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Trial watch

FDA-approved Toll-like receptor agonists for cancer therapy

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Abbreviations: BCG, bacillus Calmette-Guérin; CMV, cytomegalovirus; DAMP, damage-associated molecular pattern; dsRNA, double-stranded RNA; GPX1, glutathione peroxidase 1; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HSV-2, herpes simplex virus type 2; IL, interleukin; LPS, lipopolysaccharide; MAMP, microbe-associated molecular pattern; MPL, monophosphoryl lipid A; NRAMP1, natural resistance-associated macrophage protein 1; TLR, Toll-like receptor

Toll-like receptors (TLRs) have first been characterized for their capacity to detect conserved microbial components like lipopolysaccharide (LPS) and double-stranded RNA, resulting in the elicitation of potent (innate) immune responses against invading pathogens. More recently, TLRs have also been shown to promote the activation of the cognate immune system against cancer cells. Today, only three TLR agonists are approved by FDA for use in humans: the bacillus Calmette-Guérin (BCG), monophosphoryl lipid A (MPL) and imiquimod. BCG (an attenuated strain of *Mycobacterium bovis*) is mainly used as a vaccine against tuberculosis, but also for the immunotherapy of in situ bladder carcinoma. MPL (derived from the LPS of *Salmonella minnesota*) is included in the formulation of Cervarix®, a vaccine against human papillomavirus-16 and -18. Imiquimod (a synthetic imidazoquinoline) is routinely employed for actinic keratosis, superficial basal cell carcinoma, and external genital warts (condylomata acuminata). In this Trial Watch, we will summarize the results of recently completed clinical trials and discuss the progress of ongoing studies that have evaluated/are evaluating FDA-approved TLR agonists as off-label medications for cancer therapy.

Introduction

In 1985, the laboratory of Christiane Nüsslein-Volhard characterized for the first time *Toll*, a gene that regulates the dorsal-ventral embryonic polarity of the fruit fly *Drosophila melanogaster*.[1,2] For her discoveries concerning the genetic control of early embryonic development, Christiane Nüsslein-Volhard shared the 1995 Nobel prize in Medicine or Physiology with her collaborator Eric F. Wieschaus and with Edward B. Lewis, an American geneticist who first characterized the Drosophila bithorax gene cluster.[3,4] Besides elucidating (at least in part) the mechanisms that regulate early embryonic development, the work of Christiane Nüsslein-Volhard de facto laid the basis for the discovery and characterization of Toll-like receptors (TLRs), transmembrane proteins that are crucial for the activation of the innate immune system in response to conserved microbial products known as microbe-associated molecular patterns (MAMPs), including bacterial lipopolysaccharide (LPS, also known as endotoxin) and viral double-stranded RNA (dsRNA).[5] The discovery that TLRs exert a crucial function in innate immune responses (in a wide range of organisms) granted to the French biologist Jules Hoffmann and the American immunologist Bruce Beutler the 2011 Nobel Prize in Medicine or Physiology.[6,7]

Today, 13 distinct TLRs are known to be expressed in mammals (of which 10 in humans), and proteins of the TLR family have been identified in evolutionarily distant organisms including fish and plants.[8-10] Importantly, TLRs (in particular TLR2 and TLR4) have recently been shown to bind not only MAMPs but also a large panel of damage-associated molecular patterns (DAMPs), i.e., endogenous signals that are dispatched by stressed or dying cells to promote sterile inflammation.[11] Thus, TLRs appear to be critical for the activation of innate immunity against pathogens as well as for the orchestration of potentially therapeutic anti-cancer immune responses.[12]

In line with this notion, long-used (and relatively effective) anticancer preparations including Coley's toxin (a mixture of killed *Streptococcus pyogenes* and *Serratia marcescens* bacteria) and the bacillus Calmette-Guérin (BCG, an attenuated strain of *Mycobacterium bovis* initially developed as an anti-tuberculosis

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Table 1. TLR agonists approved by FDA for use in humans against cancer and cancer-related conditions

