1^{+} patients or subjects at increased risk for HIV-1 infection, but not in oncological indications (source www.clinicaltrials.gov). Similarly, the development of CCR5 antagonists of the spiropiperidine family appears to stand at an impasse.[294,295]

CSF1R inhibitors

Colony stimulating factor 1 receptor (CSF1R) signaling favors tumor infiltration by TAMs and their polarization toward an M2 (rather than an M1) phenotype.[296-299] A few chemical inhibitors of CSF1R are currently being assessed for their immunostimulatory activity, both in preclinical and clinical settings. PLX3397, a CSF1R inhibitor that also target the oncogenic receptors KIT and fms-related tyrosine kinase 3 (FLT3), reportedly mediates therapeutically relevant immunostimulatory effects in various rodent models of tumorigenesis, both as standalone immunotherapeutic intervention and combined with other forms of treatment.[300-304] Importantly, PLX3397 has already entered clinical development, and official sources list no less than 17 studies aimed at investigating the safety and efficacy of this agent in cancer patients (source www.clinicaltrials.gov). Three of these trials (NCT01004861: Phase I, status "Active, not recruiting;" NCT02371369: Phase III, status "Recruiting;" NCT02584647: Phase I/II, status "Recruiting") are assessing the ability of PLX3397 to inhibit the growth of synovial tumors, which are known to overexpress CSF1R. Preliminary results from the Phase II extension of NCT01004861 indicate that PLX3397 is well tolerated and promote objective responses or disease stabilization in majority of patients.[305] Moreover, five studies have investigated/are investigating the ability of PLX3397 to exert direct antineoplastic effects in patients with KIT- or FMS3-expressing neoplasms, including gastrointestinal stromal tumors (NCT02401815: Phase I/II, status "Suspended"), various forms of leukemia (NCT01349049: Phase I/II, status "Active, not recruiting;" NCT02390752: Phase I/II, status "Recruiting"), Hodgkin lymphoma (NCT01217229: Phase II, status "Completed"), and acral and mucosal melanoma (NCT02071940: Phase II, status "Recruiting) (source www.clinicaltrials.gov). The remaining nine studies have evaluated/are evaluating the capacity of PLX3397 to mediate therapeutic effects as standalone agent, or to improve the efficacy of other treatments in patients with neoplasms that do not express CSF1R, KIT or FMS3, or do not rely on these receptors for growth (source www.clinicaltrials.gov). NCT01826448 (a Phase I trial testing PLX3397 in combination with a $BRAF^{V600E}$ inhibitor in individuals with metastatic or unresectable melanoma) has been terminated for undisclosed reasons. Results from NCT01349036 (a Phase I study investigating the safety of oral PLX3397 in subjects with recurrent glioblastoma) suggest that this immunotherapeutic regimen is well tolerated but has no clinical efficiency.[306,307] Although it is listed as "Completed," the results of NCT01499043 (a Phase II study assessing the clinical profile of single-agent PLX3397 in patients with advanced castration-resistant prostate cancer) are not publicly available. NCT01790503 (a Phase I/II trial testing PLX3397 plus temozolomide and radiation therapy in individuals with newly diagnosed glioblastoma) is currently listed as "Active, not recruiting." Moreover, NCT01042379 (a Phase II study evaluating the safety and efficacy of PLX3397 combined with paclitaxel in breast carcinoma patients), NCT01525602 (a Phase I trial investigating the therapeutic profile of PLX3397 plus paclitaxel in subjects with advanced solid tumors),[308] NCT01596751 (a Phase I/II study testing PLX3397 in combination with eribulin in women with metastatic breast carcinoma), NCT02452424 (a Phase I/II trial assessing the safety and efficacy of PLX3397 plus pembrolizumab in individuals with advances solid neoplasms), and NCT02472275 (a Phase I study investigating the clinical profile of PLX3397 plus radiotherapy and androgen ablation therapy in patients with intermediate- or high-risk prostate cancer) are currently recruiting participants (Table 1) (source www.clinicaltrials.gov).

