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REVIEW

Trial Watch: Immunostimulatory monoclonal antibodies for oncological indications

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ABSTRACT

The goal of cancer immunotherapy is to establish new or boost pre-existing anticancer immune responses that eradicate malignant cells while generating immunological memory to prevent disease relapse. Over the past few years, immunomodulatory monoclonal antibodies (mAbs) that block co-inhibitory receptors on immune effectors cells – such as cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PDCD1, best known as PD-1) – or their ligands – such as CD274 (best known as PD-L1) – have proven very successful in this sense. As a consequence, many of such immune checkpoint blockers (ICBs) have already entered the clinical practice for various oncological indications. Considerable attention is currently being attracted by a second group of immunomodulatory mAbs, which are conceived to activate co-stimulatory receptors on immune effector cells. Here, we discuss the mechanisms of action of these immunostimulatory mAbs and summarize recent progress in their preclinical and clinical development.

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Introduction

Efficient anticancer immune responses rely on the robust activation of innate and adaptive immune mechanisms, ultimately resulting in the elimination of malignant cells in spite of the profound immunosuppressive mechanisms established by progressing tumors.[1-6] Although the actual role of B lymphocytes, $CD4^+$ helper T cells and natural killer (NK) cells might have been underestimated,[7-13] $CD8^+$ cytotoxic T lymphocytes (CTLs) are generally viewed as the most important effector cells for anticancer immunity, be it natural or driven by treatment.[14-17] Efficient CTL activation and consequent expansion, acquisition of effector functions and establishment of immunological memory obligatorily relies on: (1) the TCR-dependent recognition of a tumor-associated antigen (TAA) or neoantigen presented by dendritic cells (DCs) or other antigen-presenting cells (APCs) in the context of MHC Class I molecules,[18-21] along with (2) the delivery of positive signals via one or multiple co-stimulatory receptors expressed by CTLs.[21-24] Conversely, transient or chronic antigen recognition in the absence of co-stimulatory signals results in T-cell anergy or exhaustion, respectively, which contributes to peripheral tolerance.[14,21,25,26] Of note, the anticancer activity of CTLs and other immune effectors including NK cells is also regulated by multiple co-inhibitory receptors.[21,26-31] This implies that the capacity of CTLs to mount a productive anticancer immune response is regulated by a balance between the expression of co-stimulatory receptors, their co-inhibitory counterparts and the availability of their cognate ligands in the tumor microenvironment.[27,32,33] Although this balance is often tilted toward co-inhibition,[34-39] several therapeutic strategies have been devised to reverse immunosuppression and re(initiate) a clinically relevant immune response.[40]

Spectacular results in this sense have been obtained with monoclonal antibodies (mAbs) that operate as immune checkpoint blockers (ICBs), *i.e.*, they prevent co-inhibitory signaling on immune effector cells.[6,41-47] Accordingly, no less than 6 of these agents are currently approved by the US Food and Drug Administration (FDA) or equivalent regulatory agencies worldwide for use in one or multiple oncological indications.[48-50] At least in part, the unprecedented clinical success of ICBs reflects the high expression of co-inhibitory receptors such as cytotoxic lymphocyte-associated protein 4 (CTLA4) and programmed cell death 1 (PDCD1; best known as PD-1) by tumor-infiltrating lymphocytes, combined with a relative abundance of their

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cognate ligands – *i.e.*, CD80, CD86 and CD274 (best known as PD-L1) – in the tumor microenvironment.[42,51,52] However, a considerable fraction of cancer patients displays innate or acquired resistance to ICB-based immunotherapy (owing to a variety of mechanisms),[53-60] calling for the development of alternative strategies to reverse immunosuppression and (re) enable tumor-targeting immune responses.[42,49,61-66]