Agent	Main target(s)	Indications
Bacillus Calmette-Guérin	TLR2/TLR4	Superficial transitional cell carcinoma of the bladder
Monophosphoryl lipid A*	TLR2/TLR4	Adjuvant to Cervarix® for the prophylaxis of HPV-associated cervical cancer
Imiquimod	TLR7	Actinic keratosis, basal cell carcinoma, genital and perianal warts

Abbreviations: HPV, human papillomavirus. *Combined with aluminum salts (AS04).

vaccine), have recently been shown to potently activate TLR2 and TLR4.[13,14] Similarly, imiquimod (a small imidazoquinoline that was originally developed as a topic antiviral agent) has been approved by FDA in 1997 for the treatment of genital and perianal warts, but it was found to function as a TLR7 agonist only five years later.[15] While the use of Coley's toxin has been interrupted in the 1960s, mostly due to concerns raised by the thalidomide case,[16] both BCG and imiquimod are currently approved by FDA for use in humans, the former for the immunotherapy of in situ bladder carcinoma and the latter against actinic keratosis, superficial basal cell carcinoma and external genital warts (condylomata acuminata).[17] The same holds true for monophosphoryl lipid A (MPL), a derivative of *Salmonella minnesota* LPS that operates as a potent agonist of TLR4,[18] which has been authorized by FDA for use within the formulation of Cervarix®, a vaccine against human papillomavirus Type 16 and 18 (HPV16 and HPV18, the causative agents of approximately 70% of cervical carcinoma cases) (**Table 1**).[19]

In the latest issue of *OncoImmunology*, we have extensively discussed the biological properties of therapeutically relevant TLRs and portrayed the current status of clinical development of experimental TLR agonists as immunostimulatory agents for oncological indications.[20] In this Trial Watch, we will focus on recently completed or ongoing clinical trials that have evaluated/are evaluating FDA-approved TLR agonists as off-label medications for cancer therapy.

Bacillus Calmette-Guérin

In the 19th century, research in the area of infectivology witnessed several milestone achievements. These include the demonstration (by Edward Jenner) that cowpox infection provides immunity against smallpox, as well as the isolation (by Robert Koch) of *Mycobacterium tuberculosis* (the etiological determinant of human tuberculosis) and of its bovine counterpart *M. bovis*.[21,22] At the end of the same century, excited by the success of vaccination campaigns for the prevention of smallpox, scientists hypothesized that a similar principle might apply to tuberculosis, and hence begun to investigate the therapeutic potential of *M. bovis*.[23] Unfortunately, early trials conducted in Italy had disastrous outcomes, as *M. bovis* was found to be as virulent as *M. tuberculosis*.[24] A couple of decades later, however, the bacteriologist Albert Calmette and the veterinarian Camille Guérin, developed an attenuated strain of *M. bovis* that—upon prolonged culture in peculiar media (including a glycerin-bile-potato mixture)—was unable to cause overt tuberculosis in research animals. The BGC vaccine had officially been born. Since then, BCG has been used for the prevention of tuberculosis in millions of individuals worldwide.[25] According to WHO, today tuberculosis is second only to HIV as the greatest killer due to a single infectious agent, with most tuberculosis-related deaths occurring in low- and middle-income countries (source www.who.int/mediacentre/factsheets/fs104/en/). This said, in high-income countries the introduction of BCG as an obligatory vaccine coupled to highly efficient antibiotic regimens has virtually eradicated tuberculosis. Indeed, while in the late 18th century 1:3–7 deaths in the UK were due to tuberculosis, less than 200 people died in the UK in 2007 for the same cause.[26]

