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REVIEW

Trial watch: Peptide-based vaccines in anticancer therapy

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ABSTRACT

Peptide-based anticancer vaccination aims at stimulating an immune response against one or multiple tumor-associated antigens (TAAs) following immunization with purified, recombinant or synthetically engineered epitopes. Despite high expectations, the peptide-based vaccines that have been explored in the clinic so far had limited therapeutic activity, largely due to cancer cell-intrinsic alterations that minimize antigenicity and/or changes in the tumor microenvironment that foster immunosuppression. Several strategies have been developed to overcome such limitations, including the use of immunostimulatory adjuvants, the co-treatment with cytotoxic anticancer therapies that enable the coordinated release of damage-associated molecular patterns, and the concomitant blockade of immune checkpoints. Personalized peptide-based vaccines are also being explored for therapeutic activity in the clinic. Here, we review recent preclinical and clinical progress in the use of peptide-based vaccines as anticancer therapeutics.

Abbreviations: CMP: carbohydrate-mimetic peptide; CMV: cytomegalovirus; DC: dendritic cell; FDA: Food and Drug Administration; HPV: human papillomavirus; MDS: myelodysplastic syndrome; MHP: melanoma helper vaccine; NSCLC: non-small cell lung carcinoma; ODD: orphan drug designation; PPV: personalized peptide vaccination; SLP: synthetic long peptide; TAA: tumor-associated antigen; TNA: tumor neoantigen

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Introduction

Immunotherapy constitutes an efficient way to treat cancer based on the (re)activation of the natural capacity of the host immune system to recognize malignant cells as "non-self" and hence eliminate them.[1-7] Over the past years, a panoply of different approaches has been developed or repurposed to (re)initiate anticancer immunity,[8-12] including immune checkpoint blockers targeting cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PDCD1, best known as PD-1) and its main ligand CD274 (best known as PD-L1);[13-19] chemotherapy with immunogenic cell death (ICD) inducers,[20-25] recombinant cytokines,[26,27] monoclonal antibodies (mAbs) that activate co-activatory receptors,[28,29] adoptively transferred T cells engineered to express a tumor-specific chimeric antigen receptor (CAR),[30-36] as well as multiple small molecules targeting distinct immunosuppressive pathways operating within the tumor microenvironment.[37-40] Although some of these strategies have demonstrated unprecedented activity in patients with advanced tumors refractory to several lines of conventional treatment,[41] the fraction of individuals responding to single-agent immunotherapy is generally low,[42-45] arguably with the sole exception of CAR-expressing T cells, which have been associated with >70% overall response rate in pediatric patients with B-cell acute lymphocytic leukemia (ALL).[46-48] Thus, immunotherapy is most often implemented as part of combinatorial regimens involving other treatment modalities such as surgery, chemotherapy and/or radiation therapy (RT).[49-54]

Importantly, all tumors express proteins that differ in quality or quantity from their germline-encoded counterparts, owing to genetic and/or epigenetic alterations that accumulate as the disease progress.[55-57] Once processed by the proteasome, these proteins can give rise to antigens that are not covered by central or peripheral tolerance and hence can be productively presented by dendritic cells (DCs) to T lymphocytes to drive an adaptive immune response.[55,58-64] Such antigens are commonly known as "tumor-associated antigens" (TAAs).[55,65] A large list of TAAs with sequences that bind human MHC Class I or II molecules and the TCR can be found at http://cvc.dfci.harvard.edu/tadb (the Tantigen

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database). One specific class of TAAs is constituted by so-called "tumor neoantigens" (TNAs).[66-71] At odds with other variants of TAAs including oncofetal antigens and cancer-testis antigens, which can be expressed by healthy tissues (at least at some stage of development),[37,72-75] TNAs are produced as a consequence of genetic alterations that are highly specific for the tumor, or even portions thereof.[76-78] Similarly, TNAs that are fully tumor-specific occur upon the rearrangement of immunoglobulin-coding genes in clonal B-cell malignancies.[79] Finally, tumor-specific TAAs can be generated as a consequence of viral transformation,[80] as in the case of human papillomavirus type 16 (HPV-16)-driven oral and cervical tumors.[81,82]