One of these approaches is based on mAbs or fusion proteins that operate as agonists for co-stimulatory receptors expressed by CTLs, NK cells, $CD4^+$ helper T cells, or APCs (Table 1).[67-71] The most relevant receptors in this setting are CD27,[72-74] CD28,[75-77] CD40,[78-82] TNF receptor superfamily, member 4 (TNFRSF4; best known as OX40),[83-85] TNF receptor superfamily member 9 (TNFRSF9; best known as CD137 or 4-1BB),[86-89] TNF receptor superfamily member 18 (TNFRSF18; best known as GITR),[90-92] and inducible T-cell costimulatory (ICOS).[93-97] The natural ligand for CD27 is CD70,[74,98-102] CD28 is activated by CD80 and CD86 (hence sharing ligand specificity with CTLA4),[41,103-106] while CD40 is the receptor for CD40 ligand (CD40LG),[107-109] OX40 for TNF superfamily member 4 (TNFSF4; best known as OX40L),[110-113] CD137 for TNF superfamily member 9 (TNFSF9; best known as CD137L or 4-1BBL),[87,114-117] GITR for TNF superfamily member 18 (TNFSF18; best known as GITRL),[118,119] and ICOS for inducible T-cell costimulator ligand (ICOSLG).[120-123] Importantly, although some overlap in expression and some degree of functional redundancy exists,[21] engaging each of these co-stimulatory receptors with relatively untargeted measures (*e.g.*, the systemic or intratumoral administration of agonists that are not directed against a specific cell type) has a distinct functional outcome, which also depends on the precise experimental setting (at least in part). CD27, CD137, OX40 and GITR agonists have been shown to promote the differentiation of $CD4^+$ T_H1 or T_H9 T cells with anticancer activity while suppressing the differentiation or function of $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells.[119,124-135] Preclinical data suggest that – at least for some mAbs targeting mouse GITR and mouse OX40 – the inhibition of T_{REG} cells depends on a direct depleting effect consequent to the activation of Fcγ receptors and antibody-dependent cellular cytotoxicity (ADCC).[91,136-139] The relevance of this mechanism in the human system remains to be clarified. Engagement of CD27, CD137, OX40, GITR or ICOS has been documented to favor the expansion and survival of tumor-targeting CTLs, as well as to limit their functional exhaustion.[124,140-145] CD40 stimulation has been associated with improved DC activation, resulting in superior anticancer responses by CTLs and NK cells.[146,147] CD137 as well as OX40 agonists have been shown to favor tumor infiltration by CTLs,[133,148] an effect that – at least for CD137 agonists – originated from co-stimulatory signaling at the tumor endothelium.[148] Finally, specific CD40-targeting mAbs appear to inhibit the growth of some (CD40-expressing) tumors, as a consequence of direct cytostatic/cytotoxic effects or upon the activation of NK cell-mediated ADCC.[78,149]

Of note, some immunostimulatory mAbs including specific CD27-, CD40-, and CD137-targeting molecules need to interact (via their Fc domains) with inhibitory Fcγ receptors – notably Fc fragment of IgG receptor IIb (FCGR2B) – on myeloid cells for optimal potency (which depends on receptor cross-linking).[150-159] Thus, the actual biological response

Table 1. Immunostimulatory mAbs in clinical development.

Target	mAb	Aliases	Isotype	Source	Owner	Clinical trial*
CD27	Varlilumab	1F5, CDX-1127	IgG1κ	Human	Celldex Therapeutics	Yes
CD28	Theralizumab	TAB08, TGN1412	IgG4	Humanized	TheraMAB	Yes
CD40	ADC-1013	JNJ-64457107	IgG1	Human	Alligator Bioscience	Yes
	APX005M	EPI-0050	IgG1	Humanized	Apexigen	Yes
	Chi Lob 7/4	—	IgG1	Chimeric	Cancer Research UK	No
	Dacetuzumab	SGN40	IgG1	Humanized	Seattle Genetics	No
	RO7009789	CP-870,893, RG-7876	IgG2	Human	Roche	Yes
	SEA-CD40**	SEA-1C10	IgG1	Humanized	Seattle Genetics	Yes
CD137	Urelumab	BMS-663513	IgG4	Human	Bristol-Myers Squibb	Yes
	Utomilumab	PF-05082566	IgG2	Human	Pfizer	Yes
GITR	AMG-228	—	IgG1	Human	Amgen	No
	BMS-986156	—	IgG1	Human	Bristol-Myers Squibb	Yes
	GWN323	—	IgG1	Human	Novartis	Yes
	INCAGN01876	—	IgG1	Humanized	Agenus	Yes
	MEDI-1873	GITRL-Fc	IgG1	Human	MedImmune	Yes
	MK-1248	—	IgG4	Humanized	Merck	Yes
	MK-4166	—	IgG1	Humanized	Merck	Yes
	TRX518	—	IgG1	Human	Leap Therapeutics	Yes
ICOS	GSK3359609	—	IgG4	Humanized	Glaxo Smith Kline	Yes
	JTX-2011	—	IgG1	Humanized	Jounce Therapeutics	Yes
	MEDI-570	—	IgG1	Human	MedImmune	Yes
OX40	9B12	—	IgG1	Mouse	AgonOx	Yes
	BMS-986178	—	n.a.	n.a.	Bristol-Myers Squibb	Yes
	GSK3174998	—	IgG1	Humanized	Glaxo Smith Kline	Yes
	INCAGN01949	—	IgG1	Human	Agenus	Yes
	MEDI-0562	—	IgG1	Humanized	MedImmune	Yes
	MEDI-6383	OX40L-Fc	n.a.	n.a.	MedImmune	Yes
	MEDI-6469	—	n.a.	Mouse	MedImmune	Yes
	MOXR0916	RG-7888	IgG1	Humanized	Roche/Genentech	Yes
	PF-04518600	—	IgG2	Human	Pfizer	Yes

Abbreviations. mAb, monoclonal antibody; n.a., not applicable or not available. *Ongoing at the date of submission. **Non-fucosylated variant of dacetuzumab.

of a specific patient to immunostimulatory mAbs may depend on: (1) the mAb class and its ability to efficiently engage distinct Fcγ receptors on immune cells;[149] (2) the expression profile of the target within the tumor microenvironment; (3) the expression profile of Fcγ receptors – in particular FCGR2B and Fc fragment of IgG receptor IIIa (FCGR3A) – within the tumor microenvironment; (4) the overall composition of the tumor infiltrate; and (5) the expression profile of the target in extratumoral tissues.