The administration of BLZ945 as a standalone immunotherapeutic agent has been shown to limit the turnover of TAMs in murine models of transgene-driven cervical cancer, breast carcinoma and glioma, resulting in increased infiltration by CTLs, tumor growth inhibition, and improved survival.[296,309] GW2580 has been reported to limit tumor-infiltration by M2 TAMs and/or MDSCs, resulting in the inhibition of neoplastic progression in various rodent models of tumorigenesis.[310-315] Along similar lines, GW2580 remarkably increased the efficacy of radiotherapy in mice bearing prostate carcinomas,[316] gemcitabine in a transgenic mouse model of pancreatic adenocarcinoma,[317] and an mAb targeting the VEGFA receptor in mice bearing subcutaneous melanomas, prostate carcinomas or lung carcinomas.[318] It will be interesting to see whether these CSF1R inhibitors are well tolerated and exert clinical activity in cancer patients.

Kinase inhibitors

Some intracellular signal transduction pathways have been implicated in the establishment of an immunosuppressive tumor microenvironment, and hence may constitute promising targets for the development of immunostimulatory interventions based on small molecules.

ALK5 inhibitors

TGFB1-driven immunosuppression relies on the engagement of transforming growth factor, β receptor 1 (TGFBR1, also known as ALK5), resulting in the activating phosphorylation of the transcriptional regulators SMAD family member 2 (SMAD2) and SMAD family member 3 (SMAD3).[231,319-321] First-generation ALK5 inhibitors (*e.g.*, AZ12601011, AZ12799734) were associated with prominent cardiotoxicity,[322] and their development was discontinued.[37] Nowadays, a few second-generation ALK5 inhibitors are being evaluated in preclinical and clinical settings. Galunisertib (also known as LY2157299) is well known to exert therapeutically

relevant immunostimulatory effects in several models of tumorigenesis in mice.[320,323-325] These findings prompted an intense wave of investigation aimed at assessing the safety and pharmacodynamics of galunisertib in healthy individuals and its therapeutic profile in patients affected by advanced solid tumors, including glioma.[326] Preliminary findings from these Phase I studies, which include NCT01722825 (testing galunisertib monotherapy in Japanese patients with advanced or metastatic neoplasms) and NCT01682187 (investigating the clinical profile of galunisertib alone or combined with lomustine in glioma patients), indicate that the administration of galunisertib as standalone immunotherapeutic intervention is well tolerated, does not cause medically relevant cardiac toxicity, and exerts antineoplastic effects (at least in a proportion of glioma patients).[327-331] Official sources list 15 additional studies aimed at investigating the clinical profile of galunisertib (source www.clinicaltrials.gov). To the best of our knowledge the results of NCT01746004 and NCT01965808 (two Phase I trials assessing the safety and pharmacodynamics of galunisertib in healthy volunteers) have not been released yet, even though both studies appear as "Completed." NCT01220271 (a Phase I/II study testing galunisertib plus temozolomide and radiation therapy in subjects with newly diagnosed glioma),[332] NCT01373164 (a Phase I/II trial assessing the clinical profile of galunisertib combined with gemcitabine in individuals with locally advanced or metastatic pancreatic cancer),[333] NCT01582269 (a Phase II study evaluating the safety and efficacy of galunisertib plus lomustine in patients with recurrent glioblastoma),[334,335] and NCT02008318 (a Phase II/III trial investigating the therapeutic activity of galunisertib in subjects affected by myelodysplastic syndromes) are currently listed as "Active, not recruiting," while NCT02452008 (a Phase II study testing galunisertib plus androgen-receptor inhibition in patients with metastatic, castration-resistant prostate carcinoma) appears as "Not yet recruiting." Finally, NCT01246986, NCT02178358, NCT02240433 (three Phase I/II trials assessing the therapeutic profile of galunisertib combined with the multi-target tyrosine kinase inhibitor sorafenib in subjects with hepatocellular carcinoma),[336] NCT02154646 (a Phase I study evaluating the safety and efficacy of galunisertib plus gemcitabine in individuals with advanced or metastatic pancreatic cancer), NCT02304419 (a Phase I trial specifically investigating the immunological effects of galunisertib in cancer patients), NCT02423343 (a Phase I/II trial testing galunisertib plus nivolumab in subjects with advanced chemorefractory solid tumors) and NCT02538471 (a Phase II study assessing the therapeutic activity of galunisertib combined with radiation therapy in women with metastatic breast carcinoma) are currently recruiting participants (source www.clinicaltrials.gov). The safety an pharmacodynamics of another ALK5 inhibitor, *i.e.*, TEW-7197,[37] are also being tested in subjects with advanced stage solid tumors (NCT02160106: Phase I, status "Recruiting") (source www.clinicaltrials.gov). However, we were unable to find additional information on the activity of this compound in preclinical tumor models.