TAAs in all their forms have been harnessed for the development of tumor-specific vaccines for therapeutic applications,[83-86] including formulations based on recombinant or purified polypeptides generally administered together with an immunological adjuvant in suitable vehicles.[87-103] However, TAAs often display limited antigenicity (reflecting the fact that they generally resemble self-antigens that are covered by tolerance).[104-106] Moreover, tumors emerge and evolve as they become able to escape natural immunosurveillance,[107-110] either because the lose expression of potentially antigenic proteins, and/or because they establish an immunosuppressive milieu that enforces local tolerance.[111-116] Thus, besides a few exceptions and despite promising preclinical findings,[117] multiple studies demonstrate that peptide-based vaccines employed as standalone adjuvanted interventions have limited clinical activity (although they generally cause some signs of tumor-targeting immunity).[118-121] In line with this notion, no peptide-based vaccines are currently approved by the US Food and Drug Administration (FDA) or equivalent agencies worldwide for use in cancer patients are therapeutic measures (source http://www.fda.gov). However, on 2017, July 10th, the FDA has granted Orphan Drug Designation (ODD), which is designed to encourage the preparation of new molecules for indications affecting fewer than 200,000 people in the US, to DSP-7888, a new peptide-based vaccine targeting Wilms tumor 1 (WT1).[122] Of note, Gardasil®, Gardasil 9® and Cervarix® are licensed for use in healthy women as prophylactic vaccines against multiple variants of HPV which are associated with the development of cervical carcinomas and anal cancers.[123-128] That said, these agents technically represent antiviral vaccines and have limited activity against established HPV-driven tumors.[99,129-131]

Recent attempts to improve the efficacy of peptide-based vaccines converged on the development of combinatorial immunotherapeutic regimens that simultaneously drive TAA-specific immunity as they inhibit local immunosuppression.[132] Considerable attention in this sense has been attracted by immune checkpoint blockers,[86,133-136] despite initial setbacks linked to the lack of added therapeutic value when ipilimumab (an FDA-approved mAb targeting CTLA) was combined with a peptide vaccine targeting pre-melanosome protein (PMEL, also known as gp100) in melanoma patients.[137] Along the lines of previous Trial Watches from our series,[138,139] here we summarize recent clinical advances in the development of peptide-based therapeutic vaccines for cancer therapy.

Literature update

Clinical literature

Since the publication of the last Trial Watch dealing with this topic (April 2015),[118] the results of no less than 20 clinical trials testing peptide-based vaccination as a therapeutic approach in cancer patients have reported in the peer-reviewed literature (source https://www.ncbi.nlm.nih.gov/pubmed and http://meetinglibrary.asco.org/abstracts). Most of these trials were Phase I or II studies designed for testing the safety and immunogenicity (as opposed to the therapeutic efficacy) of TAA-derived peptides. Peptide-based vaccination was employed as a standalone adjuvanted intervention,[140-146] or combined with chemotherapy[147-149] radiation therapy[147,150] or other forms of treatment including other immunotherapies.[148,149,151-158] These studies enrolled patients with hematological malignancies,[151,159] brain tumors,[152,153] non-small cell lung carcinoma (NSCLC),[140,147,160] breast cancer,[141,148,161], prostate carcinoma, [142,154] melanoma,[144-146,155-158,162]. ovarian cancer.[149], cervical cancer,[163] hepatocellular carcinoma[164] and biliary tract cancer [165]. The TAAs harnessed for the construction of peptide-based vaccines in these studies included the cancer/testis antigen 1B (CTAG1B; best known as NY-ESO-1),[144] MAGE family member A3 (MAGEA3),[140,146,147] TTK protein kinase (TTK),[158] WT1,[151,166] baculoviral IAP repeat containing 5 (BIRC5; best known as survivin),[149] mutant epidermal growth factor receptor (EGFRvIII),[153] erb-b2 receptor tyrosine kinase 2 (ERBB2; best known as HER2),[148] indoleamine 2,3 dioxygenase 1 (IDO1),[157] TCR gamma alternative reading frame protein (TARP),[154] and multiple glioma-associated antigens.[152] Most often, peptide-based vaccines were well tolerated and no severe side effects were reported. Mild side effects were sporadic and included flu-like symptoms, fatigue and minor reactions at the injection site. Immunes responses driven by vaccination were documented in a variety of studies based on (1) interferon gamma (IFNG) production by T cells with enzyme-linked immunospot (ELISPOT) assays,[142,151,152,154,155] (2) tumor infiltration by $CD4^+$ and $CD8^+$ lymphocyte infiltration,[144,145,147,157,158] or (3) presence of peptide-specific antibodies in the serum.[158] Sporadic clinical responses were also documented (see below).