Despite abundant preclinical evidence on the antineoplastic effects of several immunostimulatory mAbs in a variety of tumor models, the development of these immunotherapeutic agents is not as advanced as that of ICBs. At least in part, this delay reflects the tragic outcome of the first-in-human clinical trial testing a CD28 superagonist (*i.e.*, TGN1412), which caused a life-threatening cytokine release syndrome in all 6 subjects receiving the drug (even though the agent was injected at 1/500th of the highest dose safely employed in cynomolgus macaques).[160,161] Such an unfortunate occurrence sparked an intense debate about the serious toxicities potentially associated with the systemic administration of mAbs capable of eliciting antigen-independent T cell activation.[162-164] Nowadays, an increased understanding of the biology of tumor-targeting immune responses in general (and co-stimulatory receptors in particular) has generated renewed interest into developing immunostimulatory mAbs for cancer therapy. Remarkably, TGN1412 (now known as TAB08) is still being tested (at low doses and in combination with corticosteroids) for oncological and non-oncological indications.[165-167] This exemplifies well the importance of doses, schedules and delivery routes for immunostimulatory mAbs to achieve optimal clinical activity in the absence of severe side effects. Along the lines of our Trial Watch series,[168,169] here we summarize recent preclinical and clinical advances in the development of immunostimulatory mAbs for oncological indications.

Update on the development of immunostimulatory mAbs

Preclinical and translational advances

Since the publication of the latest Trial Watch dealing with this topic (March 2015),[69] a considerable amount of literature dealing with preclinical and translation aspects of cancer immunotherapy with immunostimulatory mAbs has been published in peer-reviewed scientific journals (source https://www.ncbi.nlm.nih.gov/pubmed). Amongst such preclinical and translational papers, we found of particular interest the work of: (1) Zippelius and colleagues (from the University of Basel; Basel, Switzerland), who reported that CD40-targeting mAbs promote the expression of PD-L1 by tumor-infiltrating monocytes and macrophages, mechanistically explaining the ability of CD40 agonists to synergize with PD-1- or PD-L1-directed ICBs in rodent models of breast and colorectal carcinoma (CRC);[170] (2) White and collaborators (from the University of Southampton; Southampton, UK), who demonstrated that CD40-targeting human IgG2 mAbs exhibit superior immunostimulatory function as compared to human IgG1 mAbs, which does not depend on secondary cross-linking by Fcγ receptors;[156] (3) Ngiow et al. (from the QIMR Berghofer Medical Research Institute; Herston, Australia), who employed a mouse model of resistance to PD-1-targeting ICBs associated with increased levels of tumor-infiltrating PD-1^{high} cells to demonstrate that a CD40 agonist can reverse T-cell exhaustion and restore sensitivity to immune checkpoint blockade;[171] (4) Buchan and co-authors (from the University of Southampton; Southampton, UK), who reported that both CD27 and OX40 can be harnessed to provide co-stimulatory signals that synergize with anti-PD-L1 mAbs at restoring exhausted CD8$^+$ T-cell functions;[172] (5) Sánchez-Paulete and collaborators (from the Center for Applied Medical Research, Pamplona, Spain), who showed that the cross-presentation of TAAs by BATF3-dependent DCs is critical for the therapeutic effects of CD137-directed as well as PD-1-targeting mAbs;[173] (6) Akhmetzyanova et al. (from the University of Duisburg-Essen; Essen, Germany), who described the ability of a CD137 agonist to reprogram a subset of T_{REG} cells into cytotoxic CD4$^+$ T cells with tumoricidal activity in a model of virus-driven carcinogenesis;[125] (7) McKee and co-authors (from the University of Queensland, Brisbane, Australia), who reported an unexpected decrease in the therapeutic efficacy of a CD137 agonist when administered in the context of PD-1 blockade in a transgenic model of mouse lymphoma;[174] and (8) Homet Moreno and collaborators (from the University of California Los Angeles; Los Angeles, CA, USA), who demonstrated that the administration of CD137 or OX40 agonists can synergize with immunostimulatory tyrosine kinase inhibitors (*e.g.*, dabrafenib and trametinib)[4,22,175] in mouse model of BRAF^{V600E}-driven melanoma.[145]