The anticancer potential of BCG has been intuited as early as in the 1960s, but fully recognized only a few years later, when several authors reported not only that the growth of transplanted and viral cancers can be fully prevented by the co-administration of BGC,[27-29] but also that the inoculation of BGC into established tumors leads to tumor regression and prevents the development of metastasis.[30] Approximately in the same period, an intense wave of clinical investigation started to evaluate BCG (either as such or subjected to distinct extraction procedures, either alone or combined with radio-, chemo- or immunotherapeutic regimens) for the treatment of neoplasms as diverse as leukemia,[31-39] lymphoma,[40,41] head and neck squamous cell carcinoma (HNSCC),[42,43] breast carcinoma,[44-49] lung cancer,[50-53] melanoma,[54-69] gastric cancer,[70,71] colorectal carcinoma,[72-77] sarcoma,[78,79] prostate cancer,[80-82] cervical carcinoma,[42] renal carcinoma,[83-88] and bladder cancer.[89-96] Unfortunately, most of these studies either reported no clinical benefits or relied on small patient cohorts, often being not confirmed by the results of subsequent large trials.[97-99] As a standalone exception, the intravesical instillation of BCG was suggested to be safe and highly effective for the therapy of bladder carcinoma as soon as in 1976,[85,94] a notion that was subsequently confirmed by dozens of randomized clinical studies.[100-103] The clinical development of BCG as an adjuvant for cancer therapy culminated in 1990, when FDA approved BCG for use in humans as an immunotherapeutic intervention against superficial bladder carcinoma.

Since then, the possibility of exploiting the potent immunostimulatory properties of BCG against several types of cancer has continued to foster great expectations, and during the past 20 years BCG has been tested in hundreds of clinical studies. These trials (1) covered previously tested indications for which clear results had not been obtained; (2) investigated variations in dose,[104-107] administration route[108-111] and schedule;[111-113] and (3) evaluated the safety and efficacy of BCG or BCG components in a few previously untested or scarcely tested settings, including lymphoma,[114] and ovarian cancer.[115-117] These clinical studies led to a remarkable refinement in the dosage and schedule of BCG immunotherapy, thus lowering both the incidence and severity of

Table 2. Clinical trials evaluating BCG as an off-label medication for cancer therapy*

Indications	Trials	Phase	Status	Co-therapy	Ref.
Early clinical trials (Phase I–II)					
Breast cancer	1	I	Completed	Combined with anti-CD80 vaccine and GM-CSF	NCT00003184
Colorectal cancer	2	I–II	Completed	Combined with autologous tumor cell vaccine, 5-FU and folinic acid	NCT00016133
			Unknown	Combined with cell-based vaccine	NCT00007826
Melanoma	2	I–II	Terminated	Combined with autologous dendritoma vaccine	NCT00671554
		II	Unknown	Combined with autologous tumor cell vaccine, cyclophosphamide and IFNα	NCT00003715
Neuroblastoma Sarcoma	1	I	Completed	Combined with A1G4 anti-idiotype mAb vaccine	NCT00003023
Ovarian cancer	1	II	Completed	Combined with cell-based vaccine, carboplatin, cisplatin, cyclophosphamide and paclitaxel	NCT00003386
Prostate cancer	1	II	Unknown	Combined with ONY-P1-based vaccine	NCT00514072
Advanced clinical trials (Phase III)					
Colon cancer	1	III	Completed	As single agent	NCT00427570
Lung cancer	3	III	Completed	Combined with anti-BEC2 mAb	NCT00003279 NCT00037713
			Unknown		NCT00006352
Melanoma	3	III	Active, not recruiting	Combined with cyclophosphamide and IL-2 ± autologous vaccine	NCT00477906
			Recruiting	As single agent	NCT01013623
			Unknown	Combined with CancerVax™ vaccine	NCT00052156

Abbreviations: 5-FU, 5-fluorouracil; BCG, bacillus Calmette-Guérin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin 2; IFNα, interferon α; mAb, monoclonal antibody.

BCG-associated side effects (mainly consisting of fever, hematuria, bladder irritation/infection and a potentially lethal, but very rare, systemic reaction).[118] However, such a great clinical effort de facto failed to identify oncological settings other than bladder cancer in which BCG may be beneficial. Accordingly, the indication for which BCG has been granted FDA approval for use in humans in 1990 has never changed since.