Ott and colleagues (from the Dana-Farber Cancer Institute, Boston, MA, USA) tested a personalized peptide vaccination (PPV)[167] consisting of 20 patient-specific TNAs predicted from whole-exon DNA sequencing of malignant *versus* healthy cells, in 6 melanoma patients. This vaccine, which was named NeoVax, induced polyfunctional $CD4^+$ and $CD8^+$ T cells targeting 58 (60%) and 15 (16%) of the 97 unique TNAs used across patients, respectively. Four of 6 vaccinated patients had no recurrence at reporting (25 months follow-up). Two patients with recurrent disease received immune checkpoint inhibitors targeting PD-1 and experienced complete tumor regression.[168]

Pujol and collaborators (from the Arnaud de Villeneuve Hospital, Montpellier, France) investigated the safety and immunogenicity of a MAGEA3-targeting peptide-based

vaccine in 67 patients with stage IB-III MAGEA3$^+$ NSCLC who were or were not undergoing standard cisplatin/vinorelbine chemotherapy. In this setting, 16 out of 19 (84%) patients who underwent vaccination concurrent with adjuvant chemotherapy experienced chemotherapy-related Grade 3/4 adverse effects, which was not the case of patients who underwent vaccination after adjuvant chemotherapy.[147] Vansteenkiste and co-authors (from the University Hospital KU Leuven, Leuven, Belgium) tested a MAGEA3-targeting vaccine in 2312 patients with completely resected stage IB, II, and IIIA MAGEA3$^+$ NSCLC who did or did not receive adjuvant chemotherapy. In the context of this large, randomized, double-blind, placebo-controlled, vaccination failed to increase the disease-free survival of surgically resected NSCLC patients (as compared to placebo).[140] On the contrary, in the prospective Phase II study reported by Saiag et al. (from the Ambroise-Paré Hospital, Boulogne, France), vaccination with a MAGEA3-specific vaccine resulted in a 1-year overall survival (OS) rate of 83.5% amongst unresectable stage IIIB-C melanoma.[146] Thus, vaccination strategies targeting MAGEA3 appear to be best suited for the treatment of advanced unresectable (rather than resectable) or chemotherapy-ineligible NSCLCs.

Weller et al. (from University Hospital of Zurich, Zurich, Switzerland) designed a randomized double-blind Phase III clinical trial to investigate the efficacy of rindopepimut, a peptide-based vaccine targeting EGFRvIII, in patients with newly diagnosed glioblastoma receiving or not conventional temozolomide-based chemotherapy. No difference in OS was documented between group, calling for a re-evaluation of the therapeutic approach.[153]

Taken together, these clinical findings corroborate the notion that TAA-targeting peptide-based vaccines are well tolerated by cancer patients and initiate tumor-targeting immune responses (at least to some degree), but mediate limited therapeutic effects when employed as standalone adjuvanted interventions. The promising results obtained in melanoma patients by Ott and collaborators with a TNA-targeting approach[168] will have to be validated in larger controlled, randomized Phase II studies. Moreover, the efficacy of TNA-based PPV (employed alone or combined with immune checkpoint blockers) against tumors with a relatively low mutational burden[77,169,170] remains to be established.

Preclinical literature

Among recent preclinical studies dealing with peptide-based anticancer vaccines, we found of particular interest the works of: (1) Zhu and colleagues (from the National Institutes of Health, Bethesda, MD, USA), who developed self-assembling albumin-vaccine nanocomplexes that reportedly enable superior delivery and mediated robust therapeutic effect against transplantable tumors growing in immunocompetent mice, especially when combined with immune checkpoint blockers and chemotherapy;[94] (2) Gall et al. (from the MD Anderson Cancer Center, Houston, TX, USA), who unveiled a Fc receptor-mediated mechanism whereby the FDA-approved HER2-targeting mAB trastuzumab favors the uptake of a HER2-targeting vaccine by DCs, resulting in efficient cross-presentation of its immunodominant epitope *in vivo* and robust therapeutic effects against breast carcinoma;[171] (3) Tsuruta et al. (from Kumamoto University, Kumamoto, Japan), who developed DEP domain containing 1 (DEPDC1)- and M-phase phosphoprotein 1 (MPHOSPH1)-derived synthetic long peptides (SLPs) that efficiently induce both helper T (T_H) cells and CTLs *in vitro* and *in vivo*;[172] (4) Petrizzu and collaborators (from the Istituto Nazionale per lo Studio e la Cura dei Tumori, Naples, Italy), who showed that metronomic chemotherapy plus a PD-1-targeting immune checkpoint blocker are highly efficient in potentiating the antitumor effects of a multi-peptide vaccine in a mouse model of melanoma;[173] and (5) Tanaka and co-workers (from the Yamaguchi University, Ube, Japan), who demonstrated that miR-125b-1 and miR-378a expression levels may be harnessed to predict the efficacy of peptide-based vaccination against colorectal carcinoma.[174]