In addition, considerable efforts have recently been devoted to the development of alternative drug formats that would provide – compared to standard mAbs – improved delivery to malignant lesions, superior potency and limited toxicity.[176] Along these lines of investigation: (1) Mangsbo and co-workers (from Uppsala University; Uppsala, Sweden) developed the first CD40-targeting mAb for local administration (ADC-1013), demonstrating long-lasting therapeutic responses associated with the establishment of immunological memory upon peritumoral delivery in a syngeneic bladder cancer mouse model;[177,178] (2) Fromm and colleagues (from Heat Biologics, Inc.; Durham, NC, USA) showed that a cell-based anticancer vaccine[179-184] co-secreting heat shock protein 90 beta family member 1 (HSP90B1, best known as gp96)[185-189] fused to an immunoglobulin Fc region (gp96-Ig) and Fc-OX40L promotes (upon intraperitoneal delivery) TAA-specific T-cell proliferation and consequent tumor eradication in mice bearing established melanomas or CRCs;[190] (3) Liu and collaborators (from the University of Pittsburgh School of Medicine; Pittsburgh, PA, USA) demonstrated that tumor-primed CD4$^+$ T cells, TAA-loaded DCs and a GITR agonist administered intratumorally mediate considerable therapeutic effect in a mouse model of advanced cancer;[191] and (4) Schrand et al. (University of Miami; Miami, FL, USA) harnessed an aptamer for delivering CD137 co-stimulation to an abundant product of the tumor stroma, *i.e.*, vascular endothelial growth factor (VEGF),[192-196] resulting in potential tumor control and abscopal responses[197-200] to radiation therapy with no observable toxicities (in a mouse model of breast carcinoma).[201,202]

Taken together, these studies represent well the main lines of investigation that the field is now attempting to address at the preclinical level.

Completed clinical trials

Since the publication of the latest Trial Watch dealing with immunostimulatory mAbs,[69] preliminary and final results from no less than 10 clinical studies investigating the therapeutic profile of immunostimulatory mAbs in cancer patients have been published in peer-reviewed scientific journals (source https://www.ncbi.nlm.nih.gov/pubmed) or presented at international oncology meetings (sources http://meetinglibrary.asco.org, http://aacrjournals.org/site/Meetings/meeting_abs.xhtml and http://www.esmo.org/conferences). Most of these studies are early (Phase I) trials addressing the safety and preliminary clinical efficacy of mAbs targeting co-stimulatory receptors including CD27,[203,204] CD40,[205-208] CD137,[209-211] GITR,[212-214] ICOS,[215] and OX40.[216-218] In this setting, immunostimulatory mAbs were administered either as standalone therapeutic interventions,[203,212-216,218] or (1) in combination with ICBs[219,220] including the anti-PD-1 mAbs pembrolizumab[210,221] and nivolumab,[204,214,215] the anti-PD-L1 mAb atezolizumab,[217] and the anti-CTLA4 mAb tremelimumab;[207,222] (2) in combination with tumor-targeting mAbs such as the CD20-targeting agent rituximab;[205,211,223] or (3) in combination with conventional chemotherapy.[205,206,224,225] The majority of patients enrolled in these trials were subjects with advanced solid tumors, notably melanoma,[203,204,207,209,210,212,213,216] CRC,[203,204,209,210,212,213] renal cell carcinoma (RCC),[204,209,210,216] head and neck cancer (HNC),[204,209,212,216] and non-small cell lung carcinoma (NSCLC).[209,210,212,213,216] In addition, 3 studies involved patients with hematological malignancies including non-Hodgkin lymphoma (NHL)[209,211] and diffuse large B-cell lymphoma (DLBCL).[205]

In general, the maximum tolerated dose (MTD) has been identified for a majority of immunostimulatory mAbs (which is not the case for many ICBs, notably PD-1-targeting agents).[226] In a few patients, the CD137 agonist urelumab[227] and the CD40 agonist Chi Lob 7/4[208] caused dose-limiting toxicities that could be managed by decreasing dose. Most immunostimulatory mAbs were associated with mild-to-moderate (Grade 1–2) adverse events including fatigue, nausea or vomiting.[208] Immune-related adverse events were more frequent amongst patients receiving combinatorial immunotherapeutic regimens (which resembles the case of ICBs).[221,228] In particular, around 80% of patients receiving the CD40 agonist RO7009789 (also known as CP-870,893)[229-232] together with tremelimumab[207] or chemotherapy[206] experienced Grade 1–2 cytokine release syndrome,[233-235] which normally could be managed with standard supportive care. Although this is an "on-target" side effect, reflecting the ability of immunostimulatory mAbs to activate CTLs and NK cells,[236] it appears to be particularly relevant for RO7009789, owing to its capacity to operate as a superagonist.[237] Some CD40 and CD137 agonists have also been associated with liver toxicity, an "off-target" side effect potentially reflecting the expression of some co-stimulatory receptors by non-lymphoid cells, including hepatocytes.[208,209] A strategy currently explored to limit the toxicity of some CD40 agonists (*i.e.*, ADC-1013, APX005M and RO7009789) involves intratumoral/peritumoral (as opposed to systemic) delivery (see below). It will be interesting to see whether this approach can limit the side effects of CD40-targeting agents while preserving their immunological activity.