As BCG-based immunotherapy constitutes the gold standard approach for some types of bladder carcinoma, several clinical trials registered at www.clinicaltrials.gov were designed to compare novel therapeutic strategies to intravesical BCG for this indication. Alternatively, a few studies have been initiated to investigate the therapeutic potential—again in the context of bladder carcinoma—of BCG in association with either mitomycin C (a DNA alkylating agent) of interferon α (IFNα)-based immunotherapy, as compared with BCG alone.[119,120] Beside these studies, de facto employing BCG as an on-label medication, official sources list 15 studies that have been initiated to evaluate the safety/efficacy of BCG, most often as an adjuvant to other immunotherapeutic interventions,[121,122] in off-label indications including breast carcinoma, colorectal cancer, lung cancer, melanoma, neuroblastoma, sarcoma, ovarian carcinoma and prostate cancer. One of these trials has been terminated due to business considerations (NCT00671554) and 6 others are listed as completed (NCT00003023, NCT00003184, NCT00003279, NCT00003386, NCT00016133 and NCT00427570), but their results have not yet been released (source www.clinicaltrials.gov).

Table 2 summarizes recent clinical trials evaluating the safety and efficacy of BCG as an off-label mediation for cancer therapy.

Monophosphoryl Lipid A

MPL is a chemically modified derivative of *S. minnesota* endotoxin that exhibits greatly reduced toxicity but maintains most of the immunostimulatory properties of LPS,[123] de facto operating as a potent TLR4 agonist.[18] The immunogenic potential of lipid A emerged as early as in the 1950s, thanks to the work of Howard, Rowley and Wardlaw from the Wright-Fleming Institute of Microbiology (London, UK).[123,124] During the subsequent couple of decades, the biochemical and biological properties of lipid A from different bacterial strains have been extensively characterized.[125-134] A few years after the work of Howard and colleagues, pioneer studies performed in Japan suggested that—similar to LPS—lipid A may exert antitumor activity in vivo.[135,136] These findings were rapidly confirmed in a number of preclinical tumor models, in vitro and in vivo, along with the discovery that lipid A potently induce IFNγ and tumor necrosis factor α (TNFα).[137-139] Strikingly, in 1973 (when neither Toll nor TLRs were known), Parr and colleagues identified similarities in the antineoplastic effects of LPS, lipid A and

dsRNA,[140] hence foreseeing (by at least 25 years) the fact that all these MAMPs activate innate immune effector mechanisms by binding to TLRs.[7,141,142]

During the next few years, great efforts were dedicated to the isolation of natural lipid A analogs, as well as to the identification of chemical and/or structural alterations that would preserve the immunostimulatory potential of lipid A while limiting its side effects.[143-148] Thus, in the early 1980s, Qureshi and colleagues were the first to detail a method for the extraction and purification of MPL from the endotoxin of *Salmonella* spp.[149-151] The first Phase I clinical trial testing the intravenous administration of MPL from *Salmonella typhimurium* and *S. minnesota* in cancer patients was concluded in 1984, identifying a maximum tolerated dose of 100 μg/m^2 but no clear therapeutic benefits.[152] Approximately in the same period, Jirillo and colleagues begun to conduct pilot clinical studies in cancer patients receiving acetic acid-inactivated *S. minnesota* (strain R595 Re), reporting no severe toxicity at the dose employed (up to 6.5 μg in four consecutive intravenous injections) but a consistent improvement in both innate and cognate immune functions.[153,154] Since then, the biological and immunological properties of lipid A and some of its derivatives have been the subject of an intense wave of preclinical investigation.[18,155-174] In the meanwhile, some of these compounds including ONO-4007, OM-174 and MPL, the latter within formulations such as DETOX (MPL + *Mycobacterium phlei* cell wall), AS02B (MPL + QS21, a water soluble saponin extracted from the South American tree *Quillaja saponaria* Molina),[175] AS04 (MPL + aluminum salts) and AS15 (AS02B + CpG oligonucleotides), have also been tested in clinical trials, with mixed results. Indeed, whereas the clinical development of ONO-4007 and OM-174 as adjuvants for anticancer immunotherapy appears to stand at an impasse,[20,176,177] AS02B,[178-183] AS04 [184-197] and AS15 (Refs. 198, 199 and Annual ASCO Meeting 2008, Abstracts 9045 and 9065) have been shown to potently boost the patient's immune response against viral and tumor-associated antigens by a plethora of independent studies. The clinical development of MPL-based adjuvants culminated in 2009, when FDA approved the AS04-adjuvanted preparation Cervarix® for use in humans as a preventive measure against premalignant and malignant lesions of the cervix causally related to oncogenic HPV subtypes.[200] In multiple countries, Cervarix® is nowadays administered to young (7–25 year old) girls as part of national vaccination programs, a measure that—in a few years—will almost certainly lead to a drop in the incidence of HPV-associated cervical cancer.[200]