Alongside these promising findings, Hailemichael et al. and Huang et al. (both from the MD Anderson Cancer Center, Houston, TX, USA) highlighted pitfalls related to formulation[99] that potentially compromise therapeutic efficacy when peptide-based vaccines and immune checkpoint blockers[134] or chemotherapy[175] are combined. These data suggest that additional work is required to fully decode the pharmacological and immunological interactions between peptide-based anticancer vaccines and other treatment modalities.

Ongoing clinical trials

Since the last Trial Watch dealing with peptide-based vaccines for oncological indications has been published (April 2015),[118] no less than 66 clinical trials have been initiated to test this immunotherapeutic modality in cancer patients (source www.clinicaltrials.gov) (Table 1). A large majority of these studies involve either short TAA-derived peptides that can directly bind to MHC Class I or II molecules expressed by antigen-presenting cells [176] (42 studies), or SLPs that are processed intracellularly and then loaded on MHC Class I or II molecules[172,177,178] (22 studies), most often in combination with immunological adjuvants [179-182] like montanide ISA-51 (water-in-oil emulsion)[181,183] Hiltonol® (poly-*L*-lysine in carboxymethylcellulose, a TLR3 ligand)[184] and GM-CSF.[183,185-187] In several instances, vaccination is further combined with standard treatment regimens including conventional chemotherapy,[117,188-191] radiation therapy,[52,192-195] and targeted anticancer agents,[196-199] or with various immunotherapeutic interventions.[200-205] The latter include (1) immune checkpoint blockers such as the anti-PD-1 mAbs pembrolizumab and nivolumab,[206-208] the anti-PD-L1 mAbs durvalumab and atezolizumab,[209-211] and the anti-CTLA4 mAb ipilimumab; [137,186,212-215] (2) immunostimulatory antibodies such as utomilumab, which stimulates TNF receptor superfamily member 9 (TNFRSF9; best known as 4-1BB or CD137) signaling,[28,216-218] or the CD27 agonist varlilumab;[28,216,219,220] and immunomodulatory agents such as lenalidomide.[221-224] In line with preclinical and clinical data demonstrating that multi-epitope

Table 1. Ongoing clinical trials testing TAAs or peptides as therapeutic interventions in patients affected by cancer.