Signs of peripheral T cell activation in patients receiving CD27,[203,204] CD40[207] or OX40[217-218] agonists were documented by various studies. A trend towards higher levels of activated $CD8^+$ effector memory T cells[238-240] in the circulation was observed in patients responding to the CD137 agonist utomilumab plus pembrolizumab (as compared to non-responders).[210] Moreover, tumor infiltration by $CD8^+$ CTLs was documented in a few patients receiving the CD27-targeting mAb varlilumab[241] plus nivolumab (NCT02335918),[204] or the OX40-targeting mAb MEDI-0562 (NCT02318394).[218] Since most of these studies are early (Phase I-II) trials in patients with advanced disease, limited data on clinical efficacy are available. Some of these trials, however, currently continue to recruit participants for the proper assessment of therapeutic activity.[204,211,213-217] Nonetheless, some extent of disease control, including complete response (CR), partial response (PR), and stable disease (SD),[242-244] was achieved in 5–50% of the patients receiving immunostimulatory mAbs, depending on the specific scenario (*i.e.*, tumor type or treatment received). The most remarkable responses were documented amongst individuals receiving: (1) utomilumab plus pembrolizumab, a setting in which 6 out of 23 patients (26%) achieved CR or PR, with CRs lasting more than a year in 2 patients (NCT02179918);[210] (2) RO7009789 plus tremelimumab, a setting in which 25% of the patients (6 out of 24) achieved CR or PR (NCT01103635);[207] and (3) the OX40 agonist PF-04518600 as a standalone immunotherapeutic, a setting in which 25 out of 48 patients (52%) achieved disease stabilization for more than 24 weeks (NCT02315066).[216]

Studies deserving special attention include (but may not be limited to) the following. (1) An integrated safety analysis of urelumab administered as a standalone treatment to 346 patients with advanced solid tumors and lymphomas enrolled in 3 different studies (NCT00309023, NCT00612664, and NCT01471210) disclosed a strong association between urelumab at doses $\geq$ 1 mg/kg and treatment-related adverse events, with a prominent hepatic toxicity.[209] Conversely, a dose of 0.1 mg/kg administered every 3 weeks proved to be safe and was associated with signs of immunological activity, including the upregulation of interferon-stimulated factors,[245-247] supporting further clinical assessment of urelumab at this dose.[209] Along these lines, two clinical trials testing urelumab in combination with rituximab or the epidermal growth factor receptor (EGFR)-targeting antibody cetuximab[248,249] (NCT01775631 and NCT02110082, respectively) have been recently completed. However, to the best of our knowledge, the results of these studies have not been released. (2) A study evaluating utomilumab plus rituximab in 35 patients with relapsed or refractory $CD20^+$ NHL (NCT01307267) reported preliminary evidence of improved clinical activity for the combinatorial regimen when compared to rituximab administered as standalone therapeutic.[211] (3) The first-in-human, dose-escalation and expansion studies of varlilumab identified signs of biological activity including increased levels of pro-inflammatory cytokines and

chemokines,[250,251] markers of T-cell stimulation,[252-254] as well as T_{REG} depletion[255-259] in the blood of patients with advanced solid tumors receiving varlilumab as a standalone treatment (NCT01460134, n = 57)[203] or in combination with nivolumab (NCT02335918, n = 33).[204] (4) Equivalent CR rates were achieved by patients with DLBCL treated with the CD40 agonist dacetuzumab[260-264] (n = 75) or placebo (n = 76) together with rituximab plus chemotherapy (NCT00529503), which prompted the premature termination of this Phase IIb study (NCT00529503). However, a *post hoc* analysis reported that dacetuzumab-treated patients who subsequently underwent autologous stem cell transplantation had increased overall survival rates than their placebo-treated counterparts.[205] (5) A first-in-human open-label dose-escalation Phase 1 study of the GITR agonist AMG-228 administered as standalone immunotherapeutic intervention to 29 patients with advanced solid malignancies (NCT02437916) showed tolerability up to the highest dose tested (1200 mg). However, no clinical or immunological activity could be documented.[212]

Taken together, these clinical studies identified a MTD for many immunostimulatory mAbs, which constitute a promising starting point for future clinical development. Indeed, these agents often mediate immunological effects in cancer patients, and (at least in a subset of individuals) are associated with some clinical benefits. That said, large, randomized clinical trials are urgently awaited to precisely access the efficacy of immunostimulatory mAbs in cancer patients. Indeed, the majority of studies performed so far are early (Phase I-II) trials enrolling rather heterogeneous cohorts of patients with advanced disease (often after several previous lines of treatment), which considerably limits their informative potential on parameters other than safety.