As we have discussed in the latest issue of *OncoImmunology*, the development of AS02B and AS15 as adjuvants for cancer immunotherapy continues.[20] On the other hand, most clinical trials involving AS04 that are currently included in official databases not only are listed as completed, but also were designed to investigate Cervarix® as an on-label intervention (source www.clinicaltrials.gov). Thus, it appears that the immunostimulatory potential of AS04 has never generated a great interest for the immunotherapy of neoplasms other than HPV-associated cervical carcinoma.

Imiquimod

Imiquimod (a small non-nucleoside imidazoquinoline originally known as S-26308 or R-837) has begun to attract attention in the late 1980s, when a few reports demonstrated its therapeutic and prophylactic potential in animal models of cytomegalovirus (CMV) and herpes simplex virus type 2 (HSV-2) infection.[201-203] It was clear from the beginning that the biological targets for such an antiviral activity were not infected cells (as imiquimod was inactive against HSV-2 and CMV in vitro),[203] but rather components of the immune system.[202-206] Indeed, similar to other imidazoquinolines (e.g., S-27609), imiquimod turned out to act in vivo as a potent inducer of immunostimulatory cytokines including IFNα, TNFα, interleukin (IL)-1β and IL-6,[207-210] and to exert consistent antitumor effects.[211] Following these preclinical results, a Phase I clinical trial was conducted with 14 cancer patients to investigate maximum tolerated dose, toxicity, and biological outcome of imiquimod (100–500 mg), given per os either once or twice weekly.[212] Unfortunately, although the drug was well tolerated (main side effects being fatigue, malaise, fever, headache and lymphocytopenia) and exerted immunostimulatory effects in all patients, no clinical responses were observed.[212] A few years later, another Phase I study testing oral imiquimod in 21 patients with refractory neoplasms was concluded, reporting biological activity (measured in terms of circulating IFNα concentrations and 2–5A synthetase levels in peripheral blood mononuclear cells) but again no clear therapeutic benefit.[213]

Approximately in the same period, however, imiquimod (and some derivatives) begun to be extensively tested for the topical treatment of actinic keratosis (a precancerous lesion of the skin),[214-220] basal cell carcinoma,[221-230] and genital and perianal warts (a common sexually transmitted disease caused by HPV).[231-240] These studies (and many others that followed whose detailed discussion goes beyond the scope of this Trial Watch) demonstrated that imiquimod (as a 5% cream) is safe, generally well tolerated and highly efficient against multiple skin disorders, de facto leading to its approval by FDA for use in humans as early as in 1997, initially as a countermeasure against genital and perianal warts only. Strikingly, it was not until 2002 that imiquimod was found to exert immunostimulatory and anticancer effects by binding to TLR7,[15] a TLR predominantly expressed at the endosomal membrane of monocytes, macrophages, plasmacytoid DCs (one peculiar subset of DCs that operate at the interface between innate and adaptive immunity) [241] and mast cells.[177] In 2004, FDA granted its approval to imiquimod also for use in humans against actinic keratosis and superficial basal cell carcinoma. Since then, further insights have been gained into the cellular and molecular circuitries whereby imiquimod promotes antitumor immune responses. In particular, imiquimod has been shown to stimulate the production of pro-inflammatory cytokines by acting as an adenosine receptor antagonist,[242] as well as to promote the (CCL2-dependent) recruitment of plasmacytoid DCs into the tumor bed and their conversion into tumor-killing effector cells.[243]