Indications	Phase	Status	TAAs	Notes	Ref.
Short TAA-derived peptides					
Anal cancer	IV	Recruiting	Multiple	Single adjuvanted agent	NCT03051516
Bladder carcinoma	I	Not yet recruiting	PPV	Hiltonol®-adjuvanted intervention combined with atezolizumab	NCT03359239
Brain tumors	I	Recruiting	Multiple	Hiltonol®-adjuvanted intervention combined with varlilumab	NCT02924038
Breast carcinoma	I/II	Active	FOLR1	GM-CSF -adjuvanted intervention plus cyclophosphamide	NCT02593227
	II	Recruiting	FOLR1	GM-CSF-adjuvanted intervention plus cyclophosphamide	NCT03012100
	II	Recruiting	HER2	Adjuvanted with GM-CSF	NCT02636582
	I	Recruiting	Multiple	Montanide ISA-51- and Hiltonol®-adjuvanted intervention combined with durvalumab	NCT02826434
	I	Recruiting	Multiple	Combined with pembrolizumab	NCT03362060
Breast carcinoma Gastric carcinoma	I	Unknown	HER2	GM-CSF- and imiquimod-adjuvanted intervention combined with cyclophosphamide	NCT02276300
CRC	I	Recruiting	Multiple	Montanide ISA-51-adjuvanted intervention plus chemotherapy	NCT03391232
Glioblastoma	I/II	Active	WT1	Single adjuvanted agent	NCT02750891
	II	Recruiting	WT1	Combined with bevacizumab	NCT03149003
Glioma	I	Active	IDH1	Adjuvanted with Montanide ISA-51	NCT02454634
	I	Recruiting	H3	Adjuvanted with Hiltonol® and Montanide ISA-51	NCT02960230
	II	Recruiting	n.a.	Adjuvanted with Hiltonol®	NCT02358187
HCC	I/II	Recruiting	Multiple	CV8102-adjuvanted intervention plus cyclophosphamide	NCT03203005
HPV^{+} tumors	I	Completed	p16 (from HPV)	Adjuvanted with Montanide ISA-51	NCT02526316
Kidney cancer	I	Recruiting	PPV	Hiltonol®-adjuvanted intervention combined with ipilimumab	NCT02950766
	I/II	Active	Multiple	Adjuvanted with GM-CSF and Montanide ISA-51	NCT02429440
Leukemia	I	Not yet recruiting	PPV	Hiltonol®-adjuvanted intervention plus cyclophosphamide	NCT03219450
	I	Unknown	Multiple	Adjuvanted with GM-CSF- and Montanide ISA-51	NCT02240537
	II	Recruiting	PPV	Adjuvanted with lenalidomide and imiquimod	NCT02802943
Lung cancer	I	Recruiting	PPV	Hiltonol®-adjuvanted intervention combined with pembrolizumab, carboplatin and pemetrexed	NCT03380871
MDS	I/II	Active	WT1	Single adjuvanted agent	NCT02436252
Melanoma	n.a.	Active	MART-1	Adjuvanted with GLA-SE	NCT02320305
	I	Active	Multiple	Adjuvanted with GM-CSF	NCT02696356
	I/II	Recruiting	Multiple	Combined with dabrafenib and trametinib	NCT02382549
	I/II	Recruiting	Multiple	Montanide ISA-51-adjuvanted intervention plus ipilimumab	NCT02385669
	I/II	Recruiting	Multiple	Montanide ISA-51- and Hiltonol®-adjuvanted intervention combined with cyclophosphamide	NCT02425306
	I/II	Recruiting	Multiple	Combined with pembrolizumab	NCT02515227
	I/II	Recruiting	IDO1 PD-L1	Montanide ISA-51-adjuvanted intervention plus nivolumab	NCT03047928
	II	Recruiting	NY-ESO-1 MART-1	Montanide ISA-51- and Hiltonol®-adjuvanted intervention combined with DC vaccination	NCT02334735
Myeloma	I	Recruiting	PD-L1	Adjuvanted with Montanide ISA-51	NCT03042793
	I	Active	Multiple	Hiltonol®-adjuvanted intervention combined with durvalumab and lenalidomide	NCT02886065
NSCLC	I/II	Recruiting	UCP2 UCP4	Adjuvanted with Montanide ISA-51	NCT02818426
Ovarian cancer	II	Active	FOLR1	Combined with durvalumab	NCT02764333
	II	Recruiting	FOLR1	Adjuvanted with GM-CSF	NCT02978222
Prostate cancer	I	Not yet recruiting	BCL-X_L	Adjuvanted with Montanide CAF09b	NCT03412786
	I/II	Active	PSA	Montanide ISA-51- or GM-CSF-adjuvanted intervention combined with hyperthermia, imiquimod or RNA-based vaccine	NCT02452307
	I/II	Active	RHOC	Adjuvanted with Montanide ISA-51	NCT03199872
	II	Active	TERT	Adjuvanted with Montanide ISA-51 and imiquimod	NCT02293707
Solid tumors	I	Recruiting	PPV	Hiltonol®-adjuvanted intervention combined with nivolumab	NCT02897765
Synthetic long peptides					
Brain tumors	I	Not yet open	Multiple	GM-CSF- and Montanide ISA-51-adjuvanted intervention combined with temozolomide	NCT03299309
	I	Not yet recruiting	PPV	Adjuvanted with Hiltonol®	NCT03068832
Gastroesophageal cancer	I/II	Recruiting	HER2	Combined with cisplatin and 5-fluorouracil or capecitabine	NCT02795988

(*Continued*)

Table 1. (Continued).