Recently initiated clinical trials

Since the publication of the latest Trial Watch dealing with this topic (March 2015),[69] no less than 40 early (Phase I/II) clinical trials have been initiated evaluating the safety and/or efficacy of immunostimulatory mAbs for oncological indications (source http://clinicaltrials.gov).

These studies involve a variety of agents including: (1) the CD137 agonists urelumab (4 studies) and utomilumab (3 studies); (2) the CD27 agonist varilumab (5 studies); (3) the CD28 agonist theralizumab (1 study); (4) the CD40 agonists ADC-1013 (2 studies), APX005M (5 studies), RO7009789 (4 studies), and SEA-CD40 (1 study); (5) the GITR agonists AMG-228 (1 study), BMS-986156 (1 study), GWN323 (1 study), INCAGN01876 (1 study), MEDI-1873 (1 study), MK-1248 (1 study), and TRX518 (1 study); (6) the ICOS agonists GSK3359609 (1 study), JTX-2011 (1 study), and MEDI-570 (1 study); and (7) the OX40 agonists BMS-986178 (1 study), GSK3174998 (1 study), INCAGN01949 (1 study), MEDI-0562 (1 study), MEDI-6469 (1 study), MOXR0916 (2 studies), and PF-04518600 (1 study). These trials enroll patients with a heterogeneous panel of neoplasms, albeit most studies recruit patients with solid neoplasms including CRC (1 study), gastroesophageal carcinoma (1 study), glioma and glioblastoma[265] (2 studies), melanoma (3 studies), NSCLC (1 study), pancreatic carcinoma (1 study), RCC (2 studies), urothelial carcinoma (2 studies), and several other solid malignancies (26 studies). Additionally, 5 studies aim at assessing the safety and efficacy of immunostimulatory mAbs in patients with hematological malignancies including leukemia (1 study) and lymphoma[266] (5 studies) (Table 2).

The vast majority of these studies focus on the use of immunostimulatory mAbs as standalone immunotherapeutic interventions (22 studies) or in combination with ICBs targeting the PD-1/PD-L1 axis[219,267-269] (19 studies). The rationale behind combining immunostimulatory mAbs with ICBs is multilayered: first, ICBs have already become standard-of-care interventions for multiple oncological indications (*e.g.*, melanoma, NSCLC);[44] second, only a fraction of patients achieve long-term clinical benefits from ICBs employed as standalone immunotherapeutic interventions;[57] third, a consistent amount of preclinical data suggest that these treatment modalities can synergize at inducing robust therapeutic responses in tumor models that are refractory to ICBs or immunostimulatory mAbs used alone (see above). Specifically, CD27, CD40, CD137, GITR, ICOS and OX40 agonists are being tested in combination with: (1) the PD-1-targeting agents nivolumab (9 studies), pembrolizumab (5 studies), or PDR001 (1 study); or (2) the PD-L1-directed ICBs avelumab (2 studies), atezolizumab (4 studies), or durvalumab (1 study). A few studies in which immunostimulatory mAbs are tested in combination with CTLA4-targeting molecules[64,270] including ipilimumab (2 studies) and tremelimumab (1 study) are as well ongoing. Additional combinatorial regimens include: (1) conventional chemotherapy[4,22,271] (4 studies), (2) radiation therapy[49,272-274] (1 study), (3) surgery[275] (1 study), (4) tumor-targeting mAbs such as rituximab[276,277] (2 studies), (5) targeted anti-cancer agents including tyrosine kinase inhibitors[278-282] (2 studies), (6) anticancer vaccines[183,283] plus Toll-like receptor (TLR) agonists[284-287] (2 studies), and (7) mAbs targeting the tumor microenvironment such as the VEGF-targeting agent bevacizumab[195,288,289] (1 study), the VEGF- and angiopoietin 2 (ANGPT2)-bispecific agent vanucizumab[290-292] (1 study), the C-C motif chemokine receptor 4 (CCR4)-specific agent mogamulizumab[293,294] (1 study), and the colony stimulating factor 1 receptor (CSF1R)-specific agent emactuzumab[295-297] (1 study). All these combinatorial approaches are justified by preclinical evidence in support of a potential synergism. In particular, chemotherapy has been shown to synergize with CD40 agonists at the induction of robust therapeutic responses in multiple tumor models.[79] In this context, a particularly interesting approach is the combination of CD137 agonists (*e.g.*, utomilumab, urelumab) with ADCC-competent tumor-targeting mAbs (*e.g.*, rituximab), mainly as it may allow for the use of CD137 agonists at low doses (which are associated with limited toxicity). For similar reasons, it would be interesting to assess the therapeutic efficacy of low-dose CD137 agonists administered in combination with adoptively transferred chimeric antigen receptor (CAR)-expressing T cells. To the best of our knowledge, however, no clinical trials are currently testing this combinatorial immunotherapeutic paradigm (Table 2).