Following the demonstration that imiquimod is exceptionally efficient against actinic keratosis, basal cell carcinoma and

warts, its therapeutic potential as an off-label prescription has been intensively investigated. In the vast majority of cases, these approaches (including large, randomized trials as well as case studies) focused on conditions for which the topical application of imiquimod alone would be appropriate, encompassing infantile hemangiomas,[244-248] dysplastic nevi and in situ melanoma (lentigo maligna),[249-258] in situ squamous cell carcinoma (Bowen's disease)[259-264] keratoacanthoma,[265-267] non-genital warts,[268-272] xeroderma pigmentosum,[273] vulvar, vaginal and cervical intraepithelial dysplasia/neoplasia,[274-284] extramammary Paget disease,[285-289] Kaposi sarcoma,[290-292] desmoplastic trichoepithelioma (an uncommon adnexal tumor usually found on the face of young women),[293] cutaneous T-cell lymphoma,[294-296] as well as cutaneous metastases from multiple primary tumors.[297-301] In addition, a few groups have evaluated the therapeutic potential of imiquimod as an adjuvant to peptide- or cell-based anticancer vaccines.[302-305] Notably, the results of most—if not all—these studies support the contention that topical imiquimod might be beneficial for a very large spectrum of pre-neoplastic and malignant conditions, including primary lesions of the skin (i.e., squamous cell carcinoma, melanoma and Paget disease), accessible epithelial cancers (i.e., vulvar, vaginal and cervical intraepithelial cancer), tumors that localize to the derma (i.e., cutaneous T-cell lymphoma, Kaposi sarcoma and hemangioma) as well as cutaneous metastases from unrelated tumors. However, the actual therapeutic potential of imiquimod in all these settings will have to be confirmed by large, randomized studies.

Today, topical imiquimod, most often alone or combined with cryosurgery, continues to be extensively tested as an on-label prescription both in subjects affected by actinic keratosis (2 Phase II + 20 Phase III/IV trials registered at www.clinicaltrials.gov) and in basal cell carcinoma patients (3 Phase II + 9 Phase III/IV trials registered at www.clinicaltrials.gov). These studies are mainly intended to evaluate the safety and efficacy of reduced doses (e.g., 2.5% or 3.75% cream formulations) and/or alternative (i.e., cyclic, very prolonged) administration schedules, and in some cases promising results have already been released.[306-310] In off-label settings, imiquimod 5% cream (as a single agent) is being/has recently been evaluated in patients affected by lentigo maligna (NCT00707174, NCT01161888, NCT01088737), cutaneous neurofibromas (NCT00865644), infantile hemangiomas (NCT00601016), HNSCC (NCT00384124), breast cancer (NCT00899574), cervical dysplasia/neoplasia (NCT00031759, NCT00941811, NCT00941252, NCT01283763) and recurrent Paget's disease (NCT00504023). Topical imiquimod is also under investigation combined with paclitaxel or radiotherapy for the treatment of advanced/metastatic breast cancer (NCT00821964, NCT01421017) as well as combined with laser therapy for the control of (cutaneous) metastases of melanoma (NCT00453050).

In all these studies, imiquimod appears to be employed either as an immunostimulant per se or to exacerbate anticancer immune responses as elicited by chemo-, radio- or laser therapy. In addition to these relatively unspecific approaches, imiquimod 5% cream is being extensively investigated as an adjuvant to tumor-specific (peptide- or cell-based) vaccination strategies, including approaches directed against brain tumors (NCT00626483, NCT01171469, NCT01204684, NCT01400672, NCT01403285), neuroblastoma and sarcoma (NCT00944580, NCT01241162), melanoma (NCT00118313, NCT00142454, NCT00651703, NCT01191034, NCT01264731, NCT01543464), non-small cell lung cancer (NCT01219348), colorectal cancer (NCT00785122), cervical intraepithelial neoplasia (NCT00788164) and tumors of the reproductive tract (NCT00799110). In this case, imiquimod is applied to the vaccination site (which almost invariably consists in a subcutaneous injection) both before (often 24 h) and after (often 24 h) the injection. Of note, while the majority of clinical trials testing imiquimod as an on-label medication are listed as completed, most studies investigating imiquimod in off-label settings (in particular those in which imiquimod is used to boost anticancer vaccines) are still ongoing.

Table 3 summarizes recent clinical trials evaluating the safety and efficacy of imiquimod as an off-label mediation for cancer therapy.