Indications	Phase	Status	TAAs	Notes	Ref.
Glioblastoma	I	Active	PPV	Combined with radiation	NCT02287428
	I	Not yet recruiting	PPV	Hiltonol®-adjuvanted intervention plus nivolumab and ipilimumab	NCT03422094
	I	Recruiting	Multiple	GM-CSF- and Montanide ISA-51-adjuvanted intervention combined with tetanus booster and temozolomide	NCT02864368
	I	Recruiting	PPV	Hiltonol®-adjuvanted intervention combined with electric fields	NCT03223103
	II	Active	Multiple	Hiltonol®-adjuvanted intervention combined with bevacizumab	NCT02754362
	II	Active	Survivin	GM-CSF- and Montanide ISA-51-adjuvanted intervention combined with temozolomide and radiation	NCT02455557
HPV^+ tumors	I	Recruiting	E6 (from HPV)	Adjuvanted with Amplivant®	NCT02821494
	II	Recruiting	E6/E7 (from HPV)	Combined with utomilumab	NCT03258008
Leukemia Lymphoma	II	Active	pp65 (from CMV)	Single adjuvanted agent	NCT02396134
Leukemia MDS	I	Recruiting	Multiple	Combined with azacytidine	NCT02750995
Lymphoma	I	Not yet recruiting	PPV	Hiltonol®-adjuvanted intervention plus nivolumab and rituximab	NCT03121677
	I	Not yet recruiting	PPV	Hiltonol®-adjuvanted intervention combined with rituximab	NCT03361852
	I	Recruiting	PD-L1 PD-L2	Adjuvanted with Montanide ISA-51	NCT03381768
Myeloma	I	Recruiting	Survivin	Adjuvanted with GM-CSF, lenalidomide and Montanide ISA-51	NCT02334865
Others					
Brain tumors	I	Recruiting	PPV	Combined with radiation	NCT02722512
NSCLC	II	Recruiting	Multiple	Adjuvanted with Montanide ISA-51	NCT02264236

Abbreviations. CMV, cytomegalovirus; CRC, colorectal carcinoma; DC, dendritic cell; HCC, hepatocellular carcinoma; HPV, human papillomavirus; MDS, myelodysplastic syndrome; n.a., not available; NSCLC, non-small cell lung carcinoma; PPV, personalized peptide vaccination, SLP, synthetic long peptide; TAA, tumor-associated antigen.

vaccines are generally more powerful than their single-epitope counterparts,[117,225] the most common vaccination strategy employed by these studies consists in targeting simultaneously multiple TAAs (20 studies). Alongside, 15 studies are investigating the safety and efficacy of PPV, often consisting of MHC-matched peptides chosen from the immune repertoire of the patient before treatment.[226] Finally, several studies aim at testing the safety and therapeutic potential of peptide-based vaccines targeting one single TAA including not only viral antigens like HPV p16, E6 and E7,[227-229] but also shared TAAs like HER2, NY-ESO-1, survivin and telomerase reverse transcriptase (TERT),[161,230-252] as well as TAAs involved in the establishment of immunosuppression, such as PD-L1 and indoleamine 2,3-dioxygenase 1 (IDO1).[253-256]

Taken together, these clinical trials enroll patients with a wide panel of neoplasms, including (but not limited to) glioblastoma, glioma and other brain tumors (NCT02722512; NCT02924038; NCT03068832; NCT03299309; NCT02750891; NCT03149003; NCT02287428; NCT02455557; NCT02754362; NCT02864368; NCT03223103; NCT03422094; NCT02358187; NCT02454634; NCT02960230), breast carcinoma (NCT02276300; NCT02593227; NCT02636582; NCT03012100; NCT02826434; NCT03362060), hematological malignancies (NCT02240537; NCT02802943; NCT03219450; NCT02396134; NCT02750995; NCT03121677; NCT03361852; NCT03381768; NCT02436252), melanoma (NCT02320305; NCT02334735; NCT02382549; NCT02385669; NCT02425306; NCT02515227; NCT02696356; NCT03047928), ovarian carcinoma (NCT02764333; NCT02978222; NCT02737787; NCT02933073) and prostate cancer (NCT03412786; NCT02293707; NCT02452307; NCT03199872).