RON inhibitors

Besides being directly involved in some instances of tumorigenesis, macrophage stimulating 1 receptor (MST1R, best known as RON) has recently been shown to favor the polarization of TAMs toward the M2 phenotype.[337,338] However, the clinical development of a relatively non-selective RON inhibitor, *i.e.*, BMS-777607 (previously known as ASLAN002), appears to stand at an impasse. Indeed, official sources list only two trials evaluating the safety and efficacy of BMS-777607 in cancer patients. NCT01721148 (a Phase I trial testing BMS-777607 monotherapy in subjects with advanced or metastatic solid neoplasm) appears as "Active, not recruiting," while NCT00605618 (a Phase I/II study investigating the clinical profile of BMS-777607 as standalone therapeutic agent in a similar patient cohort) is listed as "Completed," yet results are unavailable (Table 1) (source www.clinicaltrials.gov). It will be interesting to see whether the development of immunostimulatory regimens based on known or novel RON inhibitors will be pursued or not.

PI3K inhibitors

PI3K signaling is hyperactivated in several tumors, promoting the survival and proliferation of malignant cells.[339-341] This led to the development of various PI3K inhibitors for cancer therapy, including the FDA-approved PI3Kδ-selective agent idelalisib (also known as GS-1101 or CAL-101) and PI-3065.[342-344] Recent findings indicate that PI3Kδ inhibitors may also exert robust immunostimulatory effects by inhibiting Tregs and MDSCs.[344,345] Along similar lines, PI3Kγ inhibitors like TG100-115 and AS605240 have been shown to mediate anticancer effects by virtue of their capacity to target tumor-supporting myeloid cells.[346] Currently, no clinical trials are assessing the possibility that PI3K inhibitors may exert therapeutically relevant immunostimulatory effects in cancer patients (source www.clinicaltrials.gov). Conversely, idelalisib is being extensively assessed for its ability to directly target PI3Kδ-dependent malignancies, including various forms of leukemia, follicular lymphoma, and small lymphocytic lymphoma (SLL).[342,343,347-352]

Modulators of arginine metabolism

Normal immunological functions rely on physiological levels of *L*-arginine in the tumor microenvironment.[353] Indeed, *L*-arginine withdrawal results in the depletion of the CD3ζ chain of the T-cell receptor, and the consequent suppression of T-cell responses to antigenic stimulation.[354] *L*-arginine can be hydrolyzed to ornithine and urea by arginase 1 (ARG1), which is highly expressed (and secreted) by hepatocytes, MDSCs and TAMs, or ARG2, a mitochondrial isoform of ARG1 that is expressed by a wide panel of cells.[355] Alternatively, *L*-arginine can be employed by nitric oxide synthase 2, inducible (NOS2, best known as iNOS) to generate nitric oxide (NO).[356] NO also exerts immunosuppressive effects, mostly because it favors the S-nitrosylation of key cysteine residues in proteins required for normal immunological functions and because it affects the enzymatic activity of guanylyl cyclases and cyclic GMP-dependent kinases.[357,358] Interestingly, MDSCs and TAMs are among the few cell types that co-express ARG1 and iNOS.[37] In this setting, iNOS switches to the production of superoxide, hence initiating the generation of immunosuppressive reactive oxygen and nitrogen species.[37,359] Various