Concluding Remarks

As we have discussed here and in the latest issue of *OncoImmunology*,[20] there's a vast amount of preclinical and clinical evidence indicating that TLR agonists exert potent immunostimulatory functions, in vivo. In line with this notion, BCG, MPL and imiquimod constitute—at least for the indications for which they are approved by FDA and the European Medicines Agency—an important clinical reality, being associated with consistent rates of remission and limited side effects. Moreover, whereas the MPL-based adjuvant AS04 is under clinical investigation only as an on-label medication, BCG and imiquimod are currently being tested as off-label prescriptions in a variety of oncological settings, either as single agents or combined with specific anticancer vaccines. Thus, at odds with their experimental counterparts,[20] BCG and imiquimod continue to attract great attention as immunostimulatory agents for cancer immunotherapy. We surmise that the results of ongoing clinical studies might induce regulatory agencies to extend the oncological indications for which BCG and imiquimod are approved.

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Table 3. Clinical trials evaluating imiquimod as an off-label medication for cancer therapy*

Indications	Trials	Phase	Status	Co-therapy	Ref.
Early clinical trials (Phase I–II)					
Brain tumors	5	I	Recruiting	Combined with cell-based vaccine	NCT01400672
				Combined with cyclophosphamide, GM-CSF and peptide vaccine	NCT01403285
			Suspended	Combined with DC-based vaccine	NCT01171469
		I–II	Active, not recruiting	Combined with CMV-specific CTLs, daclizumab and DC-based vaccine	NCT00626483
		II	Recruiting	Combined with DC-based vaccine	NCT01204684
Breast cancer	3	I–II	Recruiting	Combined with radiotherapy	NCT01421017
		II	Active, not recruiting	As single agent	NCT00899574
			Recruiting	Combined with paclitaxel	NCT00821964
Cervical cancer	4	I–II	Not yet recruiting	As single agent	NCT01283763
		II	Completed		NCT00031759
			Unknown	Combined with HPV16-targeting therapeutic vaccine	NCT00941811 NCT00788164
Colorectal cancer	1	I–II	Active, not recruiting	Combined with cyclophosphamide, GM-CSF and peptide vaccine	NCT00785122
Cutaneous neurofibroma	1	n.a.	Unknown	As single agent	NCT00865644
Hemangioma	1	II	Completed	As single agent	NCT00601016
Lentigo maligna	1	n.a.	Active, not recruiting	As single agent	NCT00707174
Melanoma	7	n.a.	Recruiting	Combined with peptide vaccine	NCT01264731
		I	Completed	Combined with peptide vaccine	NCT00142454
			Unknown	Combined with DMSO, GM-CSF, and multipeptide vaccine	NCT00118313
				Combined with laser therapy	NCT00453050
		I–II	Recruiting	Combined with IL-2, IFNα, GM-CSF and peptide-based vaccine	NCT01191034
		II	Completed	Combined with peptide vaccine ± montanide	NCT00651703
			Not yet recruiting	Combined with GM-CSF, peptide vaccine and temozolomide	NCT01543464
Neuroblastoma Sarcoma	2	I	Recruiting	Combined with autologous DC-based vaccine and decitabine	NCT01241162
			Terminated	Combined with multipeptide vaccine and DC-based vaccine	NCT00944580
NSCLC	1	I	Recruiting	Combined with peptide vaccine ± montanide	NCT01219348
Reproductive tract cancer	1	II	Recruiting	Combined with DC-tumor cell fusion vaccine and GM-CSF	NCT00799110
Vulvar cancer	1	n.a.	Active, not recruiting	As single agent	NCT00504023
Advanced clinical trials (Phase II–IV)					
Cervical cancer	1	II–III	Completed	As single agent	NCT00941252
HNSCC	1	II–III	Enrolling by invitation	As single agent	NCT00384124
Lentigo maligna	2	II–III	Recruiting	As single agent	NCT01088737
		IV	Active, not recruiting		NCT01161888

Abbreviations: CMV, cytomegalovirus; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DMSO, dimethylsulfoxide; GM-CSF, granulocyte-macrophage colony-stimulating factor; HNSCC, head and neck squamous cell carcinoma; HPV16, human papillomavirus Type 16; IFNα, interferon α; n.a., not available; NSCLC, non-small cell lung carcinoma.

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