Although final statistical assessments are still awaited, preliminary results from 8 clinical trials that have been completed or terminated since the publication of our last Trial Watch dealing with peptide-based anticancer vaccines (April 2015)[118] have become available (source www.clinicaltrials.gov). NCT01423760, an open-label, common safety follow-up trial testing a MUC1-targeting vaccine (tecemotide) in patients with myeloma and NSCLC has been terminated prematurely as per decision of the sponsor. Out of 27 patients enrolled in the study, 20 were evaluable for toxicity, which was more severe in the NSCLC arm. NCT00409188, a Phase III study testing tecemotide in combination with single low-dose cyclophosphamide in subjects with NSCLC has been completed. Primary endpoint was not met, but notable survival benefits were achieved in patients treated with concurrent chemoradiotherapy,[257] NCT01507103, a Phase II study testing the therapeutic profile of tecemotide combined with cyclophosphamide or cyclophosphamide plus chemoradiation in subjects with rectal cancer, has been completed. No difference in incidence and severity of adverse events were noted. NCT01380145, an open-label, single-arm, pilot study of recombinant MAGEA3 adjuvanted with AS15[258] as consolidation for multiple myeloma patients undergoing autologous stem cell transplantation, has been completed. Treatment was immunologically active, but grade 3–4 adverse events were experienced by 12 of the 13 participants in the study. One year after treatment there were 4 patients in stringent complete response (CR), 1 in CR, 4 in very good partial response (PR) and 4

with progressive disease. NCT00849875, a Phase II study testing MUC1-targeting vaccination plus dacarbazine in melanoma patients, has been terminated due to lack of scientific justification to continue collect data. Of 48 participants analyzed, 10 had serious adverse events. Seroconversion occurred in all patients, but clinical activity was limited to 1 CRs and 3 PRs. NCT00706992, a Phase 2 trial testing a peptide-based vaccine specific for melan-A (MLANA; also known as MART-1) together with MART-1-targeting lymphocytes in high-risk melanoma patients, has been terminated owing to low accrual. No robust immunological responses were documented among 40 evaluable patients. Adverse events were common, but never serious. NCT01322815, a Phase II study assessing the therapeutic profile of a peptide-based vaccine targeting mutant KRAS combined with standard chemotherapy or a mAb specific for vascular endothelial growth factor A (VEGFA)[259] in patients with colorectal carcinoma, has been terminated owing to poor accrual rate. Four months after the initiation of treatment, 50% of patients were alive and free of progression, but 2 patients receiving GI-4000 plus chemotherapy suffered from serious adverse effects. NCT00643097, a Phase I-II trial investigating the safety and preliminary therapeutic profile of an EGFRvIII-directed vaccine adjuvanted with GM-CSF in patients with glioblastoma, has been completed. Of 30 participants evaluable for the immunogenicity of the vaccine, 10 presented robust immune responses, median progression-free survival was between 11.6 and 14.2 months. NCT01307618, a Phase II study testing a multi-epitope peptide-based vaccine in combination with a CD25-specific antibody (daclizumab) ± recombinant metastatic interleukin 12 (IL12) in patients with metastatic melanoma, was terminated due to lack of efficacy.

Concluding remarks

In the past few years, tremendous progress has been made towards understanding the molecular and cellular pathways whereby the immune system can recognize and eradicate pre-malignant and malignant cells naturally as well as in response to some treatment regimens.[9,20,21,260] Such knowledge has been instrumental for the development of a wide panel of therapeutic interventions that specifically aim at (re)establishing anticancer immunosurveillance (rather than merely causing the death of malignant cells), including peptide-based vaccination.[8,105,176,261-264] Unfortunately, it has soon become clear that the majority of immunotherapies developed so far is poorly active when employed as standalone therapeutic intervention, largely reflecting (1) natural and treatment-driven immunoediting, resulting in the selection of poorly immunogenic cancer cell populations;[115,265,266] and (2) the robust immunosuppression established by malignant cells, both locally and systemically.[267-269] In line with this notion, the vast majority of peptide-based vaccines tested in the clinic so far mediated limited, if any, therapeutic activity, despite being able to elicit tumor-targeting immune responses, at least to some degree.[118] The field is therefore moving along three non-mutually exclusive directions: (1) combining peptide-based vaccination with additional forms of (immuno)therapy, with the specific aim of reverting immunosuppression and enabling therapeutically relevant immune responses,[270-272] (2) targeting private antigenic epitopes that originate from mutations affecting only malignant cells (or sub-populations thereof), with PPV,[167,272-275] and (3) identifying specific patient populations that may obtain clinical benefit from the use of peptide-based vaccination.[174,254] Although the feasibility of PPV on a large scale remains unclear, we surmise combining some variants of peptide-based vaccination with potent immunostimulatory agents including immune checkpoint blockers and oncolytic viruses may be the key to unlock the true potential of this hitherto unrealized therapeutic modality.

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