All of the abovementioned studies are ongoing ("Active, not recruiting", "Not yet recruiting", "Recruiting"), but 6, which are "Terminated" (4 studies), "Withdrawn" (1 study), or "Completed" (1 study). NCT02386111 (a Phase II study aimed at

Table 2. Recent clinical studies testing immunostimulatory mAbs in cancer patients.*

mAb	Indication(s)	Phase	Status	Notes	Ref.
CD27 agonists					
Varlilumab	B-cell lymphoma	II	Not yet recruiting	Combined with nivolumab	NCT03038672
	Glioma	I	Recruiting	Combined with a peptide vaccine and hiltonol	NCT02924038
	Melanoma	I/II	Terminated	Combined with ipilimumab +/− CDX-140 and hiltonol	NCT02413827
	Renal cell carcinoma	I/II	Terminated	Combined with sunitinib	NCT02386111
	Solid tumors	I/II	Terminated	Combined with atezolizumab	NCT02543645
CD28 agonists					
Theralizumab	Solid tumors	I	Recruiting	As a single agent	NCT03006029
CD40 agonists					
ADC-1013	Solid tumors	I	Completed	As a single agent	NCT02379741
	Solid tumors	I	Recruiting	As a single agent	NCT02829099
APX005M	Gastroesophageal neoplasms	II	Not yet recruiting	Combined with multimodal therapy	NCT03165994
	Melanoma	I/II	Recruiting	Combined with pembrolizumab	NCT02706353
	Melanoma NSCLC	I/II	Recruiting	Combined with nivolumab	NCT03123783
	Solid tumors	I	Recruiting	As a single agent	NCT02482168
RO7009789	Pancreatic carcinoma	I	Recruiting	Combined with nab-paclitaxel and gemcitabine	NCT02588443
	Solid tumors	I	Recruiting	Combined with atezolizumab	NCT02304393
	Solid tumors	I	Recruiting	Combined with emactuzumab	NCT02760797
	Solid tumors	I	Recruiting	Combined with vanucizumab	NCT02665416
SEA-CD40	Lymphomas Solid tumors	I	Recruiting	As a single agent or combined with pembrolizumab	NCT02376699
CD137 agonists					
Utomilumab	Diffuse large B-cell lymphoma	I	Recruiting	Combined with avelumab, and rituximab or azacitidine	NCT02951156
	Solid tumors	I	Recruiting	Combined with mogamulizumab	NCT02444793
	Solid tumors	I/II	Recruiting	Combined with avelumab +/− PF-04518600	NCT02554812
Urelumab	Glioblastoma	I	Recruiting	As a single agent or combined with nivolumab	NCT02658981
	Leukemia	II	Withdrawn	Combined with rituximab	NCT02420938
	Solid tumors	II	Recruiting	As a single agent or combined with nivolumab	NCT02534506
	Urothelial carcinoma	II	Not yet recruiting	Combined with nivolumab	NCT02845323
GITR agonists					
AMG-228	Solid tumors	I	Terminated	As a single agent	NCT02437916
BMS-986156	Solid tumors	I/II	Recruiting	As a single agent or combined with nivolumab	NCT02598960
GWN323	Lymphomas Solid tumors	I	Recruiting	As a single agent or combined with PDR001	NCT02740270
INCAGN01876	Solid tumors	I/II	Recruiting	As a single agent	NCT02697591
	Solid tumors	I/II	Recruiting	Combined with nivolumab and/or ipilimumab	NCT03126110
MEDI-1873	Solid tumors	I	Recruiting	As a single agent	NCT02583165
MK-1248	Solid tumors	I	Active, not recruiting	As a single agent or combined with pembrolizumab	NCT02553499
TRX518	Solid tumors	I	Recruiting	As a single agent	NCT02628574
ICOS agonists					
GSK3359609	Solid tumors	I	Recruiting	As a single agent or combined with pembrolizumab	NCT02723955
JTX-2011	Solid tumors	I/II	Recruiting	As a single agent or combined with nivolumab	NCT02904226
MEDI-570	Lymphomas	I	Recruiting	As a single agent	NCT02520791
OX40 agonists					
GSK3174998	Solid tumors	I	Recruiting	As a single agent or combined with pembrolizumab	NCT02528357
INCAGN01949	Solid tumors	I/II	Recruiting	As a single agent	NCT02923349
MEDI-0562	Solid tumors	I	Recruiting	Combined with tremelimumab or durvalumab	NCT02705482
MEDI-6469	CRC	I	Recruiting	As a single agent	NCT02559024
MOXR0916	Urothelial carcinoma	II	Recruiting	Combined with atezolizumab	NCT03029832
	Solid tumors	I	Recruiting	Combined with atezolizumab +/− bevacizumab	NCT02410512
PF-04518600	Renal cell carcinoma	II	Not yet recruiting	Combined with axitinib	NCT03092856