inhibitors of ARG1 and iNOS have been developed for investigational purposes, including the arginine analog N-hydroxy-nor-*L*-arginine (an ARG1/ARG2 inhibitor),[360] NCX-4016 and AT38 (two nitroaspirins that inhibit ARG1, ARG2 and iNOS),[358,361,362] and compound 9 (another ARG1/ARG2 inhibitor),[363] but none of these molecules is currently under clinical evaluation in cancer patients (source www.clinicaltrials.gov). In addition, it seems that the phosphodiesterase 5A, cGMP-specific (PDE5A) inhibitor tadalafil (which is approved by the US FDA and commercialized as Cialis® for the treatment of erectile dysfunction) mediates immunostimulatory effects as it reduces ARG1 and iNOS expression in MDSCs.[364] Recent clinical data from NCT00843635 (Phase II, status "Completed") and NCT00894413 (Phase II, status "Completed") demonstrate that adjuvant tadalafil is well tolerated by patients with resected head and neck squamous cell carcinoma (HNSCC) and efficiently lowers the amounts of circulating MDSCs and tumor-infiltrating Tregs, resulting in the recovery of antitumor T-cell functions.[365,366] Official sources list six additional trials aimed at investigating the ability of tadalafil to exert therapeutically relevant immunostimulatory activity in cancer patients (source www.clinicaltrials.gov). NCT01374217 (a Phase I study assessing the therapeutic profile of tadalafil plus lenalidomide[367] and dexamethasone in subjects with multiple myeloma) has been terminated according to an early stopping rule. The status of NCT01342224 (a Phase I trial evaluating the immunostimulatory activity of tadalafil in pancreatic cancer patients receiving a peptide-based vaccine and radiation therapy) is currently "Unknown." NCT01903083 (a Phase I study testing neoadjuvant tadalafil plus gemcitabine and radiation therapy in subjects with borderline resectable and locally advanced pancreatic adenocarcinoma) is listed as "Active, not recruiting", while NCT02544880 (a Phase I/II trial assessing the immunostimulatory activity of tadalafil in subjects with HNSCC receiving a peptide-based vaccine) appears as "Not yet recruiting." Finally, NCT01697800 (a Phase II study evaluating the clinical profile of tadalafil monotherapy in subjects with HNSCC of the upper aerodigestive tract) and NCT01858558 (a Phase II trial investigating tadalafil plus lenalidomide as maintenance therapy in multiple myeloma patients) are currently recruiting participants (source www.clinicaltrials.gov).

Concluding remarks

Small molecules offer several advantages over other immunotherapeutic regimens (including tumor-targeting and immunomodulatory mAbs, adoptive cell transfer, DNA-, peptide- and DC-based vaccination, and recombinant cytokines), such as an improved stability (*ex vivo* as well as in patients), limited manufacturing problems (implying reduced production costs), and optimal batch reproducibility.[368,369] Some of these agents are already approved for use in humans by the US FDA and equivalent regulatory agencies worldwide, implying that their evaluation as immunostimulatory agents in cancer patients presents limited safety concerns.[370] Along similar lines, some of these molecules have been (or are being) developed for other (oncological and non-oncological) indications, and have already been tested in Phase I clinical studies that demonstrated their safety.[370] It is therefore no surprise that small molecules targeting the immunological tumor microenvironment have attracted considerable attention over the past decade, resulting in the initiation of several clinical studies testing this immunotherapeutic paradigm in cancer patients.[37] Based on the number of ongoing clinical trials, IDO1 inhibitors (mainly indoximod and epacadostat), PLX3397 and galunisertib stand out as the most promising agents to target the immunological tumor microenvironment for therapeutic purposes. Nonetheless, the vast majority of clinical studies investigating these molecules in cancer patients are Phase I/II trials, perhaps suggesting that we will have to wait a little more to see a small molecule that mediates anticancer effects by acting on the immunological tumor microenvironment licensed for use in humans by regulatory agencies. We are looking very much forward to that moment.

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