Abbreviations. CRC, colorectal carcinoma; mAb, monoclonal antibody; NSCLC, non-small cell lung carcinoma. *Initiated after 2015, March 1st.

testing varlilumab plus the tyrosine kinase inhibitor sunitinib[298] in RCC patients), NCT02413827 (a Phase I/II study aimed at assessing the therapeutic profile of varlilumab in combination with ipilimumab and an anticancer vaccine plus the TLR agonist Hiltonol in melanoma patients), and NCT02543645 (a Phase I/II study aimed at investigating the efficacy of varlilumab plus atezolizumab in patients harboring advanced solid tumors) have been prematurely terminated due to portfolio re-prioritization/business decision of the sponsor company. NCT02437916 (a Phase I study aimed at evaluating the safety and preliminary clinical efficacy of AMG-228 as a single agent in subjects with solid tumors) has been terminated owing to its lack of clinical or immunological activity in a first patient cohort.[212] NCT02420938 (a Phase II study aimed at testing urelumab plus rituximab in patients with leukemia) has been withdrawn prior to enrollment for undisclosed reasons. Finally, NCT02379741 (a Phase I study assessing the safety and preliminary clinical efficacy of ADC-1013 administered intravenously versus intratumorally as a single therapeutic agent to patients with advanced solid malignancies) is listed as "Completed". To the best of our knowledge, 24 patients with 10 different tumor types were enrolled in this study, and results are expected to be available by the end of the year(source http://www.zymecommunications.com). NCT02379741 and NCT02706353 (a Phase I/II study testing intratumoral APX005M in combination with pembrolizumab in melanoma patients) constitute two notable exceptions to the general trend whereby immunostimulatory mAbs and ICBs are administered systemically (despite encouraging preclinical results achieved with local administration).[299,300]

The following studies listed in previous Trial Watches dealing with this topic[69,301,302] have changed status since March 2015. NCT01775631 (a Phase I study aimed at assessing the

safety and preliminary efficacy of urelumab plus rituximab in patients with chronic lymphocytic leukemia or NHL), NCT02110082 (a Phase I trial aimed at evaluating the therapeutic profile of urelumab plus cetuximab in patients harboring advanced CRC or HNC) and NCT02179918 (a Phase I study testing utomilumab plus pembrolizumab in patients with advanced solid tumors) are all listed as "Completed". To the best of our knowledge, the results of NCT01775631 and NCT02110082 have not been disclosed yet. Conversely, the findings of NCT02179918 have already been published (see above).[210] Finally, NCT02205333 (a Phase I/II trial evaluating MEDI-6469 as a single agent, or combined with tremelimumab, durvalumab, or rituximab in patients with advanced solid tumors or B-cell lymphomas) has been prematurely terminated at the sponsor's discretion.

Concluding remarks

The overall balance of co-stimulatory and co-inhibitory signals in tumor-infiltrating immune cells quantitatively and qualitatively defines anticancer immunity.[1,5] Most often, alterations in the myeloid compartment secondary to changes in the tumor secretome or metabolome[303-305] result in a reduced availability of ligands for co-stimulatory receptors, which in turn precludes the activation of productive anticancer immune responses and favors the functional exhaustion of effector lymphocytes.[1,5] In this context, mAbs capable of activating co-stimulatory receptors harbor a considerable potential for resetting immune effector functions and (re-)establish robust anticancer immunity, at least based on preclinical evidence. Despite initial delays, the clinical development of immunostimulatory mAbs has now overcome safety concerns and has established doses associated with acceptable toxicity and auspicious immunostimulatory activity. Currently, the expectation is that immunostimulatory mAbs will provide clinical benefits to cancer patients mainly as part of combinatorial regimens involving other immunotherapeutic agents, chemotherapy and/or radiation therapy.[175,271,306-308] Future will tell which (if any) of these approaches will be licensed by regulatory agencies for oncological indications. The great diversity of co-stimulatory receptors and the tools that are currently available for modulating their functions convey important challenges for the clinical development of immunostimulatory mAbs. Additional studies on key aspects such as (1) the control of the expression of co-stimulatory receptors and their ligands in distinct subsets of immune cells, (2) the relative contribution of co-stimulatory signaling to anticancer immunity, (3) the predominant mechanism of action of specific immunostimulatory mAbs in different malignant settings, and (4) the identification of efficacy or resistance biomarkers are urgently awaited to translate exciting preclinical findings into a clinical reality.

Author disclosures

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